Sex differences in risk factors for incident type 2 diabetes mellitus: the MONICA Augsburg cohort study

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Sex Differences in Risk Factors for Incident Type 2 Diabetes Mellitus

The MONICA Augsburg Cohort Study

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Objective: To examine sex-specific associations between cardiovascular risk factors, a parental history of diabetes, and type 2 diabetes mellitus (DM).

Methods: The study is based on 3052 men and 3114 women (aged 35 to 74 years) who participated in one of the 3 MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Augsburg surveys between 1984 and 1995, who were free of DM at baseline and returned a follow-up questionnaire in 1998. Sex-specific hazard ratios (HRs) were estimated from Cox proportional hazard models.

Results: A total of 128 cases of incident DM among men and 85 cases among women were registered during the follow-up period. The age-standardized incidence rate was 5.8 per 1000 person-years for men and 4.0 per 1000 person-years for women. In multivariable survival analyses, age, body mass index, and a positive parental history of diabetes were important independent risk factors

for DM in both sexes. High-density lipoprotein cholesterol level was inversely associated with DM in men and women. For other risk factors, sex-related differences were observed. Systolic blood pressure (HR per 10 mm Hg increase, 1.16), regular smoking (HR, 1.75), and high daily alcohol intake (HR, 1.95) predicted the development of DM in men only, whereas uric acid (HR per 1 mmol/L increase, 2.05) and physical inactivity during leisure time (HR, 1.80) were associated with diabetes development in women only.

Conclusions: In men and women, most variables predicting future diabetes in the present study are also known to be important risk factors for cardiovascular disease and arteriosclerosis. However, there are sex-related dissimilarities that seem to be involved in disease development.

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WORLDWIDE, there are at present approximately 110 million people with diabetes, the majority of them with type 2 diabetes, and it is estimated that this number will reach more than 220 million by 2010.[1] In Germany, at least 4 million people have diabetes mellitus.[2] In the German National Health Interview and Examination Survey 1998, the prevalence rate for diabetes was 4.7% for men and 5.6% for women in the 18- to 79-year-old population.[3] However, observations from other countries have shown that the real prevalence is probably even higher because of a high proportion of persons with undetected diabetes.[4,5]

Type 2 diabetes has a strong genetic component, which is much greater than in type 1 diabetes.[6] However, considerable evidence indicates that environmental and lifestyle factors, mainly obesity and physical

inactivity, are important in inducing type 2 diabetes mellitus in people with genetic susceptibility.[6] It is well established that even newly diagnosed diabetic subjects have an increased atherogenic cardiovascular risk profile.[7,8] Recent evidence suggests that type 2 diabetes and cardiovascular disease, rather than being related as underlying disease and complication, share common genetic and environmental antecedents.[9,10] Furthermore, cardiovascular complications are responsible for about 80% of premature deaths in diabetic subjects. Diabetic women have a 3- to 6-fold and diabetic men a 2- to 4-fold increased risk of myocardial infarction.[7,11,12]

Still, the environment-gene interactions as mechanisms for the development of type 2 diabetes are not fully clarified, justifying further studies on predictors of diabetes. Moreover, prevention programs depend on the identification of potentially modifiable risk factors. In this connection, it is of great interest whether

SUBJECTS AND METHODS

STUDY POPULATION

The data were derived from the population-based MONICA Augsburg (southern Germany) studies conducted between 1984 and 1995. The MONICA Augsburg project was part of the multinational World Health Organization MONICA Project, and the design of both projects has been described in detail elsewhere.[33,34] Three independent cross-sectional surveys were carried out in the city of Augsburg and the counties of Augsburg and Aichach-Friedberg in 1984 to 1985 (survey 1), 1989 to 1990 (survey 2), and 1994 to 1995 (survey 3) to estimate the prevalence and distribution of cardiovascular risk factors among men and women. Altogether, 13 428 persons (6725 men and 6703 women; response rate, 77%) aged 25 to 74 years participated in at least 1 of the 3 cross-sectional studies.

In 1998, vital status was assessed for all sampled persons of the 3 MONICA surveys through the population registries (Einwohnermeldeämter). In the meantime, 772 participants (531 men and 241 women) had died and vital status could not be assessed for 56 persons (31 men and 25 women) who had moved to a foreign country or to an unknown location. A questionnaire assessing the health status was mailed to the remaining 12 600 living persons (6163 men and 6437 women) with known addresses in 1998. A total of 8548 subjects (4210 men and 4338 women) returned the questionnaire (total response rate, 67.8%; for men, 68.3%; for women, 67.4%). The present analysis was restricted to nondiabetic persons aged 35 to 74 years at baseline examination (n = 6355; 3140 men and 3215 women). Participants who did not know whether they had diabetes at baseline examination were included in the group of nondiabetic persons. All men and women with missing data on any of the considered risk factors were excluded (n = 168). An additional 21 new cases of diabetes were excluded because these participants reported a manifestation of diabetes before the MONICA baseline study in the follow-up questionnaire. Finally, the prospective analyses comprised 6166 nondiabetic MONICA participants (3052 men and 3114 women) aged 35 to 74 years.

DATA COLLECTION AND LABORATORY METHODS AT THE BASELINE EXAMINATION

Baseline information on sociodemographic variables, smoking habits, physical activity level, medication use, parental history of disease, menopause, and alcohol consumption were gathered by trained medical staff (mainly nurses) during a standardized face-to-face interview. In addition, all participants underwent an extensive standardized medical examination including collection of a nonfasting blood sample. Anthropometric measurements were performed with the subjects in light clothing and without shoes, according to the World Health Organization MONICA protocol.[35]

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Systolic and diastolic blood pressure was measured on the right arm in a sitting position by means of a random-zero sphygmomanometer (Hawksley & Sons Ltd, Lancing, England),[36] adhering to the World Health Organization MONICA protocol[37] and the recommendations of the American Heart Association.[38] After the subject had been at rest for approximately 30 minutes, 3 measurements were taken with 3-minute intervals between the measurements. For the present analysis, the results of the second and third measurements were averaged. Persons who were aware of having hypertension, who were taking antihypertensive medication, and/or who had blood pressure of 160/95 mm Hg or higher at baseline were defined as having actual hypertension.[39]

Education level was categorized as low (<12 years of schooling) and high (≥12 years of schooling). Angina pectoris was defined as pain after exercise retrosternally, in the left arm, and in the left side of the chest and was categorized according to Rose et al.[40]

Subjects were assigned to the positive parental history category if at least 1 parent had diabetes. If neither parent had diabetes, subjects were assigned to the negative parental history category. Subjects who answered "I don't know" for both parents or those who answered "I don't know" for one parent and "no" for the other parent were assigned to the unknown parental history category.

A regular smoker was defined as a subject who currently smoked at least 1 cigarette per day. Each subject was

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cardiovascular risk factors are predictors of type 2 diabetes and whether these risk factors are similar in men and women. As shown in **Table 1**, few studies have provided data on various cardiovascular risk factors and subsequent diabetes in both sexes within the same study population.[20,25]

To our knowledge, the MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study is the first prospective population-based study that assessed the sex-specific incidence of type 2 diabetes mellitus in a middle European population that is characterized by a relatively low risk of cardiovascular morbidity and mortality.[32] Therefore, the aim of this study was to analyze the importance of cardiovascular risk factors and a parental history of diabetes at baseline as predictors of the conversion to type 2 diabetes. To answer the question of whether the risk factors for type 2 diabetes mellitus are similar in both sexes, all analyses were performed separately for men and women.

RESULTS

In total, 128 incident cases of diabetes among men and 85 cases among women were registered in the 35- to 74-year-old study population between 1984 and 1998; 2924 men and 3029 women remained nondiabetic. The diabetic persons were treated as follows: 12 persons received insulin only; 118 received tablets only; 16 received insulin and tablets; and 62 were only following a specific diet. Two diabetic persons declared that they received no antidiabetic treatment, and an additional 3 had missing values for antidiabetic treatment. There was a male predominance in the incidence of diabetes; the

asked how much beer, wine, and spirits he or she had drunk on the previous workday and during the previous weekend. This information was used to calculate the alcohol consumption in grams per day. Alcohol intake in men came mainly from beer, whereas wine was the main contributor of alcohol intake in women; intake of distilled spirits was very low in both sexes. The detailed method has been described elsewhere.[41,42] Alcohol intake was classified into 3 categories: 0, 0.1 to 19.9, and 20.0 or more g/d for women; and 0, 0.1 to 39.9, and 40 or more g/d for men.

The physical activity level was estimated by means of 2 separate 4-category interview questions asking about the time per week spent on sports activities during leisure time in summer and winter. The winter and summer responses were combined to define one sport variable, whereby a participant was considered active if he or she participated in sports in summer and in winter and for more than 1 hour per week in at least 1 season. A participant was classified as inactive if he or she was less active during leisure time.

Total cholesterol and high-density lipoprotein (HDL) cholesterol analyses were carried out with an autoanalyzer using an enzymatic method (CHOD-PAP; Boehringer Mannheim, Mannheim, Germany). The HDL cholesterol was precipitated with phosphotungstic acid and magnesium ions. Regular internal and external quality control measures for serum total cholesterol and HDL cholesterol measurements were performed before and during the data-gathering phase of the survey. The external quality control was performed by the World Health Organization MONICA Quality Control Centre for Lipids in Prague, Czechoslovakia.[43]

Serum uric acid was measured by the uricase method in surveys 1 and 2. In survey 3, serum uric acid was determined with an enzymatic colorimetric reaction (Uric Acid PAP; Boehringer Mannheim).

FOLLOW-UP AND END POINT

The main outcome was the development of type 2 diabetes mellitus during the follow-up period. Subjects were classified as diabetic if they reported a diagnosis of diabetes or if they were taking antidiabetic medication. The same definition was used to exclude subjects with preexisting diabetes from enrollment. A total of 210 persons (127 men and 83 women) reported the development of diabetes during the follow-up period. Another 3 persons (1 man and 2 women) reported having no diabetes although they took antidiabetic drugs; these subjects were classified as diabetic for the analyses presented in this article.

Although type 1 diabetes can occur at any age, it is rare beyond 35 years of age. In this study, all participants were 35 years old or older at study entry, and only 12 diabetic persons were treated with insulin only; therefore, it can be assumed that most of the newly diagnosed diabetes in this study population was type 2 diabetes. Thus, the term *type 2 diabetes* is used throughout this article.

The mean follow-up period was 7.6 years, with a minimum of 46 days and a maximum of 13.8 years.

STATISTICAL ANALYSIS

All analyses were performed separately for men and women. Incidence rates were based on person-years from the date of baseline examination until the diagnosis of diabetes or the date when the questionnaire was filled in as the censoring date. They were calculated by dividing the number of incident cases by person-years in each age group. Age-standardized incidence was calculated by direct standardization with the use of the population of the Federal Republic of Germany in 1989 as the standard population (weights: 35-44 years, 0.2791; 45-54 years, 0.3125; 55-64 years, 0.2397; 65-74 years, 0.1687). General linear models were used for comparison of diabetic and nondiabetic subjects (means and prevalences were adjusted for age and survey). Cox proportional hazards analysis was used[44] to determine the age-, survey- and BMI-adjusted as well as the multivariable adjusted relative risk of type 2 diabetes mellitus. As a potential confounder, the variable *survey* was forced into the multivariable models. Variables were analyzed by means of a backward stepwise procedure (P value for inclusion of variables <.20). We plotted the log [−log (survival)] curves for each risk factor to assess the proportional hazard assumptions. This assumption was met for all variables. Results are presented as hazard ratios (HRs) and 95% confidence intervals. Significance tests were 2-tailed, and P values less than .05 are stated as statistically significant. All analyses were performed with SAS software (version 6.12; SAS Institute Inc, Cary, NC).

age-standardized incidence rate of diabetes was 5.8 per 1000 person-years in men aged 35 to 74 years and 4.0 per 1000 person-years in women of the same age range (**Table 2**).

Table 3 describes the age- and survey-adjusted baseline characteristics of subjects by conversion status to type 2 diabetes mellitus at follow-up separately in men and women. In both sexes, subjects who converted to type 2 diabetes were significantly older and had higher BMI, systolic and diastolic blood pressure, and uric acid values than subjects who remained nondiabetic. In addition, future diabetic subjects had lower HDL cholesterol levels. Significantly more prediabetic subjects were actual hypertensive, and significantly more reported angina pectoris and a positive parental history of diabetes. Prediabetic men had significantly higher total cholesterol values and were more often regular smokers, and the percent-

age with a high daily alcohol intake was also increased compared with nondiabetic men. Significantly more prediabetic women drank no alcohol and were physically inactive during leisure time in comparison with nondiabetic women.

Since age and BMI are important predictors of diabetes and were strongly correlated with most other potential risk factors, age and BMI- and survey-adjusted HRs were calculated to assess the effect of the remaining risk factors that was independent of age and BMI (**Table 4**). A positive parental history of diabetes showed a strong positive association with diabetes in both sexes. Actual hypertension was also associated with diabetes in both sexes but the effect was stronger in women. The HDL cholesterol level was inversely associated with diabetes in men and women. Systolic as well as diastolic blood pressure was related to diabetes

Table 1. Selected Prospective Cohort Studies of Risk Factors and Type 2 Diabetes*

Study	Baseline Study, y	Study Region	Study Population	Follow-up, y	Outcome Diabetes
Zutphen Study[13]	1960	Zutphen, the Netherlands	878 Men Age, 40-59 y	25	Type 2
Pennsylvania Alumni Health Study[14]	1962	Pennsylvania	5990 Men Age, 39-68 y	14	Type 2
Israel Ischemic Heart Disease Study[15]	1963	Israel	10 059 Men Age, ≥40 y	5	Type 2
The Honolulu Heart Program[16]	1965	Oahu, Hawaii	8006 Men Age, 45-68 y	25	Type 2, HIA
Göteborg Study[17,18]	1967	Göteborg, Sweden	792 Men Age, 54 y	13.5	Type 2, IGT
Prospective study in Dallas[19]	1970	Dallas, Tex	8633 Men Age, 30-79 y	6	Type 2
Framingham Study[20]	1971-1974	Framingham, Mass	906 Men and 1282 women Age, ≥50 y	8	Type 2
Rancho Bernardo Cohort[21]	1972-1974	Rancho Bernardo, Calif	6155 Men and women Age, 30-79 y	14	Type 2
Nurses' Health Study[22-24]	1976	11 US states	121 700 Women Age, 30-55 y	8	Type 2
Finnmark Study[25]	1977-1978	Finnmark, Norway	6098 Men and 5556 women Age, 35-52 y	12	Type 2
British Regional Heart Study[26]	1978-1980	Great Britain	7735 Men Age, 40-59 y	12.8	Type 2
Physicians' Health Study[27,28]	1982	United States	22 071 Men Age, 40-84 y	5	Type 2
Health Professionals' Follow-up Study[29]	1986	Across United States	51 529 Men Age, 40-75 y	6	Type 2
Iowa Study[30]	1986	Iowa	41 836 Women Age, 55-69 y	12	Type 2
Pitt County Study[31]	1988	Pitt County, NC	1784 Men and women Age, 25-50 y	5	Type 2
MONICA Augsburg Cohort Study	1984-1985 1989-1990 1994-1995	Augsburg, Southern Germany	3052 Men and 3114 women Age, 35-74 y	7.6	Type 2

*MONICA indicates Monitoring of Trends and Determinants in Cardiovascular Disease; HIA, hyperinsulinemia; and IGT, impaired glucose tolerance.

in men only. Total cholesterol level, an unknown parental history of diabetes, smoking, and a high daily alcohol intake were also associated with a higher risk of diabetes in men only. In contrast, uric acid level and physical inactivity during leisure time were related to diabetes in women only (Table 4).

To investigate which of the baseline characteristics identified as risk factors in the previous analysis were also independent predictors of diabetes, a backward stepwise multiple logistic regression analysis was performed. **Table 5** shows the results from the fully adjusted models for men and women. Diastolic blood pressure was not included in the multivariable model because of a high correlation with systolic blood pressure (Pearson $r=0.68$) and a weaker association with diabetes in the age-, BMI-, and survey-adjusted analysis in comparison with systolic blood pressure. Furthermore, the variable *actual hypertension* was also omitted in the multivariable model. Age (men and women: HR per 1 year increase, 1.04) and BMI (men: HR per 4 kg/m² increase, 1.98; women: HR, 1.49) were independently related to the risk of diabetes in men and women. A positive parental history of diabetes was also a strong predictor for the development of type 2 diabetes in both sexes (men: HR, 2.06; women: HR, 2.37). In men, the association with an unknown parental history of diabetes was no longer

significant in the multivariable model. The HDL cholesterol level showed an inverse association with disease development in men (HR per 15-mg/dL [0.4-mmol/L] increase, 0.72) and women (HR, 0.60). Systolic blood pressure was independently associated with diabetes in men only (HR per 10–mm Hg increase, 1.16). Furthermore, regular smoking (HR, 1.75) as well as a daily alcohol intake of 40 g or more compared with occasional drinkers (HR, 1.95) were also independently related to diabetes in men only. On the contrary, uric acid level (HRE [1 mmol/L] per 17 mg/dL increase, 2.05) and physical inactivity during leisure time (HR, 1.80) were independent predictors in women only.

These findings were unchanged if the factors shown to be independently associated with diabetes were examined in a separate analysis in which 77 men and 61 women with preexisting coronary heart disease, ie, persons with a diagnosis of either myocardial infarction or angina pectoris at baseline examination, were excluded (data not shown).

COMMENT

To our knowledge, the MONICA Augsburg Cohort Study is the first prospective population-based study to assess the sex-specific incidence of type 2 diabetes mellitus in

Table 2. Diabetes Incidence per 1000 Person-Years by Age and Sex: MONICA Augsburg Cohort Study*

Age, y	No. of Subjects	Person-Years of Follow-up	Incident Diabetes Cases	Incidence Rate per 1000 Person-Years
Women				
35-44	981	8051	9	1.1
45-54	962	7771	27	3.5
55-64	769	5764	35	6.1
65-74	402	2123	14	6.6
Total	**3114**	**23 709**	**85**	**4.0†**
Men				
35-44	874	7175	21	2.9
45-54	930	7519	41	5.5
55-64	794	5807	48	8.3
65-74	454	2402	18	7.5
Total	**3052**	**22 903**	**128**	**5.8†**

*MONICA indicates Monitoring of Trends and Determinants in Cardiovascular Disease.
†Age-standardized incidence rate based on the German population on December 31, 1989.

Table 3. Sex-Specific Mean Levels (SE) and Prevalence of Baseline Characteristics (Age- and Survey-Adjusted) by Diabetic Status at Follow-up: MONICA Augsburg Cohort Study*

Baseline Characteristics	Women Nondiabetic Subjects (n = 3029)	Women Diabetic Subjects (n = 85)	P Value	Men Nondiabetic Subjects (n = 2924)	Men Diabetic Subjects (n = 128)	P Value
Age, y†	50.8 (0.2)	56.4 (1.1)	<.001	51.6 (0.2)	54.8 (0.9)	<.001
Education <12 y, %	82.3	84.8	.56	62.7	65.2	.56
BMI, kg/m²	26.3 (0.1)	30.7 (0.5)	<.001	27.2 (0.1)	30.0 (0.3)	<.001
Systolic blood pressure, mm Hg	129.4 (0.3)	136.3 (1.9)	<.001	135.1 (0.3)	143.1 (1.5)	<.001
Diastolic blood pressure, mm Hg	79.4 (0.2)	82.2 (1.1)	.02	83.5 (0.2)	87.9 (1.0)	<.001
Actual hypertension, %	19.5	45.0	<.001	25.0	43.3	<.001
Total cholesterol, mg/dL	236 (0.7)	230 (4.5)	.21	240 (0.8)	249 (3.9)	.02
HDL cholesterol, mg/dL	64 (0.3)	53 (1.8)	<.001	51 (0.3)	45 (1.3)	<.001
Uric acid, mg/dL	4.0 (0.02)	4.8 (0.10)	<.001	5.7 (0.02)	6.0 (0.11)	<.001
Angina pectoris, %	3.5	7.8	<.05	3.3	6.8	<.05
Regular smoker, %	13.7	11.7	.61	22.3	32.8	<.01
No alcohol consumption, %	40.0	55.9	<.01	15.0	18.0	.36
Alcohol intake ≥20 (40‡) g/d, %	20.4	13.7	.13	33.1	45.7	<.01
Inactive during leisure time, %	60.0	75.6	<.01	55.1	62.6	.09
Positive parental history of DM, %	22.1	41.9	<.001	19.3	32.0	<.001
Unknown parental history of DM, %	17.4	13.5	.34	21.2	25.7	.23

*MONICA indicates Monitoring of Trends and Determinants in Cardiovascular Disease; BMI, body mass index; HDL, high-density lipoprotein; and DM, diabetes mellitus. To convert cholesterol levels to millimoles per liter, multiply by 0.02586. To convert uric acid levels to millimoles per liter, multiply by 0.0595.
†Only adjusted for survey.
‡Limiting value for men.

a middle European population characterized by a relatively low risk of cardiovascular morbidity and mortality.[32] The Augsburg study identified age, BMI, a parental history of diabetes, and low HDL cholesterol values as independent determinants of type 2 diabetes mellitus in both sexes. High systolic blood pressure, regular cigarette smoking, and high daily alcohol intake predicted diabetes in men only, whereas high uric acid values and physical inactivity during leisure time were associated with a higher risk of diabetes in women only.

The MONICA Augsburg Cohort Study is one of the few studies that examined the association between a variety of cardiovascular risk factors and the incidence of diabetes in both sexes in the same study population. This facilitates the comparison between men and women, since one can be sure that the same methods have been used

to determine risk factors in both sexes. While both men and women have been examined in some other studies,[20,25,21,31] the Framingham Study[20] and the Finnmark Study[25] were the only ones that assessed the impact of several risk factors on the incidence of diabetes. Thus, for most risk factors, one has to rely on results from different studies to compare the effects in men and women, which makes comparisons more difficult.

Like the MONICA Augsburg Cohort Study, the Framingham Study[20] and the Finnmark Study[25] demonstrated a strong positive association between BMI and diabetes in both sexes. However, in the Finnmark Study,[25] the effect of a high BMI was much stronger in men. Concerning the predictive importance of low HDL cholesterol levels, contradictory results were reported from the Framingham Study,[20] which showed significant effects

Table 4. Age-, Survey-, and BMI-Adjusted Hazard Ratios for the Risk of Incident Diabetes by Sex: MONICA Augsburg Cohort Study*	HR (95% CI)	
Variable	**Women**	**Men**
Age (y)†	1.06 (1.04-1.08)	1.03 (1.01-1.05)
BMI (4 kg/m²)‡	1.87 (1.65-2.12)	2.22 (1.89-2.61)
Systolic blood pressure (10 mm Hg)	1.10 (0.98-1.22)	1.18 (1.08-1.30)
Diastolic blood pressure (5 mm Hg)	1.03 (0.93-1.14)	1.11 (1.03-1.19)
Actual hypertension (yes/no)	2.29 (1.42-3.70)	1.68 (1.16-2.43)
Total cholesterol (39 mg/dL [1 mmol/L])	0.89 (0.73-1.09)	1.19 (1.03-1.37)
HDL cholesterol (15 mg/dL [0.4 mmol/L])	0.55 (0.42-0.71)	0.77 (0.62-0.95)
Uric acid (17 mg/dL [1 mmol/L])	2.20 (1.63-2.98)	1.07 (0.85-1.36)
Regular smoker (yes/no)	1.05 (0.48-2.33)	1.88 (1.28-2.77)
Alcohol intake		
0 g/d vs 0.1-19.9 (39.9§) g/d	1.51 (0.92-2.47)	1.59 (0.96-2.63)
≥20 (40§) g/d vs 0.1-19.9 (39.9§) g/d	0.94 (0.46-1.91)	2.06 (1.39-3.04)
Inactive during leisure time (yes/no)	1.81 (1.04-3.16)	1.20 (0.83-1.74)
Parental history of diabetes mellitus		
Positive vs negative	2.54 (1.57-4.11)	2.29 (1.50-3.48)
Unknown vs negative	1.21 (0.65-2.25)	1.59 (1.03-2.44)

*BMI indicates body mass index; MONICA, Monitoring of Trends and Determinants in Cardiovascular Disease; HR, hazard ratio; CI, confidence interval; and HDL, high-density lipoprotein.
†Only adjusted for survey.
‡Only adjusted for age and survey.
§Limiting value for men.

Table 5. Predictors of Type 2 Diabetes Mellitus in Multivariable Analysis by Sex*	HR (95% CI)	
Variable	**Women**	**Men**
Age (y)	1.04 (1.01-1.06)	1.04 (1.02-1.06)
BMI (4 kg/m²)	1.49 (1.29-1.73)	1.98 (1.66-2.35)
Systolic blood pressure (10 mm Hg)	...	1.16 (1.06-1.27)
HDL cholesterol (15 mg/dL [0.4 mmol/L])	0.60 (0.46-0.78)	0.72 (0.57-0.90)
Uric acid (17 mg/dL [1 mmol/L])	2.05 (1.49-2.81)	...
Regular smoker (yes/no)	...	1.75 (1.18-2.58)
Alcohol intake		
0 g/d vs 0.1-19.9 (39.9†) g/d	...	1.31 (0.78-2.19)
≥20 (40†) g/d vs 0.1-19.9 (39.9†) g/d	...	1.95 (1.30-2.91)
Inactive during leisure time (yes/no)	1.80 (1.04-3.14)	...
Parental history of diabetes mellitus		
Positive vs negative	2.37 (1.47-3.84)	2.06 (1.35-3.16)
Unknown vs negative	1.03 (0.55-1.92)	1.53 (0.99-2.35)
Survey		
Survey 1 vs survey 3	0.63 (0.26-1.53)	0.68 (0.34-1.37)
Survey 2 vs survey 3	0.87 (0.41-1.86)	0.83 (0.44-1.56)

*HR indicates hazard ratio; CI, confidence interval; BMI, body mass index; HDL, high-density lipoprotein; and ellipses, that the variable is not a predictor of type 2 diabetes mellitus in men and women in the multivariable model.
†Limiting value for men.

in men only, and from the Finnmark Study,[25] which demonstrated a significant predictive relevance in women only.

In the MONICA Augsburg Cohort Study, systolic blood pressure was positively associated with diabetes in men, but not in women. Similar results have been observed in 3 other prospective cohort studies in men.[13,17,26] In the Framingham Study,[20] systolic blood pressure was associated with the incidence of diabetes in the univariate analysis, but this effect lost significance after multiple adjustment in both sexes. In contrast to systolic blood pressure, in the present study, actual hypertension was strongly associated with diabetes in men and women. Thus, the low impact of systolic blood pressure in women might be attributed to the fact that more women with actual hypertension had controlled blood pressure values in comparison with men.[45]

In accordance with the present study, several prospective studies conducted in men—the Honolulu Heart Program,[16] the Pennsylvania Alumni Health Study,[14] and a study from Dallas, Tex[19]—also observed a high impact of parental history on diabetes incidence. No prospective studies investigating the association between a parental history of diabetes and the incidence in their female offspring were found in the literature; thus, the Augsburg results of an approximately 2.5 times higher risk of incident diabetes in women with a positive parental history of diabetes compared with women with-

out such parental history have to be confirmed by further studies.

The positive association between cigarette smoking and incident diabetes in men shown in the present analysis confirmed the results of the Zutphen Study[13] and the Health Professionals' Follow-up Study.[29] The nonsignificant impact of smoking in women is in contrast to the results of the large American Nurses' Health Study,[22] which showed a significant dose-response trend between the number of cigarettes smoked and the incidence of diabetes for 30- to 55-year-old nurses. However, it is possible that the smoking behavior of nurses does not represent the smoking behavior of the "normal" female population, since the high stress level typical of nurses may have an impact on their smoking behavior. In the present analysis, the number of cigarettes smoked was not taken into account; however, it is known that the number of cigarettes smoked is higher among men than among women in the Augsburg population.[46] Furthermore, the prevalence of regular cigarette smoking among men was considerably greater than among women. Because of this sex difference in smoking behavior, it is possible that smoking as a risk factor had an effect in men but not in women. The Framingham Study[20] and the Finnmark Study[25] observed that cigarette smoking was not a risk factor among men or women.

In accordance with the Rancho Bernardo Cohort,[21] a significant association between heavy alcohol intake and incident diabetes in men was observed in the Augsburg study. Other prospective studies suggested an inverse as-

sociation between alcohol consumption and risk of type 2 diabetes mellitus in men[26,27,29] and women[23] or reported no significant impact on disease development in men[17] and women.[21] The apparent lack of association between alcohol intake and type 2 diabetes in women may be due to the fact that there were too few heavy drinkers among women or the fact that women consumed wine more often than men did in the present study.

In the MONICA Augsburg Cohort Study, physical inactivity during leisure time was associated with an 80% increased risk of type 2 diabetes only in women. In general, a positive association between physical inactivity and type 2 diabetes independent of obesity has been noted in many prospective studies in men[14,28,31] and women.[24,30,31] In the Nurses' Health Study, women who engaged in vigorous exercise at least once per week had a relative risk of type 2 diabetes mellitus of 0.8 ($P=.005$) compared with women who did not exercise weekly.[24] In contrast to the Augsburg study, the Physicians' Health Study documented that male physicians who exercised at least once per week had a relative risk of type 2 diabetes of 0.71 ($P=.006$) compared with those who exercised less frequently; the relative risk of diabetes decreased with increasing frequency of exercise.[28] The physical activity measure used in the present study categorized individuals on the basis of their regular participation in leisure time activity. In general, men from a population-based study engage in more strenuous physical activity at work in comparison with women; thus, men are altogether more physically active, if both occupational and leisure time physical activity is taken into consideration. Therefore, the sex-related dissimilarities between physical activity and type 2 diabetes in the Augsburg study could be due to the fact that men who are classified as inactive are in fact quite active at work.

Uric acid was a strong independent risk factor of diabetes in women in the present study. As far as we know, no prospective analysis of uric acid and incident type 2 diabetes has been published for women, but significant associations between uric acid values and risk of diabetes in men were established by British,[26] Swedish,[18] and Israeli studies.[15] Whether the observed sex-related differences in the present study are due to genetically determined sex-specific metabolic processes or to other factors, such as different dietary patterns in men and women, for example, warrant further investigations.

The MONICA Augsburg Cohort Study has a number of strengths. The study is characterized by its large number of subjects drawn from the general population, the availability of data on multiple cardiovascular risk factors, and the ability to examine risk factors measured an average of 7.6 years earlier as potential predictors of subsequent type 2 diabetes. Furthermore, in comparison with most other prospective cohort studies, a larger number of relevant variables could be examined simultaneously in men and women. However, several limitations of this study also need to be considered. First, in the present study only self-reported information on diabetes status of the subjects was available; however, validation studies have shown that self-reported diabetes reflects the true situation reasonably well.[47,48,49] Nevertheless, it is likely that the group of nondiabetic persons may include subjects with undetected diabetes mellitus. This implies that the observed hazard ratios in the present study may underestimate the effect of risk factors on total diabetes incidence. Second, we were unable to differentiate between persons with normal glucose metabolism and those with borderline hyperglycemia at baseline examination and at follow-up. Moreover, it was impossible to investigate the influence of fasting plasma glucose on the development of diabetes because baseline examination included collection of a nonfasting blood sample. Third, in the present study only risk factors that were collected in all of the 3 cross-sectional studies could be taken into consideration. Therefore, important risk factors, such as low-density lipoprotein cholesterol level, triglyceride level, and waist-to-hip ratio, could not be included in this analysis. Fourth, incomplete follow-up could also bias the study results. One can suppose that persons who have diabetes are under regular physician care and might therefore be less interested in participating in studies like the Augsburg study. Since diabetic patients have an increased risk of dying of cardiovascular disease,[7,11,12] they could also be lost by selective mortality during follow-up. Thus, the incidence rates for men and women in the Augsburg study are most likely underestimated. Moreover, the follow-up rate of our study was 68%; both male and female nonrespondents had a slightly higher risk factor profile at baseline in comparison with the respondents.[50] Thus, response bias cannot be excluded in the present study. However, it seems unlikely that the low response rate would be responsible for the fact that several risk factors work in one sex but not the other, since very similar response rates were observed for both sexes and similar differences in risk factors between participants and nonparticipants were observed among men and women.

In conclusion, most variables predicting future diabetes in men and women in the present study are also known to be important risk factors for cardiovascular disease and arteriosclerosis. Thus, early diagnosis of persons who are at high risk will be of greatest importance for the prevention of type 2 diabetes mellitus as well as atherosclerotic vascular disease. However, further studies are needed to explore the sex-related dissimilarities that seem to be involved in disease development.

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