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Sex Differences in Risk Factors for Clinical Diabetes Mellitus in a General Population: A 12-Year Follow-up of the Finnmark Study

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The associations among obesity, height, cardiovascular risk factors, and the incidence of clinical diabetes mellitus were investigated in the Norwegian population-based Finnmark Study of 11,654 men and women aged 35–52 years at baseline in 1977–1978. A total of 87 cases of diabetes among men and 75 cases among women were registered during 12 years of follow-up. The incidence of diabetes was 1.1 per 1,000 person-years in women and 1.2 per 1,000 person-years in men, but sex-related differences in risk factors were noted. Body mass index was the dominant risk factor in men and predicted diabetes in a dose-response relation in both sexes. However, in women, the association between body mass index and diabetes was greatly attenuated after multivariable adjustment. Serum lipid concentrations were similar in prediabetic men and women; thus, prediabetic women had a relatively more adverse metabolic risk profile as compared with nondiabetics of the same sex. In multivariable analysis, high density lipoprotein cholesterol was inversely related to diabetes in women (relative risk per 0.3 mmol/liter, 0.53; 95% confidence interval 0.41–0.70) but not in men (relative risk, 0.97; 95% confidence interval 0.78–1.19). Serum glucose was a highly significant predictor in both sexes, while height was inversely related to diabetes only in women (relative risk per 5 cm, 0.71; 95% confidence interval 0.58–0.87). *Am J Epidemiol* 1998;147:49–58.

diabetes mellitus, non-insulin-dependent; prospective studies; risk factors; sex

The incidence and prevalence of non-insulin-dependent diabetes mellitus (NIDDM) are increasing in many populations (1), and diabetes mellitus has become one of the most prevalent chronic diseases worldwide. NIDDM is believed to have a strong genetic basis (2), but rapid changes in lifestyle including diet and physical activity are rapidly followed by changes in diabetes incidence and prevalence (3–5). This points to a large influence of modifiable risk factors and to a great potential for disease prevention. Still, the causes and pathogenesis of NIDDM are not fully clarified (2), justifying further studies on risk factors for and consequences of diabetes.

There is increasing evidence that cardiovascular disease and NIDDM share some common antecedents (6–8). Further, coronary heart disease is the major cause of death among persons with diabetes, with a twofold to fourfold increased mortality compared with the general population (9). Importantly, the coronary mortality is relatively more increased in diabetic women than in diabetic men (9–11), which may imply that women with diabetes for some reason have lost their "female protection" against cardiovascular disease. It has been advocated that the diabetic state has a more atherogenic effect in women (12). However, both diabetic (11, 12) and prediabetic (7) women are reported to have serum lipid concentrations similar to those in men, in contrast to the nondiabetic population, where women have a more favorable lipid profile (7, 11, 12). The question then arises: Are risk factors for diabetes mellitus similar in men and women, or could the attenuated sex differential in coronary disease among diabetics be associated with sex-related differences in diabetes determinants? This possibility has been little investigated. Population-based studies of risk factors for diabetes in middle-aged women are sparse (7, 13, 14). Few prospective studies had the opportunity to investigate the association between obesity and NIDDM in both men and women (13, 15, 16), and few studies (7, 13, 16) published data on cardiovascular risk factors and subsequent diabetes in both sexes within the same study population. Moreover, several of the few prospective studies on diabetes were carried out in populations with a high prevalence of diabetes but a low prevalence of cardiovascular disease (7, 15, 17).

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Abbreviations: NIDDM, non-insulin-dependent diabetes mellitus; HDL, high density lipoprotein.

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The aim of the present 12-year follow-up study was to investigate risk factors for diabetes mellitus among 11,654 free-living middle-aged men and women. Sex-stratified analyses with validated and identical endpoints allowed a comparison of risk factor patterns in the two sexes. We focused mainly on cardiovascular risk factors and height in addition to obesity and glucose, which are established risk factors for NIDDM (2).

MATERIALS AND METHODS

Subjects

A population-based survey of cardiovascular risk factors and disease was performed in 1977–1978 in Finnmark, the northernmost county in Norway. The survey was conducted by the National Health Screening Service in collaboration with the University of Tromsø and local health authorities, and details of study design and procedures have been published (18, 19). All resident men and women aged 35–52 years and a sample of those aged 20–34 years were invited through a personal, mailed letter. The present analysis is restricted to those aged from 35 to 52 years at screening. The attendance rate in this age group was 87.8 percent. Fifty percent of the cohort were defined as Norse, 36 percent were of Finnish or Saami (Lappish) origin, and 14 percent were of unknown ethnicity.

Screening procedures and baseline data

Enclosed with the letter of invitation was a questionnaire that included cardiovascular history and symptoms, smoking habits, ethnicity, and usual level of leisure physical activity (self reported as low, moderate, regular training, or hard training). At the examination, the questionnaire was checked for consistency. Menopausal status in women was recorded. Time since the last meal was recorded in hours. Body height was measured to the nearest centimeter and weight to the nearest half kilogram. Body mass index was defined as weight (kg)/height $(m)^2$. Blood pressure was measured twice with a mercury sphygmomanometer with the subject sitting and after 4 minutes' rest. The lower values were used. Details of laboratory methods have been published (18, 19). Nonfasting serum glucose, total cholesterol, and triglycerides were analyzed at the Central Laboratory, Ullevål Hospital, Oslo (20). Serum high density lipoprotein (HDL) cholesterol was determined at the Institute of Medical Biology, University of Tromsø, after precipitation of low density lipoprotein and very low density lipoprotein with the heparin-manganese method (19).

Follow-up and case identification

Among the 12,785 persons who participated, 35 men and 21 women were excluded from follow-up because of a physician-verified diagnosis of diabetes before screening or within 3 months thereafter, or because of a screening serum glucose concentration of $\geq$11.1 mmol/liter. Persons with missing values for body height or HDL cholesterol were also excluded, leaving 6,098 men and 5,556 women available for analysis. They were followed from screening through December 31, 1989, for an average of 12 years.

Incident cases of diabetes were detected through hospital discharge diagnosis lists and a systematic survey of hospital records in the only two hospitals in Finnmark. To detect cases among unhospitalized persons and among those who had moved from the county during follow-up, a postal survey was undertaken among all 10,714 participants who were alive by June 1991; 81.8 percent responded. Replies that indicated diabetes were validated by medical records in hospitals and primary health care with the respondent's written consent. We then accepted a doctor-confirmed diagnosis without an evaluation of whether World Health Organization diagnostic criteria (21) had been met. Eight cases were not confirmed because of nonresponse from the doctor in charge, and nine subjects who reported diabetes did not give a written permission for validation. They were not included as cases. If no exact date of diagnosis was given, the date midway in the time interval stated was used. Deceased persons, with date and underlying and contributing causes of death, were identified by linkage to the Norwegian Registry of Deaths.

Study approval

The study was approved by the Regional Ethical Committee for Medical Research and by the Norwegian Data Inspectorate. The Norwegian State Health Directorate permitted access to medical record files.

Statistical methods

Incidence rates were based on person-years from the date of screening until the diagnosis of diabetes, with the date of death, emigration, or December 31, 1989, as censoring date, whichever came first. Two persons were censored when secondary diabetes mellitus was diagnosed. Age adjustment of the incidence rates was done by the direct method on 5-year age groups and with the total cohort as standard population. Baseline variables were age adjusted and compared by analysis of covariance. Age-adjusted and multiple-adjusted relative risks were obtained by Cox proportional hazards analysis. Preliminary analyses revealed significant in-

teractions between sex and serum HDL cholesterol and between sex and body mass index. Accordingly, all analyses were sex stratified. Systolic blood pressure was not included in the multivariable model because of a high correlation with diastolic blood pressure (Pearson's $r > 0.6$ in both sexes), and serum triglycerides were omitted because of a high correlation with HDL cholesterol ($r = -0.4$ in both sexes). Relative risks for continuous variables are shown for units of increase arbitrarily chosen to approximate standard deviations for both sexes. Adjustment for ethnicity was done in analyses that include height, since the two variables are strongly correlated in this study population. Adjustment for time since the last meal and for menopausal status at baseline (in women) did not change relative risk estimates materially and was omitted from the final analyses.

Because of different distributions for several baseline variables, the relative risk by sex-specific rather than combined quartiles was used. The quartile (Q1-Q4) cutpoints were the following: body mass index (kg/m^2): men: <23.2, 23.2–25.0, 25.1–27.0, ≥27.1; women: <22.0, 22.0–24.1, 24.2–27.1, ≥27.2; height (cm): men: <168, 168–172, 173–177, ≥178; women: <156, 156–160, 161–164, ≥165; HDL cholesterol (mmol/liter): men: <1.05, 1.05–1.22, 1.23–1.45, ≥1.46; women: <1.26, 1.26–1.48, 1.49–1.73, ≥1.74; glucose (mmol/liter): men: <5.38, 5.38–5.76, 5.77–6.37, ≥6.38; women: <5.27, 5.27–5.76, 5.77–6.21, ≥6.22; systolic blood pressure (mmHg): men: <123, 123–132, 133–142, ≥143; women: <119, 119–126, 127–138, ≥139; and diastolic blood pressure (mmHg): men: <79, 79–86, 87–92, ≥93; women: <75, 75–80, 81–88, ≥89.

The number of subjects included in the individual analyses varies slightly because of missing values. Significance tests were two tailed, and the significance level was chosen at 5 percent. SAS version 6.09 software (SAS Institute, Inc., Cary, North Carolina) was used.

RESULTS

In total, 87 incident cases of diabetes among men and 75 cases among women were registered. The mean age at entry was higher in future diabetic subjects, and baseline variables adjusted for age are shown for prediabetic and nondiabetic subjects in table 1. Future diabetic subjects were more obese and less physically active, and they had higher blood pressure, serum glucose, and triglycerides than did the others. Prediabetic women were shorter than other women, but no relation between height and diabetes was seen among men. A significantly larger proportion of prediabetic women than of prediabetic men were treated for hypertension (age-adjusted $p = 0.0277$). In general, baseline values were relatively more adverse for female than for male future diabetic subjects, and the

TABLE 1. Age-adjusted baseline variables in men and women initially free of diabetes by future diabetic status, the Finnmark Study, 1977–1989

	Age not adjusted for age (years)		Blood pressure (mmHg)				Body mass index (kg/m^2)		Body height (cm)	
			Systolic		Diastolic					
	Mean	SD†	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Men										
Developed diabetes ($n = 87$)	45.9	4.2	140.3	17.1	93.4	11.4	29.6	4.6	173.2	6.6
Remained nondiabetic ($n = 6,011$)	43.4	5.3	134.2	16.2***	86.0	11.1***	25.3	3.1***	172.7	7.0§
Women										
Developed diabetes ($n = 75$)	46.9	4.5	141.7	22.7	89.7	12.2	31.5	6.1	157.2	6.9
Remained nondiabetic ($n = 5,481$)	43.3	5.3	129.2	17.5***	81.8	10.8***	25.0	4.3***	159.8	6.5***

	Nonfasting serum (mmol/liter)								Current smokers (%)	Physically active‡ (%)	Hypertension treatment (%)
	Glucose		Total cholesterol		HDL cholesterol†		Triglycerides				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Men											
Developed diabetes ($n = 87$)	6.45	1.07	6.80	1.42	1.17	0.33	2.36	1.34	45.7	66.8	14.1
Remained nondiabetic ($n = 6,011$)	5.92	0.90***	6.70	1.23§	1.29	0.35**	1.81	0.99***	57.0*	77.4*	3.4***
Women											
Developed diabetes ($n = 75$)	6.64	1.34	6.76	1.42	1.22	0.27	2.24	1.16	35.7	67.9	28.3
Remained nondiabetic ($n = 5,481$)	5.81	0.75***	6.51	1.30§	1.52	0.36***	1.34	0.72***	44.3§	77.2§	5.3***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
† SD, standard deviation; HDL cholesterol, high density lipoprotein cholesterol.
‡ Those who reported moderate leisure physical activity or regular or hard training.
§ Not significant.

sex differences in baseline variables seen in the nondiabetic population (table 1) were largely eliminated. Serum HDL cholesterol was relatively more reduced in the prediabetic women; the mean HDL cholesterol was not significantly different from that of prediabetic men. The mean HDL cholesterol was lower in prediabetic subjects who were treated for hypertension than in those who were not (age-adjusted means in men, 1.03 mmol/liter vs. 1.20 mmol/liter; in women 1.12 mmol/liter vs. 1.27 mmol/liter) (not shown in table).

Pearson's correlation coefficients between baseline serum lipids were generally similar in men and women but were different for body mass index and height ($r = -0.05$ in men, $r = -0.21$ in women, $p < 0.0001$), in contrast to the correlation coefficients for body mass index and triglycerides ($r = 0.3$), HDL cholesterol ($r = -0.2$), total cholesterol ($r = 0.2$), and diastolic blood pressure ($r = 0.3$), where no sex differences were seen. In men, there was no correlation between body mass index and glucose ($r = 0.0$), whereas a weak, positive correlation ($r = 0.1$, $p < 0.001$) was seen in women. An inverse correlation between height and HDL cholesterol was seen in men ($r = -0.1$, $p < 0.001$) but not in women ($r = 0.0$) (not shown in tables).

Figure 1 presents the relative risk of diabetes by sex-specific quartiles of various baseline variables. A strong dose-response relation between diabetes and body mass index was present in both sexes. Sex-related differences in the relations between diabetes and height, HDL cholesterol, and glucose are apparent in figure 1. Adjustment for body mass index attenuated in particular the relation of diabetes with blood pressure (in both sexes) and HDL cholesterol (in men).

The 12-year incidence rate of diabetes was 1.1 per 1,000 person-years in women and 1.2 per 1,000 person-years in men (table 2). However, the distribution of cases according to serum HDL cholesterol differed by sex. In table 2, common cutoff points were chosen to allow comparison between the sexes. HDL cholesterol concentrations less than 1.5 mmol/liter were associated with a higher incidence of diabetes in women than in men, while the situation was reversed at HDL cholesterol concentrations greater than 1.5 mmol/liter. Correspondingly, age-adjusted relative risk estimates were 0.07 (95 percent confidence interval 0.03–0.16) in women and 0.43 (95 percent confidence interval 0.22–0.82) in men in the highest compared with the lowest HDL cholesterol group, and the sex differences were even more pronounced when adjusted for other risk factors, of which body mass index was the major confounder.

The relation between body mass index and diabetes was explored in more detail in table 3, subdividing subjects with a body mass index ≥ 27.1 kg/m^2 into strata with common cutoff points for men and women. The age-adjusted relative risk rose greatly with increasing body mass index. However, in women the relation was heavily confounded. At a body mass index ≥ 35.0 kg/m^2, the relative risk in women was reduced from 36.6 to 11.1 (95 percent confidence interval 4.6–26.5) after multiple adjustment, while the relative risk among men was less influenced.

Table 4 presents age-adjusted and multiple-adjusted risk factors for diabetes. Adjusted only for age, systolic and diastolic blood pressures were highly significant risk factors, and the relative risks were similar in the sexes, whereas serum triglycerides and HDL cholesterol were stronger risk factors for women. Total cholesterol did not predict diabetes in either sex and was not included in the final model. Adjusted for age, HDL cholesterol was a significant predictor in both sexes. In the fully adjusted model, the risk of diabetes was 47 percent lower in women but only nonsignificantly 3 percent lower in men for every 0.3-mmol/liter increment in HDL cholesterol. Physical activity was inversely associated with diabetes in the age-adjusted model, but the association was weaker after adjustment for other risk factors. In a multivariable analysis that included only those with a body mass index ≥ 27.1 kg/m^2, leisure physical activity had a protective effect of borderline significance among men (relative risk per level increase, 0.69; 95 percent confidence interval 0.46–1.04). Otherwise, the risk factor patterns remained virtually unchanged (data not shown).

One third of the prediabetic women but only 15 percent of the prediabetic men were treated for hypertension at baseline. Therefore, a multivariable analysis similar to the one in table 4 was performed, but without those on antihypertensive treatment. The analysis included 74 cases among men and 51 cases among women. Only small changes in relative risk estimates occurred. In particular, the relative risk associated with HDL cholesterol was 0.63 (95 percent confidence interval 0.46–0.85) in women and 0.99 (95 percent confidence interval 0.80–1.24) in men (data not shown in table).

At baseline, 1,169 women (21 percent) reported having undergone menopause. Serum total cholesterol and triglycerides, body mass index, and smoking frequency differed significantly by menopausal status, while diastolic blood pressure, serum HDL cholesterol, and glucose did not (not shown). Menopausal status (yes/no) did not predict diabetes when included in an analysis as in table 4 (relative risk, 0.67; 95 percent confidence interval 0.37–1.22), did not confound the associations between other risk factors and diabetes, and was not included in the final model.

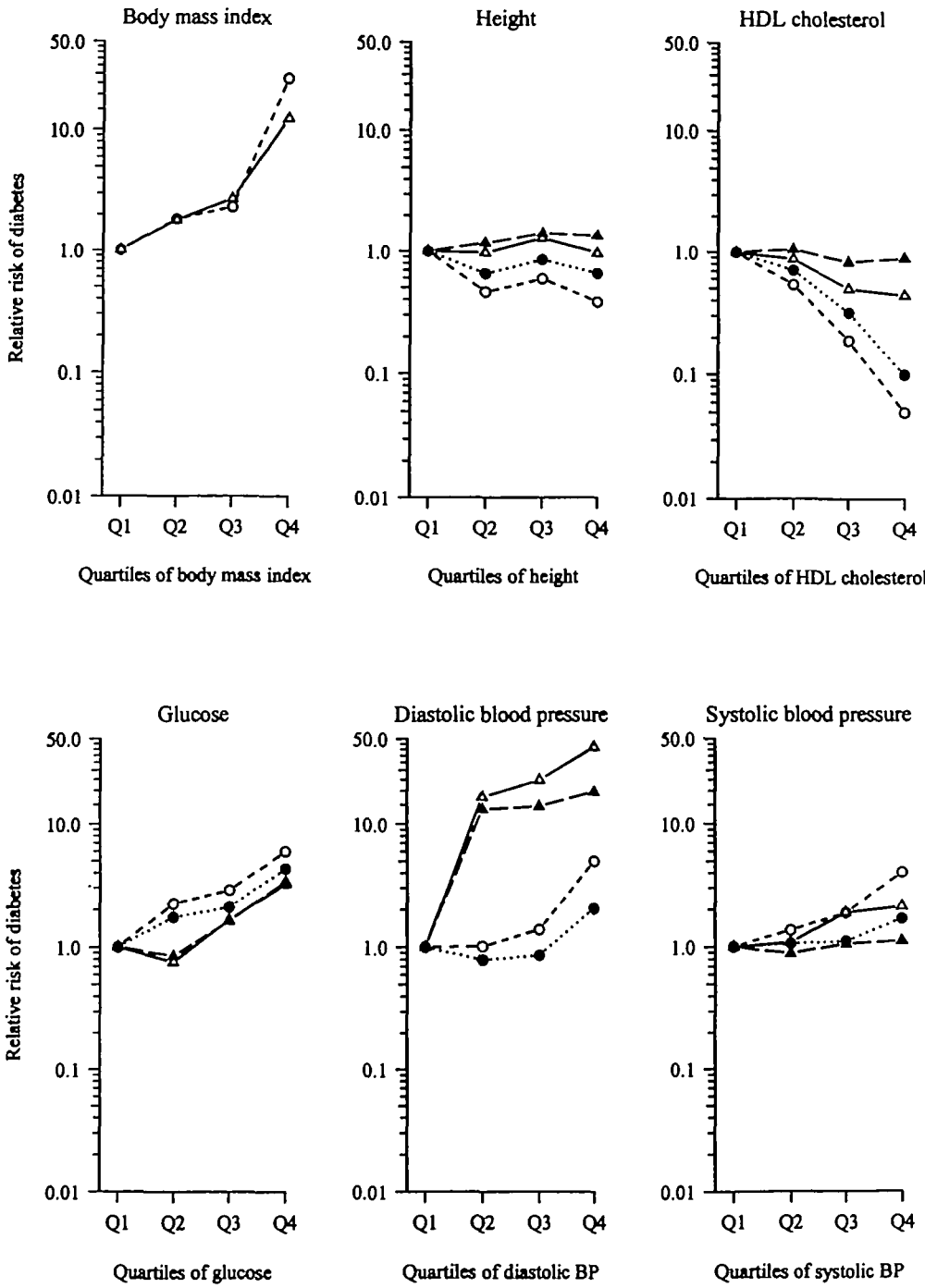

FIGURE 1. Relative risk of diabetes mellitus in men and women by sex-specific quartiles of baseline factors, the Finnmark Study, 1977–1989. Quartile (Q1-Q4) cutpoints: *body mass index* (weight (kg)/height (m)^2): men: <23.2, 23.2–25.0, 25.1–27.0, ≥27.1; women: <22.0, 22.0–24.1, 24.2–27.1, ≥27.2; *height* (cm): men: <168, 168–172, 173–177, ≥178; women: <156, 156–160, 161–164, ≥165; *glucose* (mmol/liter): men: <5.38, 5.38–5.76, 5.77–6.37, ≥6.38; women: <5.27, 5.27–5.76, 5.77–6.21, ≥6.22; *high density lipoprotein cholesterol* (HDL cholesterol) (mmol/liter): men: <1.05, 1.05–1.22, 1.23–1.45, ≥1.46; women: <1.26, 1.26–1.48, 1.49–1.73, ≥1.74; *systolic blood pressure* (BP) (mmHg): men: <123, 123–132, 133–142, ≥143; women: <119, 119–126, 127–138, ≥139; *diastolic blood pressure* (mmHg): men: <79, 79–86, 87–92, ≥93; women: <75, 75–80, 81–88, ≥89. △, age-adjusted relative risk, men; ▲, age- and body mass index-adjusted relative risk, men; ○, age-adjusted relative risk, women; ●, age- and body mass index-adjusted relative risk, women.

DISCUSSION

This population-based study demonstrates several sex-related differences in risk factors for diabetes mellitus. First, body mass index was the dominant risk factor in men, and a dose-response relation was seen in both sexes. However, in women, the strong relation

TABLE 2. Age-adjusted incidence rates of diabetes per 1,000 person-years and age-adjusted and multiple-adjusted relative risk by high density lipoprotein cholesterol (HDL cholesterol) and sex, the Finnmark Study, 1977–1989

HDL cholesterol (mmol/liter)	Men					Women				
	Person-years	Cases (no.)	Rate/1,000†	Relative risk		Person-years	Cases (no.)	Rate/1,000	Relative risk	
				Age adjusted	Multiple adjusted†				Age adjusted	Multiple adjusted
<1.0	13,491	26	1.98	1.00	1.00	3,289	14	4.47	1.00	1.00
1.0–1.49	42,234	47	1.14	0.58	1.06‡	30,369	51	1.71	0.39	0.60‡
≥1.5	15,812	14	0.85	0.43	1.06‡	33,036	10	0.30	0.07	0.17**
Total	71,537	87	1.22			66,694	75	1.12		
p, test for trend					0.8514					<0.0001

* $p < 0.05$; ** $p < 0.001$.

† Adjusted for age, body mass index, glucose, diastolic blood pressure, height, smoking, antihypertensive treatment, physical activity, and ethnicity.

‡ Not significant.

TABLE 3. Relative risk of diabetes according to body mass index (BMI), by sex, the Finnmark Study, 1977–1989

BMI (kg/m^2)	Men (87 cases)			Women (75 cases)		
	Cases (no.)	Relative risk		Cases (no.)	Relative risk	
		Age adjusted	Multiple adjusted*		Age adjusted	Multiple adjusted
≤27.0	27	1.00	1.00 (ref.)	10	1.00	1.00 (ref.)
27.1–28.9	16	3.19	2.53 (1.34–4.79)†	12	7.85	5.60 (2.36–13.28)
29.0–31.9	20	6.72	5.47 (2.97–10.07)	24	18.94	9.23 (4.25–20.02)
32.0–34.9	13	20.04	13.05 (6.23–27.32)	10	14.18	6.49 (2.53–16.65)
≥35.0	11	42.00	27.89 (12.27–63.42)	19	36.60	11.07 (4.63–26.46)
p, test for trend			<0.0001			<0.0001

* Relative risk adjusted for age, diastolic blood pressure, high density lipoprotein cholesterol, glucose, smoking, height, antihypertensive treatment, physical activity, and ethnicity.

† Numbers in parentheses, 95% confidence interval.

between body mass index and diabetes was confounded by other factors. Second, there were sex-related differences in the associations between serum HDL cholesterol and diabetes and between height and diabetes. Physical activity was inversely related with diabetes, especially among obese subjects. This observation accords with previous studies (22) and carries an important public health message. Physical activity increases insulin sensitivity in working muscles (23) and may exert a direct protective effect among those who are otherwise at a high risk for diabetes.

In general, a strong positive association between obesity and NIDDM has been noted in prospective studies among men (13, 15, 16, 24–28) and women (13, 14–16, 29) but, with few exceptions (15), possible differences by sex have not been taken into account. Therefore, the observed sex-related difference in the relation between body mass index and diabetes is of particular interest. Multivariable adjustment greatly attenuated the association between body mass index and diabetes in women, while the relation was less influenced in men. The Nurses' Health Study reported a strong, continuous relation between body mass index and diabetes in women (29) but did not adjust for serum lipids or blood pressure.

In men, adipose tissue tends to accumulate in the abdominal region. In women, both "feminine" and "masculine" obesity may occur, with adipose tissue preponderance for the gluteofemoral or the abdominal region, respectively (30). Abdominal obesity is associated with metabolic aberrances in both sexes (30–32) and with hyperandrogenicity in women (33). It is an independent risk factor for NIDDM in both men and women (14, 15, 25). The clustering of high serum triglycerides, low HDL cholesterol, hypertension, hyperinsulinemia, and insulin resistance, which was labeled the metabolic syndrome or Syndrome X (34), is often accompanied by abdominal obesity (35). A study by Krotkiewski et al. (30) showed that women seemed to tolerate moderate obesity better than men do. Only the most obese women in their study had metabolic aberrances similar to those of men. The future diabetic women in our study "were like men" in a metabolic sense with regard to baseline levels of HDL choles-

TABLE 4. Risk factors for diabetes mellitus in men and women, the Finnmark Study, 1977–1989

Variables	Men (87 cases)		Women (75 cases)	
	Relative risk*	Relative risk†	Relative risk*	Relative risk†
Age (5 years)	1.61 (1.30–1.99)‡	1.52 (1.21–1.90)	2.02 (1.58–2.58)	1.44 (1.10–1.89)
BMI§ (3 kg/m²)	2.22 (1.98–2.50)	2.09 (1.79–2.43)	1.72 (1.57–1.88)	1.35 (1.21–1.51)
Body height (5 cm)	1.07 (0.90–1.26)	1.15 (0.97–1.35)	0.65 (0.53–0.79)	0.71 (0.58–0.87)
Systolic BP§ (15 mmHg)	1.33 (1.13–1.55)		1.50 (1.30–1.72)	
Diastolic BP (10 mmHg)	1.73 (1.47–2.05)	1.17 (0.96–1.43)	1.79 (1.49–2.13)	1.19 (0.95–1.50)
Total cholesterol (1 mmol/liter)	1.08 (0.91–1.28)		1.14 (0.97–1.34)	
HDL cholesterol§ (0.3 mmol/liter)	0.71 (0.57–0.88)	0.97 (0.78–1.19)	0.41 (0.32–0.52)	0.53 (0.41–0.70)
Triglycerides (1 mmol/liter)	1.48 (1.28–1.72)		2.14 (1.83–2.50)	
Glucose (1 mmol/liter)	1.68 (1.39–2.01)	1.67 (1.38–2.02)	2.46 (2.04–2.96)	2.34 (1.91–2.87)
Daily smoking (yes/no)	0.66 (0.43–1.01)	0.85 (0.55–1.30)	0.72 (0.45–1.16)	0.79 (0.47–1.31)
Hypertension treatment (yes/no)	4.23 (2.33–7.68)	1.98 (1.03–3.80)	5.52 (3.32–9.18)	2.68 (1.53–4.67)
Physical activity (one level)	0.67 (0.49–0.92)	0.84 (0.61–1.16)	0.66 (0.44–0.99)	0.91 (0.61–1.36)

* Relative risk adjusted for age (height also adjusted for ethnicity).
† Relative risk adjusted for the other risk factors and for ethnicity.
‡ Numbers in parentheses, 95% confidence interval.
§ BMI, body mass index; BP, blood pressure; HDL cholesterol, high density lipoprotein cholesterol.

terol, triglycerides, and blood pressure, but their mean body mass index was higher. Our data cannot disclose, but may support, a possible connection between abdominal obesity, androgenicity, and diabetes.

Serum HDL cholesterol was a strong independent risk factor of diabetes in women. An increment of 0.3 mmol/liter in HDL cholesterol was associated with a 47 percent lower risk among women but did not predict diabetes in men after multiple adjustment. Among men in the British Regional Heart Study (27), the highest versus lowest quintile of HDL cholesterol carried a relative risk of 0.7 (95 percent confidence interval 0.5–1.2, p for linear trend = 0.03) after multiple adjustment. Only two prospective studies (7, 36) offer data on HDL cholesterol levels in prediabetic women. Future diabetics in the San Antonio Heart Study (7) had lower HDL cholesterol concentrations than did nondiabetics, and the differences of 0.3 mmol/liter in women and 0.09 mmol/liter in men were almost identical to our findings. However, that study included only 17 male and 26 female prediabetic subjects. Among elderly persons in the Framingham Study, HDL cholesterol was 0.2 mmol/liter lower in prediabetic men and women (36). To our knowledge, no prospective analysis of HDL cholesterol and diabetes with relevant multivariable adjustment has been published for women until the present one. Sex differences in the relations of body mass index and serum lipids with diabetes warrant further investigations.

Antihypertensive treatment was associated with a twofold (men) to threefold (women) increased risk of diabetes in this study. Antihypertensive agents may precipitate diabetes (26, 37), but the coincidence between hypertension and diabetes could be due to insulin resistance (38). In this study, serum HDL cholesterol was lower in prediabetic subjects who were treated for hypertension at screening compared with those who were not. Whether this was a treatment side effect or whether it simply reflects the common association between hypertension and serum lipids (34) is not known.

Serum glucose was a highly significant predictor of diabetes, in accordance with previous findings in men (7, 13, 16, 25, 26) and women (7, 13, 14, 16). A high serum glucose concentration may indicate glucose intolerance and may be regarded as an intermediate step along the causal pathway to diabetes. The relative risk associated with glucose was significantly higher in women than in men. No glucose tolerance test or other indices of insulin resistance were performed at baseline. We treated a casual serum glucose ≥11.1 mmol/liter as prevalent diabetes (21) and excluded those subjects from follow-up. Of the 162 subjects who later developed diabetes, 14.2 percent (14 women, 9 men) had a random serum glucose concentration from 7.8 mmol/liter to 11.0 mmol/liter, while the percentage was 2.6 among the remaining subjects, suggesting that baseline manifest glucose intolerance was not a major feature of this study population.

Of the classic cardiovascular risk factors, only blood pressure emerged as a significant risk factor for diabetes in our study after age adjustment, and relative risks were slightly higher (nonsignificant) in women. Diastolic blood pressure was not a significant risk factor after multiple adjustment. The study confirms previous findings that blood pressure is increased in prediabetic subjects, (7, 16, 25–28, 36) but is not always a significant risk factor in multivariable models (13, 27, 28). Serum total cholesterol did not predict diabetes in this and several other studies (16, 27, 28).

We observed a nonsignificant, inverse relation between smoking and diabetes in both sexes, while others reported smoking and diabetes to be positively (27, 28, 39) or not (16, 25) related.

This is the first prospective study to report an inverse relation between height and diabetes in women, and the finding is at variance with the Nurses' Health Study where no association was seen (29). The risk of diabetes was 29 percent lower per 5-cm increase in height after adjustment for age, body mass index, and other risk factors. There seems to be no obvious explanation for the observed sex difference. Adult height is determined by genetics and by environmental factors during early life (40). An inverse correlation between adult height and glucose tolerance was noted in men and women in the Isle of Ely Diabetes Project (41). In a study of 50-year-old men and women, those with Syndrome X were shorter than others (42), but there was no such association in a sample of men aged 59–70 years (42). In a diabetes prevalence study from Bangladesh, adult women with hyperglycemia were significantly shorter than other women, but no similar association was observed among men (43). The authors ascribe this finding to more prevalent malnutrition among girls than among boys in early childhood. As recently reviewed by Stern (8), increasing evidence connects low birth weight and possibly inadequate nutrition in early life to the metabolic syndrome and to NIDDM in adults. Glucose intolerance (44), insulin resistance (45), and Syndrome X and NIDDM (42) have been linked to reduced fetal and infant growth. Theoretically, the association between height and diabetes in women in the present study may express an adverse influence from early life factors. On the other hand, the lack of such an association among men should caution against premature conclusions.

The population-based approach, the large study size, and factual, not self reported, biologic baseline measurements are strengths of the present study, but some limitations should be considered. No baseline data were collected to identify glucose-intolerant subjects. The diagnosis of diabetes during follow-up was clinical. Preferably, screening for diabetes using fasting glucose and a glucose tolerance test (21) should be undertaken in the whole cohort by the end of follow-up, since diabetes may go clinically unrecognized (21), but this was not feasible. A recent Norwegian population-based prevalence study that did make use of fasting glucose and glucose tolerance tests (46) showed that the prevalence of undetected diabetes was far less than the estimated 50 percent commonly referred to from the United States (47). Among subjects >40 years old, 83 percent of the cases had been detected prior to the screening. Misclassification of cases would tend to dilute the observed associations between risk factors and disease. Based on the incidence rates of diabetes among those who responded to the postal survey in 1991, we estimated that 11 cases of diabetes were missed among the questionnaire nonresponders. Available data on insulin treatment could not be used to distinguish between insulin-dependent and non-insulin-dependent diabetes, since the latter may be treated with insulin. However, insulin-dependent diabetes mellitus is relatively rare in Finnmark (48), and all study subjects were at least 35 years old at study entry.

Alcohol consumption raises HDL cholesterol (49), and heavy alcohol intake may induce secondary diabetes, but no baseline data were collected on this potential confounder. However, alcohol use is rather modest in Norway, with alcohol-related disease accounting for less than 1 percent of all deaths (50). By 1987, 40 percent of the women and 13 percent of the men in Finnmark were alcohol abstainers (51). Among users, alcohol intake was more frequent in men. In the present study, among the 531 men and 195 women who died during follow-up, 44 men and three women had some alcohol-related condition mentioned on the death certificate. None of them had diabetes. Only two subjects in this cohort had a diagnosed secondary (pancreatic) diabetes and were not included as cases. A sex difference in drinking habits may therefore have influenced our findings through an effect on HDL cholesterol, but this is unlikely to be a major confounder.

Existing knowledge of the role of menopause with regard to diabetes incidence is very limited. At baseline, 21 percent of the women in this study had undergone menopause. We observed higher serum total cholesterol and triglyceride concentrations in post- than in premenopausal women, while HDL cholesterol, glucose, and diastolic blood pressure did not vary by menopausal status. This finding accords with previous studies (52, 53). Menopausal status at baseline did not predict diabetes and did not act as a confounder in multivariable models. In the San Antonio Heart Study, there was no significant interaction between menopausal status and conversion to NIDDM (54).

No information on hormonal replacement treatment was collected in the baseline survey. However, by 1987, only 2 percent of Finnmark women aged 45–62 years used exogenous estrogen (51). Further, few data exist to assess whether estrogen could be a true confounder of the relative risks reported. Postmenopausal estrogen use may affect the levels of HDL cholesterol (55) and of triglycerides and glucose (56) but did not increase the risk of clinical diabetes in the Nurses' Health Study (57).

Diabetes is an important risk factor for coronary heart disease (10, 11), but risk factors for the two diseases overlap only partially in the present study population. Total cholesterol and smoking were not related to the risk of diabetes, and blood pressure was not a significant predictor in the multivariable model. On the other hand, the classic cardiovascular risk factors, but not body mass index, were significant predictors of myocardial infarction in both sexes (58). Walden et al. (12) found HDL cholesterol to be more reduced in women with type 2 diabetes than in men, and they concluded that diabetes has a more adverse effect on lipoproteins in women. However, lipid abnormalities preceded and were indeed a strong predictor (in women) for diabetes in our study, not a consequence of the diabetic state. Since HDL cholesterol is an equally important coronary risk factor in men and women (58), the sex-specific relations between serum lipids and diabetes may be one reason for diluted sex differences in coronary disease among diabetic subjects, and they may be involved in the apparently accelerated atherosclerotic process in diabetic women (12).

In conclusion, several sex-related dissimilarities were noted in the relations between body mass index, height, serum lipids, and glucose and subsequent diabetes mellitus in this middle-aged population. After multivariable adjustment, body mass index was a stronger predictor in men, possibly because an increased body mass index is more directly related to abdominal obesity and the amount of visceral fat in men. Serum HDL cholesterol and glucose were stronger risk factors among women. The risk factor patterns were suggestive of insulin resistance and may shed some light on attenuated sex differences in coronary disease among diabetic subjects. Further studies are needed to elucidate the temporal sequence of events that lead to diabetes and concomitant coronary disease and to explore the sex-related differences that seem to be involved.

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ADDENDUM

Note added in proof: The following study was published after the submission of this article: Haffner SM, Miettinen H, Stern MP. Relatively more atherogenic coronary heart disease risk factors in prediabetic women than in prediabetic men. Diabetologia 1997;40:711–17.