

Online appendix for: Sex differences in the prediction of type 2 diabetes by inflammatory markers: Results from the MONICA/KORA Augsburg case-cohort study, 1984-2002 by Thorand et al.

Table I. Weighted means (standard error) and proportions of demographic and clinical characteristics for subjects with and without incident type 2 diabetes mellitus.

Characteristics	Men			Women		
	Cases	Non-cases	<i>P value</i>	Cases	Non-cases	<i>P value</i>
Number	305	889	-	222	809	-
Age (years)*	56.1 (0.6)	51.7 (0.4)	< 0.001	56.2 (0.6)	51.7 (0.4)	< 0.001
Education < 12 years (%)	74.8	65.8	0.003	92.8	83.7	< 0.001
Body mass index (kg/m ²)*	29.6 (0.2)	27.1 (0.1)	< 0.001	30.9 (0.3)	26.4 (0.2)	< 0.001
Waist circumference (cm)*,‡	103.5 (0.8)	95.4 (0.4)	< 0.001	94.3 (1.0)	82.6 (0.5)	< 0.001
Waist-hip-ratio*,‡	0.966 (0.004)	0.926 (0.003)	< 0.001	0.857 (0.006)	0.804 (0.003)	< 0.001
Systolic BP (mm Hg)*	142.5 (1.0)	134.6 (0.7)	< 0.001	142.3 (1.3)	130.6 (0.7)	< 0.001
Diastolic BP (mm Hg)*	85.4 (0.7)	83.3 (0.4)	0.008	84.5 (0.8)	79.6 (0.4)	< 0.001
Use of antihypertensive medication (%)	23.9	14.0	< 0.001	40.5	13.8	< 0.001
Actual Hypertension (%)	66.2	43.6	< 0.001	69.4	36.0	< 0.001
Ratio TC/HDL-C*	6.0 (0.1)	5.0 (0.1)	< 0.001	5.0 (0.1)	3.9 (0.04)	< 0.001
Use of lipid lowering medication (%)	6.2	3.0	0.04	2.7	1.9	0.52
Low level of physical activity (%)	65.6	57.3	0.01	75.7	61.4	< 0.001
Smoking status (%)			0.02			0.40
Never smoker	22.6	30.3		67.1	64.7	
Former smoker	42.0	40.2		17.6	16.3	
Current smoker	35.4	29.5		15.3	19.0	

Table I. continued:

Alcohol intake (%)			0.10			0.02
0 g/day	20.0	15.9		51.8	41.3	
0.1 – 39.9/19.9 g/day [§]	44.6	51.4		32.9	37.3	
≥ 40/20 g/day [§]	35.4	32.7		15.3	21.4	
Parental history of DM (%)			0.005			< 0.001
Negative	47.2	58.2		41.9	61.2	
Positive	24.6	18.4		33.3	21.1	
Unknown	28.2	23.4		24.8	17.8	
Prevalent stroke (%)	1.6	1.6	0.96	1.8	0.4	0.14
Prevalent MI (%)	6.9	3.3	0.02	2.7	0.9	0.11
Angina pectoris (%)	6.9	4.0	0.07	5.9	4.8	0.54
Current HRT (%)			-	8.2	11.7	0.19
Current use of OC (%) [#]			-	7.7	15.3	0.08
CRP (mg/l) [†]	2.1 (1.1)	1.4 (1.0)	< 0.001	3.3 (1.1)	1.3 (1.0)	< 0.001
IL-6 (pg/ml) [†]	2.9 (1.1)	2.1 (1.0)	< 0.001	3.2 (1.1)	1.9 (1.0)	< 0.001

* arithmetic mean (SE); [†] geometric mean (antilog of SE); [‡] only for survey 2 and 3

[§] for men 0.1 – 39.9 g/day and ≥ 40 g/day; for women 0.1 – 19.9 g/day and ≥ 20 g/day

^{||} only for women aged ≥ 50 years (n=606) with no current use of OC; [#] only for women aged < 50 years (n=413) with no current HRT

Weights: cases = 1; non-cases = 1/sfrac with sfrac = Subcohort/full cohort without cases for each sex and survey

BP: blood pressure, DM: diabetes mellitus, MI: myocardial infarction, CRP: C-reactive protein, TC: total cholesterol, HDL-C: high density lipoprotein cholesterol, HRT: hormone replacement therapy, OC: oral contraceptives

Table II. Hazard ratios for the risk of developing type 2 diabetes mellitus according to baseline levels of CRP for men and women

	Men			<i>P for trend</i>	Women			<i>P for trend</i>	<i>P for sex interaction</i>
	Tertiles of CRP				Tertiles of CRP				
	T1	T2	T3		T1	T2	T3		
Model 4* + antihypertensive medication									
HR	1.0	1.19	1.07	0.897	1.0	1.99	2.63	0.017	0.101
(95% CI)		(0.81-1.77)	(0.70-1.63)			(1.08-3.67)	(1.41-4.91)		
Model 4* + lipid-lowering medication									
HR	1.0	1.23	1.13	0.903	1.0	2.07	2.80	0.007	0.067
(95% CI)		(0.83-1.82)	(0.74-1.73)			(1.12-3.82)	(1.50-5.22)		
Model 4* + use of oral contraceptives + use of HRT									
HR	--	--	--	--	1.0	2.12	2.88	0.010	
(95% CI)						(1.15-3.92)	(1.52-5.46)		
Model 4* after exclusion of subjects with CHD [†]									
HR	1.0	1.12	0.92	0.486	1.0	2.30	3.02	0.014	0.034
(95% CI)		(0.72-1.74)	(0.56-1.51)			(1.18-4.49)	(1.53-5.94)		
Model 4* after exclusion of subjects with follow-up ≤ 5 years [‡]									
HR	1.0	1.21	0.93	0.436	1.0	2.01	2.56	0.043	0.124
(95% CI)		(0.77-1.91)	(0.56-1.54)			(1.02-3.95)	(1.26-5.21)		
Model 4* after restriction of follow up to ≤ 5 years [§]									
HR	1.0	1.25	1.45	0.376	1.0	2.31	3.14	0.149	0.261
(95% CI)		(0.66-2.40)	(0.72-2.94)			(0.63-8.51)	(0.88-11.13)		

Table II. continued

Hazard ratios were estimated by Cox proportional hazard model. Correction for standard errors was made by the SAS macro ROBPHREG using the method by Barlow. Tertiles of the weighted distributions in the subcohort, stratified by sex, were used.

*Model 4: adjusted for age and survey and lifestyle factors i.e. smoking status (never smoker, former smoker, current smoker), alcohol consumption (0, 0.1-39.9, ≥ 40 g/d for men; 0, 0.1-19.9, ≥ 20 g/d for women) and physical activity (inactive, active), BMI, systolic blood pressure, TC/HDL-C and parental history of diabetes (positive, unknown, negative)

Models contained continuous variables unless otherwise indicated.

†n after exclusion of CHD (i.e. prevalent myocardial infarction, prevalent stroke, prevalent angina pectoris or incident myocardial infarction): men 1,012 (237 cases, 775 non-cases), women 948 (195 cases, 753 non-cases)

‡n after exclusion follow-up ≤ 5 years: men 962 (184 cases, 778 non-cases), women 880 (146 cases, 734 non-cases)

§n after restriction of follow-up to ≤ 5 years: men 1,194 (121 cases, 1,073 non-cases), women 1,031 (76 cases, 955 non-cases)

HR: hazard ratio, HRT: hormone replacement therapy

Table III. Hazard ratios for the risk of developing type 2 diabetes mellitus according to baseline levels of IL-6 for men and women

	Men				Women				<i>P for sex interaction</i>
	Tertiles of IL-6			<i>P for trend</i>	Tertiles of IL-6			<i>P for trend</i>	
	T1	T2	T3		T1	T2	T3		
Model 4* + antihypertensive medication									
HR	1.0	1.22	1.59	0.018	1.0	1.54	2.08	0.009	0.746
(95% CI)		(0.83-1.81)	(1.09-2.31)			(0.88-2.67)	(1.21-3.55)		
Model 4* + lipid-lowering medication									
HR	1.0	1.20	1.56	0.021	1.0	1.41	2.10	0.004	0.781
(95% CI)		(0.81-1.78)	(1.08-2.28)			(0.82-2.42)	(1.24-3.54)		
Model 4* + use of oral contraceptives and use of HRT									
HR	--	--	--	--	1.0	1.39	2.08	0.005	--
(95% CI)						(0.81-2.38)	(1.23-3.50)		
Model 4* after exclusion of subjects with CHD [†]									
HR	1.0	1.32	1.33	0.296	1.0	1.43	2.16	0.006	0.532
(95% CI)		(0.86-2.02)	(0.87-2.04)			(0.79-2.57)	(1.22-3.79)		
Model 4* after exclusion of subjects with follow-up ≤5 years [‡]									
HR	1.0	1.21	1.44	0.119	1.0	1.70	2.28	0.011	0.608
(95% CI)		(0.77-1.90)	(0.93-2.25)			(0.91-3.15)	(1.23-4.22)		
Model 4* after restriction of follow up to ≤5 years [§]									
HR	1.0	1.27	1.82	0.051	1.0	0.78	1.49	0.153	0.938
(95% CI)		(0.67-2.43)	(1.00-3.31)			(0.31-1.95)	(0.65-3.44)		

Table III. continued

Hazard ratios were estimated by Cox proportional hazard model. Correction for standard errors was made by the SAS macro ROBPHREG using the method by Barlow. Tertiles of the weighted distributions in the subcohort, stratified by sex, were used.

*Model 4: adjusted for age and survey and lifestyle factors i.e. smoking status (never smoker, former smoker, current smoker), alcohol consumption (0, 0.1-39.9, ≥ 40 g/d for men; 0, 0.1-19.9, ≥ 20 g/d for women) and physical activity (inactive, active), BMI, systolic blood pressure, TC/HDL-C and parental history of diabetes (positive, unknown, negative)

Models contained continuous variables unless otherwise indicated.

†n after exclusion of CHD (i.e. prevalent myocardial infarction, prevalent stroke, prevalent angina pectoris or incident myocardial infarction): men 1,012 (237 cases, 775 non-cases), women 948 (195 cases, 753 non-cases)

‡n after exclusion follow-up ≤ 5 years: men 962 (184 cases, 778 non-cases), women 880 (146 cases, 734 non-cases)

§n after restriction of follow-up to ≤ 5 years: men 1,194 (121 cases, 1,073 non-cases), women 1,031 (76 cases, 955 non-cases)

HR: hazard ratio, HRT: hormone replacement therapy

Table IV. Hazard ratios for the risk of developing type 2 diabetes mellitus according to baseline levels of CRP and IL-6 for men and women stratified by BMI and smoking status

	Men				Women				
	Tertiles of CRP			<i>P for trend</i>	Tertiles of CRP			<i>P for trend</i>	<i>P for sex interaction</i>
	T1	T2	T3		T1	T2	T3		
Model 4*: BMI <30 kg/m ²									
HR	1.0	1.25	1.81	0.014	1.0	2.18	3.70	0.001	0.349
(95% CI)		(0.78-2.01)	(1.13-2.90)			(1.12-4.24)	(1.85-7.39)		
Model 4*: BMI ≥30 kg/m ²									
HR	1.0	1.61	0.93	0.233	1.0	2.69	4.46	0.018	0.022
(95% CI)		(0.56-4.63)	(0.32-2.70)			(0.50-14.66)	(0.90-22.19)		
Model 4*: Non-smokers and ex-smokers									
HR	1.0	1.03	0.95	0.761	1.0	1.94	2.69	0.018	0.074
(95% CI)		(0.65-1.61)	(0.57-1.57)			(1.00-3.78)	(1.36-5.33)		
Model 4*: Current smokers									
HR	1.0	2.05	1.77	0.623	1.0	1.59	1.77	0.591	0.727
(95% CI)		(0.88-4.78)	(0.74-4.21)			(0.36-7.07)	(0.44-7.17)		
	Tertiles of IL-6				Tertiles of IL-6				
	Tertiles of IL-6			<i>P for trend</i>	Tertiles of IL-6			<i>P for trend</i>	<i>P for sex interaction</i>
	T1	T2	T3		T1	T2	T3		
Model 4*: BMI <30 kg/m ²									
HR	1.0	1.35	2.16	0.001	1.0	1.27	1.97	0.033	0.788
(95% CI)		(0.84-2.17)	(1.38-3.36)			(0.68-2.37)	(1.03-3.74)		
Model 4*: BMI ≥30 kg/m ²									
HR	1.0	0.88	1.21	0.414	1.0	1.91	3.67	0.002	0.243
(95% CI)		(0.42-1.83)	(0.58-2.53)			(0.70-5.24)	(1.49-9.06)		
Model 4*: Non-smokers and ex-smokers									
HR	1.0	1.12	1.54	0.059	1.0	1.54	2.18	0.007	0.547
(95% CI)		(0.70-1.79)	(0.98-2.44)			(0.85-2.80)	(1.24-3.83)		
Model 4*: Current smokers									
HR	1.0	1.66	1.93	0.162	1.0	0.80	1.02	0.840	0.742
(95% CI)		(0.75-3.68)	(0.90-4.11)			(0.23-2.82)	(0.30-3.51)		

Table IV. continued

Hazard ratios (HRs) were estimated by Cox proportional hazards model. Correction for standard errors was made by the SAS macro ROBPHREG using the method by Barlow. Tertiles of the weighted distributions in the subcohort, stratified by sex, were used.

*Model 4: adjusted for age and survey and lifestyle factors i.e. smoking status (never smoker, former smoker, current smoker), alcohol consumption (0, 0.1-39.9, ≥ 40 g/d for men; 0, 0.1-19.9, ≥ 20 g/d for women) and physical activity (inactive, active), BMI, systolic blood pressure, TC/HDL-C and parental history of diabetes (positive, unknown, negative)

Models contained continuous variables unless otherwise indicated.