

Blood pressure and risk of type 2 diabetes mellitus in men and women from the general population: the Monitoring Trends and Determinants on Cardiovascular Diseases/ Cooperative Health Research in the Region of Augsburg Cohort Study

Christa Meisinger^{a,b}, Angela Döring^a and Margit Heier^{a,b}

Objective To examine sex-specific associations between blood pressure levels and incident type 2 diabetes mellitus in a representative population sample in Germany.

Methods The study was based on 5556 men and 5445 women (aged 25–74 years) who participated in one of the three Monitoring Trends and Determinants on Cardiovascular Diseases Augsburg surveys between 1984 and 1995 and who were free of diabetes at baseline. Sex-specific hazard ratios were estimated from Cox proportional hazard models.

Results A total of 410 cases of incident type 2 diabetes among men and 263 among women were registered during the median follow-up period of 12.5 years. Higher blood pressure levels were associated with older age, higher body mass index (BMI), a higher prevalence of dyslipidemia, a lower prevalence of regular smoking, high alcohol consumption (men only), and a lower education level. Compared with individuals with normal blood pressure, the hazard ratios (95% confidence interval) of incident diabetes associated with an optimal blood pressure, high normal blood pressure, and hypertension were 0.67 (0.36–1.27), 1.76 (1.24–2.51), and 1.93 (1.41–2.65) for men and 0.74 (0.41–1.32), 1.07 (0.67–1.73), and 2.05 (1.41–2.99) for women. The found association was present in the subgroup with low BMI as well as in the group with high BMI supporting the assumption that blood pressure may

contribute to the manifestation of type 2 diabetes independent of BMI.

Conclusion Established hypertension was significantly associated with incident type 2 diabetes in men and women from the general population, whereas high normal blood pressure significantly increased the risk of diabetes in men only. *J Hypertens* 26:1809–1815 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Journal of Hypertension 2008, 26:1809–1815

Keywords: cohort study, hypertension, population, risk, type 2 diabetes mellitus

Abbreviations: HDL-cholesterol, high density lipoprotein cholesterol; MONICA, Monitoring trends and determinants on cardiovascular diseases

^aHelmholtz Zentrum München, German Research Center for Environmental Health (GmbH), Institute of Epidemiology, Neuherberg and ^bCentral Hospital of Augsburg, MONICA/KORA Myocardial Infarction Registry, Augsburg, Germany

Correspondence to Christa Meisinger, MD, MPH, Central Hospital of Augsburg, MONICA/KORA Myocardial Infarction Registry, Stenglinstr. 2, D-86156 Augsburg, Germany
Tel: +49 821 400 4373; fax: +2838;
e-mail: christa.meisinger@helmholtz-muenchen.de

Received 12 February 2008 Revised 22 April 2008
Accepted 7 May 2008

See editorial commentary on page 1740

Introduction

The prevalence of type 2 diabetes mellitus has increased dramatically in recent decades and it is expected that between 2000 and 2030, the worldwide prevalence of diabetes will increase by a further 37% [1]. Next to the aging of the population, diet and lifestyle factors are largely responsible for this epidemic [2]. Diabetes is associated with high rates of morbidity [3] and premature mortality [4]. It is well known that many patients with diabetes develop hypertension and that high blood pressure is a risk factor for cardiovascular and microvascular complications [5]. Hypertension is part of the metabolic syndrome, a cluster of numerous metabolic risk factors associated with the development of type 2 diabetes and cardiovascular disease [6]. However, recent evidence indicated that blood pressure *per se* is independently associated with the development of type 2 diabetes in adults [7]. In the Women's Health

Study [7], baseline blood pressure and blood pressure progression were significant predictors of incident type 2 diabetes after multivariable adjustment among women. So far data on this issue are scarce [7–9] and there are no studies on the association between different blood pressure categories and incident type 2 diabetes in men and women from the general population. As high blood pressure is one of the most prevalent cardiovascular risk factors worldwide and also in Germany [10,11], an association between hypertension and incident type 2 diabetes may have great public health implications.

In the present large prospective population-based cohort study, we, therefore, estimated the risk of type 2 diabetes in men and women with optimal blood pressure, high normal blood pressure, and established hypertension in comparison with persons with normal blood pressure

values. In particular, we investigated whether the associations were modified by BMI.

Methods

The presented data were derived from the population-based MONICA (Monitoring trends and determinants on cardiovascular diseases) Augsburg (Germany) studies carried out between 1984 and 1995 [12]. Three independent cross-sectional surveys covering the city area of Augsburg and two adjacent counties were conducted in 1984/85 (S1), 1989/90 (S2), and 1994/95 (S3). Altogether 13 427 persons aged 25–74 years participated in at least one of the three surveys. Within the framework of KORA (Cooperative Health Research in the Region of Augsburg), incident cases of type 2 diabetes were assessed using follow-up questionnaires in 1987/1988, 1997/1998, and 2002/2003 and were validated by hospital records or by contacting the participants' treating physician [12]. Persons with prevalent diabetes ($n = 597$), without information on diabetes status at follow-up (1449), with other types of diabetes than type 2 diabetes, and with incomplete data on all required factors ($n = 380$) were excluded from the cohort. The present analysis was based on 5556 men and 5445 women aged 25–74 years at baseline. Written informed consent was obtained from each study participant, and the study was approved by the local ethics committee.

Data collection

Baseline information on sociodemographic variables, smoking habits, physical activity level, medication use, and alcohol consumption were gathered by trained medical staff during a standardized interview. In addition, all participants underwent an extensive standardized medical examination including the collection of a blood sample. All measurement procedures have been described elsewhere in detail [12]. Dyslipidemia was defined as the ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol of at least 5.0. Participants were classified as active during leisure time if they regularly participated in sports in summer and winter and if they were active for at least 1 h per week in either season.

Clinical chemical measurements

A nonfasting venous blood sample was obtained from all study participants while sitting. Total serum cholesterol analyses were carried out using an enzymatic method (CHOD-PAP; Boehringer Mannheim, Mannheim, Germany). HDL cholesterol was also measured enzymatically after precipitation of the apoprotein B-containing lipoproteins with phosphotungstate/Mg²⁺ (Boehringer Mannheim, Germany).

Definition of hypertensive conditions

Systolic and diastolic blood pressure was measured by specially trained nurses on the right arm in a sitting

position using a random-zero sphygmomanometer after the participant had been at rest for approximately 30 min. The participants were explicitly asked not to cross their legs during measurement. Three measurements were taken with 3-min intervals between the measurements. For the present analysis, the results of the second and third measurements were averaged [11]. Men and women were classified into the following blood pressure categories: optimal blood pressure, below 120 mmHg for systolic and below 75 mmHg for diastolic blood pressure; normal blood pressure, 120–129 mmHg for systolic or 75–84 mmHg for diastolic blood pressure; high normal blood pressure, 130–139 mmHg for systolic or 85–89 mmHg for diastolic blood pressure. In case of established hypertension, participants were defined as being hypertensive if they had a systolic blood pressure of at least 140 mmHg and/or a mean diastolic blood pressure of at least 90 mmHg or if they were taking antihypertensive medication, given that the participants were aware of having hypertension.

Ascertainment of diabetes

In the follow-up questionnaires, we inquired about the diagnosis of diabetes. All incident cases of type 2 diabetes that had been diagnosed up to 31 December 2002 were included. Self-reported incident cases of diabetes mellitus and the date of diagnosis were validated by hospital records or by contacting the proband's treating physician. Furthermore, the hospital records of those deceased during the follow-up period without a diagnosis of type 2 diabetes mellitus at baseline were also examined and/or their last treating physicians were contacted. The records were searched for or the physicians were asked for a history of diabetes and if a person had suffered from diabetes, the type of diabetes and the date of diagnosis were ascertained. Thus, only clinically diagnosed type 2 diabetes cases were included in the analysis.

Statistical analysis

The duration of the follow-up was calculated as the interval between the baseline examination and the diagnosis of type 2 diabetes mellitus, death, or the date, when the follow-up questionnaire was completed. Follow-up times were censored for men and women at death, date when they filled out the follow-up questionnaire or at 31 December 2002. All analyses were performed separately for men and women. Means or proportions for baseline demographic and clinical characteristics were computed for categories of blood pressure. The χ^2 test was used to test the differences in prevalences. The general linear model was used to compare means (F -test). Different Cox proportional hazard models were computed to estimate the effect of blood pressure on the risk of an incident type 2 diabetes. We calculated hazard ratios and 95% confidence intervals (95% CI) with the blood pressure category '120–129/75–84 mmHg (normal blood pressure)' as the reference group. The first

model included blood pressure and in addition, age (continuous) and survey. The second model included all previous factors and dyslipidemia (yes/no), parental history of diabetes (yes/no, unknown), smoking status (regular smoking, that is, a participant who smoked at least one cigarette per day at baseline, yes/no), alcohol intake (men: 0, >0 and <40, or ≥ 40 g/day; women: 0, >0, and <20, or ≥ 20 g/day), BMI (continuous), physical activity (active/inactive), and education (<12 years, ≥ 12 years). To assess the contribution of waist circumference instead of BMI to the observed effects, analyses adjusting for waist circumference were also performed ($n = 3696$ men and $n = 3599$ women with complete data, because waist circumference was measured in S2 and S3 only).

In addition, it was assessed whether hypertension would increase the risk of an incident type 2 diabetes mellitus in persons with low and with high BMI, respectively. For this subgroup analyses, the cut-point BMI more than 26.7 kg/m^2 was used as defined by the Adult Treatment Panel III [13]. Interactions between categories of hypertension (coded as dummy variables) and BMI ($\leq / > 26.7 \text{ kg/m}^2$) were examined using likelihood ratio tests which compared the $-2 \log(\text{likelihood})$ between the model which contained only the main effects and the model which contained both the main effects and interaction terms. The assumption of proportionality of hazards was assessed by fitting models stratified by

risk factor categories, and then plotting the log ($-\log(\text{survival})$) curves to check parallelism. No severe deviations from parallelism were evident. Significance tests were two-tailed and P values less than 0.05 are stated as statistically significant. All analyses were performed using the Statistical Analysis System (Version 9.1; SAS Institute Inc., Cary, North Carolina, USA).

Results

In total, 410 incident cases of type 2 diabetes among men and 263 among women were registered in the 25–74-year-old study population between 1984 and 2002. The median follow-up period was 12.5 (interquartile range 7.7–13.2) years.

Table 1 describes the baseline characteristics by blood pressure categories. Compared with men and women with optimal blood pressure values, persons in the higher blood pressure categories were older, were more likely to have dyslipidemia, and less likely to be regular smokers; they were more likely to have a higher mean BMI, to drink alcohol (men only), and to have an education of less than 12 years.

Table 2 describes the observed crude incidence rates of type 2 diabetes by blood pressure categories. In all blood pressure categories, diabetes incidence was higher in men than in women and in both sexes type 2 diabetes incidence increased with increasing blood pressure level.

Table 1 Means (\pm SD) and prevalences (%) of baseline variables according to blood pressure category (men and women)

Variables	Blood pressure (<120/75 mmHg)	Blood pressure (120–129/75–84 mmHg)	Blood pressure (130–139/85–89 mmHg)	Hypertension ^a	P^b
Men ($n = 5556$)	$n = 554$	$n = 1379$	$n = 1235$	$n = 2388$	
Age (years)	44.3 (13.1)	42.9 (12.4)	45.3 (13.0)	52.4 (12.7)	<0.0001
Education (<12 years, %)	58.3	61.2	66.2	67.5	<0.0001
BMI (kg/m^2)	25.3 (3.2)	26.0 (3.2)	26.7 (3.4)	28.0 (3.6)	<0.0001
Systolic blood pressure (mmHg)	111.5 (5.6)	122.1 (5.0)	131.7 (5.0)	148.0 (15.6)	<0.0001
Diastolic blood pressure (mmHg)	67.8 (5.2)	76.5 (5.7)	81.5 (6.7)	89.7 (11.1)	<0.0001
Dyslipidemia (%)	35.9	39.2	40.6	49.7	<0.0001
Regular smoking (%)	32.0	33.0	29.0	26.0	<0.0001
Physically active (%)	47.8	49.8	48.1	39.6	<0.0001
Alcohol intake					
0 g/day (%)	20.9	15.4	15.2	15.5	<0.0001
0.1–39.9 g/day (%)	55.4	52.7	50.9	48.2	
≥ 40 g/day (%)	23.7	31.9	33.9	36.3	
Parental history of diabetes (%)	18.1	16.5	18.0	18.7	0.4018
Women ($n = 5445$)	$n = 1482$	$n = 1495$	$n = 840$	$n = 1628$	
Age (years)	39.3 (10.6)	43.8 (11.7)	48.7 (12.2)	55.9 (10.8)	<0.0001
Education (<12 years, %)	71.2	79.1	83.3	86.9	<0.0001
BMI (kg/m^2)	23.7 (3.5)	25.3 (4.1)	26.5 (4.5)	28.5 (5.2)	<0.0001
Systolic blood pressure (mmHg)	108.2 (6.7)	120.0 (6.1)	131.4 (5.5)	149.5 (16.9)	<0.0001
Diastolic blood pressure (mmHg)	66.7 (5.6)	76.9 (4.8)	81.5 (6.3)	88.0 (10.9)	<0.0001
Dyslipidemia (%)	8.4	12.4	15.1	27.6	<0.0001
Regular smoking (%)	23.6	20.1	17.3	12.7	<0.0001
Physically active (%)	47.0	44.0	37.5	29.4	<0.0001
Alcohol intake					
0 g/day (%)	39.9	37.9	41.9	45.3	0.0009
0.1–19.9 g/day (%)	39.4	41.9	39.6	35.2	
≥ 20 g/day (%)	20.7	20.2	18.5	19.5	
Parental history of diabetes (%)	17.9	20.2	21.8	21.6	0.0406

^a Participants with a systolic blood pressure of at least 140 mmHg and/or a mean diastolic blood pressure of at least 90 mmHg or taking antihypertensive medication, given that the participants were aware of having hypertension. ^b χ^2 test for categorical variables and F -test for continuous variables.

Table 2 Relative risk of incident type 2 diabetes according to blood pressure category among men and women

	Blood pressure (<120/75 mmHg)	Blood pressure (120–129/75–84 mmHg)	Blood pressure (130–139/85–89 mmHg)	Hypertension ^c
Men (n = 5556)	n = 554	n = 1379	n = 1235	n = 2388
No. of incident cases	12	48	89	261
Person years	6341	16 082	13 806	23 952
Crude incidence per 10 000 person years	18.9	29.8	64.5	109.0
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1 ^a	0.61 (0.32–1.14)	1.0	2.00 (1.41–2.84)	2.55 (1.86–3.50)
Model 2 ^b	0.67 (0.36–1.27)	1.0	1.76 (1.24–2.51)	1.93 (1.41–2.65)
Women (n = 5445)	(n = 1482)	(n = 1495)	(n = 840)	(n = 1628)
No. of incident cases	17	37	32	177
Person years	17 916	17 787	9790	16 649
Crude incidence per 10 000 person years	9.5	20.8	32.7	106.3
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1 ^a	0.57 (0.32–1.01)	1.0	1.28 (0.80–2.07)	3.29 (2.27–4.78)
Model 2 ^b	0.74 (0.41–1.32)	1.0	1.07 (0.67–1.73)	2.05 (1.41–2.99)

CI, confidence interval; HR, hazard ratio. ^aModel 1: age-adjusted and survey-adjusted. ^bModel 2: adjusted for age, survey, regular smoking, alcohol intake, parental history of diabetes, dyslipidemia, physical activity, BMI, and education. ^cParticipants with a systolic blood pressure of at least 140 mmHg and/or a mean diastolic blood pressure of at least 90 mmHg or taking antihypertensive medication, given that the participants were aware of having hypertension.

In Cox proportional hazard models, blood pressure was significantly associated with incident type 2 diabetes in both sexes (Table 2). Compared with individuals with normal blood pressure, the age-adjusted and survey-adjusted hazard ratios (95% CI) of incident diabetes associated with an optimal blood pressure, high normal blood pressure, and hypertension were 0.61 (0.32–1.14), 2.00 (1.41–2.84), and 2.55 (1.86–3.50) for men, and 0.57 (0.32–1.01), 1.28 (0.80–2.07), and 3.29 (2.27–4.78) for women. After adjusting for age, survey, parental history of diabetes, regular smoking, alcohol intake, education, BMI, dyslipidemia, and physical activity, the hazard ratios were attenuated but did not markedly change the found associations in both sexes. In men with high normal blood pressure and hypertension, the hazard ratios remained significant (hazard ratios 1.76; 95% CI 1.24–2.51 and 1.93; 95% CI 1.41–2.65, respectively) and the hazard ratio remained significantly increased in hypertensive women (hazard ratio 2.05; 95% CI 1.41–2.99). Adjustment for waist circumference instead of BMI did not alter the found relationship, but even strengthened the associations in men and women (data not shown).

We repeated the analyses after exclusion of all participants with antihypertensive medication at baseline. Multivariable-adjusted hazard ratios estimated from these models were almost the same as the hazard ratios estimated in the whole study sample. For men with hypertension, the hazard ratio was then 1.90 (95% CI 1.35–2.69) and for women with blood pressure values at least 140/90 mmHg, the hazard ratio was 1.63 (95% CI 1.07–2.50) after multivariable adjustment (data not shown).

When systolic blood pressure was included as a continuous variable in the Cox proportional hazard models, an increment of 10 mmHg in systolic blood pressure was also associated with a significant increase in the risk of an incident type 2 diabetes in men and women in the

age-adjusted and survey-adjusted (men: hazard ratio 1.19; 95% CI 1.13–1.25, women: hazard ratio 1.23; 95% CI 1.16–1.30) as well as the multivariable-adjusted analysis (men: hazard ratio 1.10; 95% CI 1.04–1.16, women: hazard ratio 1.10; 95% CI 1.04–1.17) (data not shown).

Stratification by BMI showed generally similar results as the unstratified analyses (Table 3).

Furthermore, a formal test for interaction containing blood pressure levels and BMI ($\leq/\geq 26.7 \text{ kg/m}^2$) revealed no significant interaction.

Figure 1a and b present the Kaplan–Meier curves for incident type 2 diabetes by blood pressure categories in men and women. The survival analysis showed a greater probability of an incident type 2 diabetes in women with an established hypertension, but in men with high normal as well as established hypertension (log-rank test $P = <0.0001$ for both sexes).

Discussion

In this large cohort, drawn from the general population, high normal blood pressure as well as established hypertension was strongly and independently related to the development of an incident type 2 diabetes in men, even after controlling for a variety of potential confounders. However, in women only established hypertension significantly increased the risk of type 2 diabetes after multivariable adjustment. Furthermore, the present study suggested that blood pressure may contribute to the manifestation of type 2 diabetes independent of BMI in both sexes.

The association between blood pressure and incident diabetes has been examined only in a few studies so far [7–9,14]. Very recently, in the Women's Health Study [7], it was found that there was still a three-fold increased risk among women with hypertension compared with

Table 3 Relative risk of incident type 2 diabetes according to blood pressure category among obese and nonobese men and women

	Blood pressure (<120/75 mmHg)	Blood pressure (120–129/75–84 mmHg)	Blood pressure (130–139/85–89 mmHg)	Hypertension ^c
Men				
BMI ≤26.7 kg/m ²	n = 396	n = 853	n = 656	n = 907
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1 ^a	0.94 (0.36–2.47)	1.0	2.35 (1.19–4.64)	2.47 (1.32–4.62)
Model 2 ^b	0.88 (0.33–2.33)	1.0	2.51 (1.27–4.97)	2.41 (1.28–4.53)
BMI >26.7 kg/m ²	n = 158	n = 526	n = 579	n = 1481
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1 ^a	0.55 (0.23–1.31)	1.0	1.66 (1.10–2.50)	2.03 (1.41–2.92)
Model 2 ^b	0.56 (0.23–1.32)	1.0	1.58 (1.05–2.39)	1.92 (1.34–2.77)
Women				
BMI ≤26.7 kg/m ²	n = 1247	n = 1040	n = 487	n = 644
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1 ^a	0.63 (0.23–1.74)	1.0	0.90 (0.31–2.64)	3.24 (1.52–6.89)
Model 2 ^b	0.61 (0.22–1.70)	1.0	0.83 (0.28–2.44)	3.01 (1.41–6.44)
BMI >26.7 kg/m ²	n = 235	n = 455	n = 353	n = 984
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 1 ^a	0.85 (0.42–1.71)	1.0	1.16 (0.68–1.98)	2.44 (1.60–3.73)
Model 2 ^b	0.90 (0.45–1.83)	1.0	1.15 (0.67–1.97)	2.21 (1.45–3.38)

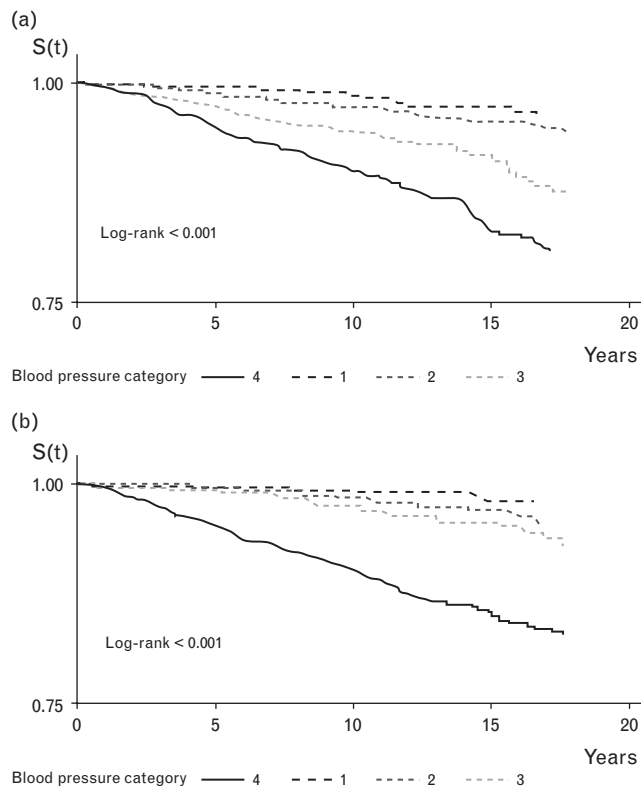
CI, confidence interval; HR, hazard ratio. ^aModel 1: age-adjusted and survey-adjusted. ^bModel 2: adjusted for age, survey, regular smoking, alcohol intake, parental history of diabetes, dyslipidemia, physical activity, and education. ^cParticipants with a systolic blood pressure of at least 140 mmHg and/or a mean diastolic blood pressure of at least 90 mmHg or taking antihypertensive medication, given that the participants were aware of having hypertension.

women with optimal blood pressure even after multi-variable adjustment. In line with the present study, in that study the associations persisted also after stratification by BMI. Contrary to our findings, in the Women’s

Health Study, women with high normal blood pressure had a significantly higher risk to develop type 2 diabetes than women with normal blood pressure, and women with optimal blood pressure had a significantly reduced risk. In the present study, men with high normal blood pressure had a significantly increased risk of type 2 diabetes compared with men with normal blood pressure values. Furthermore, in the present study, for optimal blood pressure values, a negative association with the incidence of type 2 diabetes was found in both sexes that did not reach statistical significance. Possibly, this could be due to the fact that the present study was smaller than the Women’s Health Study in which more than 38 000 women were included. Finally, the Atherosclerosis Risk in Communities Study [8] found that 45–64-year-old adults with hypertension had a more than two-fold increased risk to develop type 2 diabetes in comparison with persons without hypertension.

The pathophysiological mechanisms underlying the association between high blood pressure and incident type 2 diabetes have not been defined so far. A possible explanation could be that elevated blood pressure is associated with endothelial dysfunction, which is also related to insulin resistance and the development of type 2 diabetes [15]. On the contrary, elevated blood pressure could be a marker for underlying insulin resistance, which constitutes a common soil for diabetes, blood pressure, and cardiovascular disease [16]. Furthermore, research has demonstrated that high blood pressure levels are accompanied by an elevation of inflammatory markers [17], which could also enhance the development of type 2 diabetes [18,19]. Finally, recent studies have shown that pharmacological treatment of hypertension, in particular the use of thiazide diuretics and β-blockers, could lead to glucose intolerance and at least to the manifestation of type 2 diabetes [20]. Gress *et al.* [8] could show

Fig. 1



Kaplan–Meier curves for incident type 2 diabetes by blood pressure categories. (a) Association of blood pressure categories with incident type 2 diabetes mellitus in men. (b) Association of blood pressure categories with incident type 2 diabetes mellitus in women.

that antihypertensive treatment with thiazide diuretic, angiotensin-converting enzyme (ACE) inhibitor, or calcium-channel antagonist was not associated with the development of type 2 diabetes, whereas the use of β -blockers appeared to increase the risk of diabetes. However, in that study dose was not listed, a well known determinate of new onset diabetes. Recently, Almgren *et al.* [21] found that treated hypertensive patients are at an increased risk of type 2 diabetes and that this is associated with a high risk for cardiovascular complications and mortality. In the present study, exclusion of persons with antihypertensive medication did not alter the found associations and therefore it seems that hypertension *per se* is a risk factor for type 2 diabetes. Another explanation for the found association between hypertension in mid-life with later type 2 diabetes could be the influence of low birth weight and poor fetal growth, often in combination with a rapid catch-up growth pattern during the first months/years of postnatal life [22]. Because in the present study no data on birth weight was available, a possible relationship could not be investigated.

The MONICA/KORA Augsburg Study has several limitations that need to be considered. The follow-up was not complete for all participants of the original study who were still alive in 1987, 1998, and 2002, which might have introduced a selection bias. As patients with diabetes have an increased risk of dying of a cardiovascular disease, they could also be lost by selective mortality during follow-up. Furthermore, response bias cannot be excluded in the present study. Although we adjusted for a variety of confounders, residual confounding cannot be entirely excluded. In addition, blood pressure measured on only one occasion and only data on antihypertensive treatment at baseline was used in the prediction of diabetes incidence. It could be assumed that many individuals with a high normal blood pressure at baseline will develop established hypertension during follow-up and will therefore most likely be treated by antihypertensive drugs. However, in the present study, antihypertensive drug treatment profiles as well as blood pressure measurements at follow-up could not be taken into consideration. Because the study was limited to 25–74-year-old men and women of German nationality, caution should be taken in generalizing these results to other age groups and ethnicities. Finally, in the present study, only self-reported information on diabetes status of the individuals or use of antidiabetic medication was available. Although this information was validated with medical records, it is likely that the group of individuals without diabetes may include persons with undetected diabetes mellitus. Thus, the methodology used in the present study is second-best, because without an oral glucose tolerance test at baseline and follow-up, the true prevalence and incidence of type 2 diabetes cannot be evaluated. The strengths of the present study

are primarily its prospective design, the population representativeness of the cohort, and the availability of data on lifestyle and multiple cardiovascular risk factors.

In conclusion, the present study showed that established hypertension plays an important role in the development of type 2 diabetes in men and women from the general population, independent of other risk factors for diabetes, in particular independent of BMI. Although high normal blood pressure in comparison to normal blood pressure was also a strong predictor in men, this was not the case in women. Thus, the present findings suggested that blood pressure values in addition to other risk factors can modify the incidence of type 2 diabetes. In particular, men with high normal blood pressure values might benefit from regular blood glucose measurements. Furthermore, the present study provides an additional reason for aggressive blood pressure lowering.

Acknowledgements

The KORA research platform and the MONICA/KORA Augsburg studies are financed by the Helmholtz Zentrum München, German Research Center for Environmental Health (GmbH), which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria. Morbidity and Mortality follow-ups were in addition supported by grants from the Federal Ministry of Education, Science, Research and Technology (01 ER 9701/4) and the German Research Foundation (DFG) (TH 784/2-1). We thank all members of the Helmholtz Zentrum München, Institute of Epidemiology and the field staff in Augsburg who were involved in the conduct of the studies. There are no conflicts of interest.

References

- 1 Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27**:1047–1053.
- 2 Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001; **414**:782–787.
- 3 Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 1995; **18**:258–268.
- 4 Hu FB, Stampfer MJ, Solomon CG, Liu S, Willett WC, Speizer FE, *et al.* The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. *Arch Intern Med* 2001; **161**:1717–1723.
- 5 Mancia G. Optimal control of blood pressure in patients with diabetes reduces the incidence of macro- and microvascular events. *J Hypertens* 2007; **25** (Suppl 1):S7–S12.
- 6 Wilson PW, D'Agostino RB, Parise H, Sullivan L, Meigs JB. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* 2005; **112**:3066–3072.
- 7 Conen D, Ridker PM, Mora S, Buring JE, Glynn RJ. Blood pressure and risk of developing type 2 diabetes mellitus: the Women's Health Study. *Eur Heart J* 2007; **28**:2937–2943.
- 8 Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med* 2000; **342**:905–912.
- 9 Stolk RP, van Splunder IP, Schouten JS, Witteman JC, Hofman A, Grobbee DE. High blood pressure and the incidence of noninsulin dependent diabetes mellitus: findings in an 11.5 year follow-up study in The Netherlands. *Eur J Epidemiol* 1993; **9**:134–139.

- 10 Ezzati M, Lopez AD, Rodgers A, Van der Hoorn S, Murray CJ. Selected major risk factors and global and regional burden of disease. *Lancet* 2002; **360**:1347–1360.
- 11 Meisinger C, Heier M, Völzke H, Löwel H, Mitusch R, Hense HW, Luedemann J. Regional disparities of hypertension prevalence and management within Germany. *J Hypertens* 2006; **24**:293–299.
- 12 Meisinger C, Thorand B, Schneider A, Stieber J, Doering A, Löwel H. Sex differences in risk factors for incident type 2 diabetes mellitus. The MONICA Augsburg Cohort Study. *Arch Intern Med* 2002; **162**:82–89.
- 13 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP). (Adult Treatment Panel III). *JAMA* 2001; **285**:2486–2497.
- 14 Bengtsson C, Blohme C, Lapidus L, Lundgren H. Diabetes in hypertensive women: an effect of antihypertensive drugs or the hypertensive state per se? *Diabet Med* 1988; **5**:261–264.
- 15 Julius S, Gudbrandsson T, Jamerson K, Tariq SS, Andersson O. The hemodynamic link between insulin resistance and hypertension. *J Hypertens* 1991; **9**:983–986.
- 16 Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, *et al.* Insulin resistance in essential hypertension. *N Engl J Med* 1987; **317**:350–357.
- 17 Chae CU, Lee RT, Rifai N, Ridker PM. Blood pressure and inflammation in apparently healthy men. *Hypertension* 2001; **38**:399–403.
- 18 Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes* 2004; **53**:693–700.
- 19 Thorand B, Löwel H, Schneider A, Kolb H, Meisinger C, Fröhlich M, Koenig W. C-reactive protein as a predictor for incident diabetes among middle-aged men. Results from the MONICA Augsburg Cohort Study. *Arch Intern Med* 2003; **163**:93–99.
- 20 Taylor EN, Hu FB, Curhan GC. Antihypertensive medications and the risk of incident type 2 diabetes. *Diabetes Care* 2006; **29**:1065–1070.
- 21 Almgren T, Wilhelmsen L, Samuelsson O, Himmelmann A, Rosengren A, Andersson OK. Diabetes in treated hypertension is common and carries a high cardiovascular risk: results from a 28-year follow-up. *J Hypertens* 2007; **25**:1201–1204.
- 22 Osmond C, Barker DJP. Fetal, infant, and childhood growth are predictors of coronary heart disease, diabetes, and hypertension in adult men and women. *Environ Health Perspect* 2000; **108 (suppl 3)**:545–553.