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Serum γ-glutamyltransferase and risk of type 2 diabetes mellitus in men and women from the general population

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Abstract. Meisinger C, Löwel H, Heier M, Schneider A, Thorand B for the KORA Study Group (MONICA/KORA Myocardial Infarction Registry, Augsburg; and Institute of Epidemiology, Neuherberg; Germany). Serum gamma-glutamyltransferase and risk of type 2 diabetes mellitus in men and women from the general population. *J Intern Med* 2005; **258**: 527–535

Objectives. To examine gender-specific associations between γ-glutamyltransferase (GGT) and incident type 2 diabetes mellitus in a representative population-based sample in Germany.

Design. Prospective population-based study.

Methods. The study was based on 1851 men and 1836 women (aged 25–64 years) who participated in the first Monitoring Trends and Determinants on Cardiovascular Diseases (MONICA) Augsburg Survey 1984/1985, and who were free of diabetes at baseline. Incident cases of type 2 diabetes were assessed using follow-up questionnaires in 1987/1988, 1997/1998 and 2002/2003 and were validated with medical records. Gender-specific hazard ratios (HRs) were estimated from Cox proportional hazard models.

Results. A total of 172 cases of incident type 2 diabetes amongst men and 109 amongst women were registered during a mean follow-up period of 14.7 years. In both sexes the risk of type 2 diabetes increased with increasing levels of serum GGT. After multivariable adjustment HRs for incident type 2 diabetes across GGT categories (<25th, <50th, <75th, <87.5th and ≥87.5th percentiles) were 1.0, 1.81, 2.37, 3.41 and 4.24 (*P*-value for trend <0.0001) in men and 1.0, 1.42, 1.48, 1.95 and 2.41 (*P*-value for trend 0.0179) in women. Obesity appeared to be more strongly associated with type 2 diabetes in women with GGT equal or greater than the median compared to women with GGT below the median. However, in men the association between obesity and type 2 diabetes was almost identical in the two groups.

Conclusions. The GGT is an important predictor for incident type 2 diabetes in men and women from the general population.

Keywords: diabetes, epidemiology, obesity, risk factors.

Introduction

Serum γ-glutamyltransferase (GGT) has been well known as a marker of alcohol-induced liver disease [1]. In addition, recent studies have demonstrated an association between serum levels of GGT within normal range and many cardiovascular disease risk factors and components of the metabolic syndrome [2–4]. Serum GGT levels rise with old age, male gender, smoking, lack of exercise, hypertension, glycaemic disorders, hypertriglyceridaemia and low high-density lipoprotein (HDL) cholesterol [2–4]. Moreover, elevated GGT is strongly associated with obesity and excess deposition of fat in the liver, termed nonalcoholic fatty liver disease, which is thought to cause hepatic insulin resistance and to contribute to the development of systemic insulin resistance and hyperinsulinaemia [5]. Thus, GGT might reflect metabolic alterations and could serve as a marker of the insulin resistance syndrome. Other studies suggested that GGT plays an important role in antioxidant systems [6, 7]. Because GGT has

a central role in glutathione homeostasis by initiating the breakdown of extracellular glutathione, a critical antioxidant defence for the cell, increases in GGT may be a marker of oxidative stress [7, 8]. It was shown that serum GGT is an independent risk factor for the development of hypertension, stroke and heart disease [9–11]. Furthermore, serum GGT showed a strong and graded relation with diabetes, which suggested a role for GGT in the pathogenesis of this disease [7, 9]. So far, several studies investigated whether raised serum GGT is an independent predictor for type 2 diabetes mellitus [3, 7, 9, 12–14]. Most of these studies included males only and were performed in specific groups of subjects such as male office workers or men working in a steel factory [3, 7, 12]. Data on the association of GGT and incident type 2 diabetes in the general population are scarce [13, 14] and to our knowledge, so far only one study in this area has included middle-aged women in addition to men [13]. Therefore, we examined serum levels of GGT in relation to risk for type 2 diabetes prospectively in a large cohort of men and women from the general population.

Materials and methods

The presented data were derived from the first population-based Monitoring Trends and Determinants on Cardiovascular Diseases (MONICA) Augsburg (southern Germany) survey conducted between October 1984 and June 1985. The MONICA Augsburg project was part of the multinational WHO MONICA project and the design of both projects has been described in detail elsewhere [15, 16]. Briefly, the cross-sectional survey was carried out in the city of Augsburg and the counties Augsburg and Aichach-Friedberg to estimate the prevalence and distribution of cardiovascular risk factors amongst men and women. Altogether 4022 persons (2023 men, 1999 women, response 79.3%) aged 25–64 years participated in the cross-sectional study. All subjects were prospectively followed within the frame of the Cooperative Research in the Region of Augsburg (KORA).

In 1987/1988, 1997/1998 and 2002/2003 vital status was assessed for all sampled persons of the first MONICA Survey through the population registries; the health status of all living persons was assessed by follow-up questionnaires. Follow-up information was available for 3923 persons. Up to 31 December 2002, 588 participants (385 men, 203 women) had died. All subjects who had died between baseline and follow-ups were also included in the analyses if follow-up information could be ascertained (see section 'Ascertainment of diabetes').

For the present analyses, we excluded persons with prevalent type 2 diabetes at baseline ($n = 115$), and subjects with other types of diabetes than type 2 diabetes ($n = 3$). Furthermore, we excluded 25 subjects, from whom no information about diabetes status at follow-up was available (22 deceased and three alive subjects), and all subjects with incomplete data on any of the covariables ($n = 93$). Finally, the prospective analyses comprised 3687 nondiabetic MONICA participants (1851 men and 1836 women) aged 25–64 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 socio-demographic variables, smoking habits, physical activity level, medication use and parental history of diabetes were gathered by trained medical staff during a standardized interview. Alcohol intake was assessed by asking all participants [1] 'How much beer, wine and spirits did you drink the previous weekend (Saturday and Sunday)' and [2] 'How much beer, wine and spirits did you drink during the previous workday (or on the previous Thursday, if Friday was the previous workday)'? Based on these questions mean alcohol intake was calculated in g day^{-1}. 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 week^{-1} in either season.

In addition, all participants underwent an extensive standardized medical examination including the collection of a nonfasting blood sample. All measurement procedures have been described elsewhere in detail [15, 16]. Hypertension was defined as blood pressure values ≥160/95 mmHg and/or use of antihypertensive medication given that the subjects were aware of being hypertensive. Dyslipidaemia was defined as the ratio of total cholesterol to high-density cholesterol ≥5.0.

Clinical chemical measurements

A nonfasting venous blood sample was obtained from all study participants whilst sitting. Total serum cholesterol analyses were carried out with an autoanalyzer 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/Mg^{2+} (Boehringer Mannheim). Serum GGT was determined by a photometric method (smac autoanalyzer, Technicon, Instruments Corporation, Tarrytown, NY, USA).

Ascertainment of diabetes

In the 1987/1988, 1997/1998 and 2002/2003 follow-up questionnaires, we inquired about the diagnosis of diabetes. All incident cases of type 2 diabetes, which had been diagnosed up to 31 December 2002 were included. Incident type 2 diabetes was identified by self-report or by intake of antidiabetic medication. Initially identified self-reported incident cases of diabetes mellitus and the self-reported date of diagnosis were validated by hospital records or by contacting the probands treating doctor. 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 doctors were contacted. The records were searched for or the doctors 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. For the present analysis in 3687 men and women, 216 of the initially 241 incident cases of type 2 diabetes identified by self-report or intake of antidiabetic medication could be confirmed. Furthermore, 65 validated cases of incident type 2 diabetes amongst the deceased men and women were included in this study.

Statistical analyses

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 1987, 1998, or 2002 follow-up questionnaire was completed. All analyses were performed separately for men and women. The chi-square test was used to test the differences in prevalences. The general linear model was used to compare mean values (*F*-test). The study population was stratified into five categories of GGT concentrations with use of cut-points of 13, 20, 35 and 56 units L^{-1} for men and 8, 10, 16 and 24 units L^{-1} for women (25th, 50th, 75th and 87.5th percentiles), respectively. Relative risks (RR) of incident type 2 diabetes were computed for category 2, 3, 4 and 5, when compared to persons with GGT values <13 (men) and <8 units L^{-1} (women) in different Cox proportional hazards models. The first model included GGT as the sole explanatory variable. The second model included GGT and in addition age (continuous). The third model included all previous factors plus education (</≥12 years), parental history of diabetes (yes/no and unknown), hypertension (yes/no), dyslipidaemia (yes/no), physical activity (active/inactive), smoking status (regular smoking that is a subject who smoked at least one cigarette per day at baseline, yes/no), alcohol intake (continuous). The fourth model included in addition to all previous factors body mass index (BMI; continuous). The above analyses were repeated by including GGT as a continuous variable. As GGT was not normally distributed, it was logarithmically transformed before inclusion in Cox proportional hazards models. Hazard ratios (HRs) were computed for an increase of 1 SD of the logarithmically transformed variable. Tests for linear trend across increasing categories of GGT were conducted by assigning the median value within each category to the respective category and by treating the categories as a continuous variable. Finally, it was assessed whether the association between obesity and incident type 2 diabetes was modified by baseline serum GGT concentration. The median serum GGT value was used as the cut-off point in this stratified analysis. Results are presented as HRs and 95% confidence interval (CI). Significance tests were two-tailed and *P*-values of <0.05 are stated as statistically significant. All analyses were performed using the STATISTICAL ANALYSIS SYSTEM (Version 8.2, SAS Institute Inc., Cary, NC, USA).

Results

In total, 172 incident cases of type 2 diabetes amongst the 1851 men and 109 amongst the 1836 women were registered in the 25–64 years old study

population between 1984 and 2002 (mean follow-up period 14.7 years). At baseline average serum GGT concentration in men was 9.7 units L^{-1} (SD = 1.9), and the average concentration in women was 5.8 units L^{-1} (SD = 1.2).

The baseline characteristics of the study sample according to serum GGT are shown in Table 1. In both sexes higher GGT levels were associated with higher prevalences of obesity, a greater frequency of hypertension and dyslipidaemia. Men and women with higher GGT showed lower prevalences of leisure time physical activity. Amongst male and female subjects, higher GGT was associated with a higher alcohol intake and more advanced age. Amongst men an increase in GGT was related to a higher prevalence of smoking.

Serum GGT showed a strong and graded relationship with incident type 2 diabetes in men and women (Table 2). After adjustment for age, hypertension, dyslipidaemia, parental history of diabetes, smoking, alcohol intake, physical activity and education the HRs in men were 2.13, 3.04, 4.47 and 5.83 for the GGT categories 2, 3, 4 and 5 when compared with persons in the first category (*P*-value for trend <0.0001). The respective HRs in women were 1.69, 1.92, 2.57 and 3.63 (*P*-value for trend 0.0005). Further adjustment for BMI attenuated the association; comparing the highest versus the lowest category of GGT the HR for incident diabetes was 4.24 (95% CI: 2.11–8.54) amongst men and 2.41 (95% CI: 1.05–5.52) amongst women. When GGT was included as a continuous variable in the Cox

Table 1 Mean (SD) and prevalence of baseline variables according to GGT values, men and women aged 25–64 years at baseline

	GGT (units L^{-1})					
Men (n = 1851)	<13 (n = 391)	13 to <20 (n = 509)	20 to <35 (n = 485)	35 to <56 (n = 229)	≥56 (n = 237)	*P*-value
Age (years)	40.9 (12.0)	45.3 (11.7)	46.4 (10.8)	46.5 (10.8)	44.9 (9.6)	<0.0001
BMI (kg m^{-2})	25.1 (3.0)	26.5 (3.3)	27.5 (3.3)	27.9 (3.4)	27.9 (3.5)	<0.0001
Obesity (BMI ≥ 30 kg m^{-2}, %)	6.1	13.2	19.6	22.7	26.2	<0.0001
Hypertension (%)[a]	11.0	14.3	19.8	27.5	31.7	<0.0001
Dyslipidaemia (%)[b]	29.4	39.1	50.1	53.3	52.3	<0.0001
Regular smoking (%)	26.1	30.7	36.5	35.8	46.4	<0.0001
Alcohol intake (g day^{-1}; %)						
0	20.5	12.8	11.3	8.3	8.0	<0.0001
0.1–39.9	56.3	53.6	42.5	38.4	25.3	
≥40.0	23.3	33.6	46.2	53.3	66.7	
Physically active (%)	48.9	47.2	41.7	38.0	37.1	0.0054
Parental history of DM (yes, %)	13.0	19.3	22.3	20.1	18.6	0.0131
Education (<12 years, %)	66.5	66.6	69.7	70.3	75.1	0.1399
Women (n = 1836)	<8 (n = 437)	8 to <10 (n = 333)	10 to <16 (n = 594)	16 to <24 (n = 237)	≥24 (n = 235)	
Age (years)	40.2 (10.5)	42.9 (10.8)	45.4 (10.9)	48.7 (10.9)	49.6 (10.0)	<0.0001
BMI (kg m^{-2})	24.1 (3.5)	25.0 (4.0)	26.4 (4.8)	27.0 (4.7)	27.6 (5.5)	<0.0001
Obesity (BMI ≥ 30 kg m^{-2}, %)	6.9	12.9	18.0	24.5	27.7	<0.0001
Hypertension (%)[a]	6.0	8.1	15.2	24.9	28.5	<0.0001
Dyslipidaemia (%)[b]	5.5	10.5	18.4	22.4	25.5	<0.0001
Regular smoking (%)	15.8	15.3	20.4	18.1	19.2	0.2346
Alcohol intake (g day^{-1}; %)						
0	40.1	39.3	35.4	38.8	37.0	<0.0001
0.1–19.9	44.4	36.6	40.9	35.0	27.7	
≥20.0	15.6	24.0	23.7	26.2	35.3	
Physically active (%)	42.3	41.7	37.9	30.0	28.5	0.0003
Parental history of DM (yes, %)	18.3	21.6	20.0	20.3	21.3	0.8154
Education (<12 years, %)	81.5	80.2	81.5	86.1	83.8	0.3871

[a]Blood pressure values ≥160/95 mmHg and/or use of antihypertensive medication given that the subjects were aware of being hypertensive.
[b]Ratio of total cholesterol to high-density cholesterol ≥5.0.
GGT, γ-glutamyltransferase; BMI, body mass index; DM, diabetes mellitus.

Table 2 Relative risks for type 2 diabetes according to GGT values amongst men and women aged 25–64 years at baseline

	GGT (units L^{-1})					
Men ($n = 1851$)	<13 ($n = 391$)	13 to <20 ($n = 509$)	20 to <35 ($n = 485$)	35 to <56 ($n = 229$)	≥56 ($n = 237$)	*P*-value for trend
Number of incident cases	11	35	51	36	39	
Person-years (PY)	5963	7438	6898	3145	3181	
Crude rate per 10 000 PY	18.4	47.1	73.9	114.5	122.6	
HR (95% CI)						
Model 1	1.0	2.58 (1.31–5.08)	4.09 (2.13–7.85)	6.38 (3.25–12.53)	6.87 (3.52–13.42)	<0.0001
Model 2	1.0	2.18 (1.11–4.30)	3.28 (1.71–6.31)	5.21 (2.65–10.25)	6.37 (3.26–12.44)	<0.0001
Model 3	1.0	2.13 (1.08–4.20)	3.04 (1.57–5.86)	4.47 (2.24–8.92)	5.83 (2.92–11.64)	<0.0001
Model 4	1.0	1.81 (0.91–3.57)	2.37 (1.22–4.60)	3.41 (1.70–6.86)	4.24 (2.11–8.54)	<0.0001
Women ($n = 1836$)	<8 ($n = 437$)	8 to <10 ($n = 333$)	10 to <16 ($n = 594$)	16 to <24 ($n = 237$)	≥24 ($n = 235$)	
Number of incident cases	8	14	32	25	30	
Person-years (PY)	7056	5169	8782	3419	3158	
Crude rate per 10 000 PY	11.3	27.1	36.4	73.1	95.0	
HR (95% CI)						
Model 1	1.0	2.41 (1.01–5.74)	3.26 (1.50–7.08)	6.62 (2.98–14.67)	8.71 (3.99–18.99)	<0.0001
Model 2	1.0	1.92 (0.80–4.60)	2.32 (1.06–5.06)	3.87 (1.72–8.71)	4.99 (2.25–11.04)	<0.0001
Model 3	1.0	1.69 (0.71–4.06)	1.92 (0.87–4.22)	2.57 (1.12–5.94)	3.63 (1.61–8.22)	0.0005
Model 4	1.0	1.42 (0.59–3.42)	1.48 (0.67–3.28)	1.95 (0.84–4.51)	2.41 (1.05–5.52)	0.0179

Model 1: crude HR; model 2: age-adjusted HR; model 3: adjusted for age, hypertension, dyslipidaemia, parental history of diabetes, regular smoking, alcohol intake, physical activity, education; model 4: adjusted for the same variables as in model 3 + BMI.
HR, hazard ratio; BMI, body mass index; GGT, γ-glutamyltransferase; CI, confidence interval.

Table 3 Obesity and relative risks of type 2 diabetes amongst men and women aged 25–64 years at baseline with serum GGT levels less than the median and equal or greater the median, respectively

	Obesity (BMI ≥ 30 kg m^{-2})			
	Men**		Women**	
	No	Yes	No	Yes
GGT (<median)*	$n = 809$	$n = 91$	$n = 697$	$n = 73$
Number of incident cases	34	12	16	6
Person-years (PY)	12 181	1220	11 200	1026
Crude rate per 10 000 PY	27.9	98.4	14.3	58.5
HR (95% CI)				
Model 1	1.0	3.64 (1.88–7.03)	1.0	4.39 (1.72–11.22)
Model 2	1.0	2.75 (1.40–5.37)	1.0	2.31 (0.85–6.26)
Model 3	1.0	2.06 (1.04–4.08)	1.0	1.44 (0.51–4.03)
GGT (≥median)*	$n = 742$	$n = 209$	$n = 836$	$n = 230$
Number of incident cases	80	46	39	48
Person-years (PY)	10 513	2711	12 448	2912
Crude rate per 10 000 PY	76.1	169.7	31.3	164.8
HR (95% CI)				
Model 1	1.0	2.27 (1.58–3.26)	1.0	5.42 (3.55–8.28)
Model 2	1.0	2.05 (1.42–2.95)	1.0	4.31 (2.81–6.63)
Model 3	1.0	1.85 (1.27–2.69)	1.0	3.08 (1.95–4.86)

Model 1: crude HR; model 2: age-adjusted HR; model 3: adjusted for age, hypertension, dyslipidaemia, parental history of diabetes, regular smoking, alcohol intake, physical activity, education.
*Median: 20 units L^{-1} (men), 10 units L^{-1} (women).
***P*-value for interaction between obesity and GGT: 0.5949 (men), 0.4912 (women).
GGT, γ-glutamyltransferase; BMI, body mass index; HR, hazard ratio; CI, confidence interval.

proportional hazards models, an increment of 1 SD of GGT was associated with a significant increase in the risk of type 2 diabetes in men (HR 1.52, 95% CI: 1.30–1.77) and in women (HR 1.23, 95% CI: 1.03–1.46) after multivariable adjustment. Table 2 describes the observed crude incidence rates of type 2 diabetes by GGT levels. In all categories of GGT, diabetes incidence was higher in men than in women and increased with increasing levels of GGT in both sexes.

To assess whether obesity increases the risk of type 2 diabetes mellitus for men and women with GGT levels below or above the median, respectively, we analysed the association between obesity (i.e. BMI ≥ 30 kg m^{-2}) and incident type 2 diabetes mellitus separately for the two groups (Table 3). Amongst persons with GGT levels below the median obese men and women were observed to have a significantly higher risk of incident type 2 diabetes compared with nonobese (men: HR 3.64, 95% CI: 1.88–7.03; women: HR 4.39, 95% CI: 1.72–11.22) in the unadjusted model. After multivariable adjustment the observed HR remained significant for obese men (HR 2.06, 95% CI: 1.04–4.08), but lost significance for obese women (HR 1.44, 95% CI: 0.51–4.03). However, amongst persons with GGT levels equal or greater than the median a significantly increased risk of diabetes was observed for both obese men (HR 1.85, 95% CI: 1.27–2.69) and obese women (HR 3.08, 95% CI: 1.95–4.86) compared with nonobese after multivariable adjustment. Formal test for interaction containing BMI and GGT as categorized variables (BMI < vs. ≥30 kg m^{-2} × GGT < vs. ≥median value), however, revealed no significant interaction in men ($P = 0.5949$) and women ($P = 0.4912$). The observed crude incidence rate for obese persons with GGT equal or greater than the median was almost identical in men (169.7/10 000 person-years) and women (164.8/10 000 person-years). However, in persons with GGT levels below the median the crude incidence rate was higher in obese men than in obese women (male/female ratio 1.7).

Discussion

In this cohort of men and women, drawn randomly from the general population, we observed a

significant positive association between serum GGT and incident type 2 mellitus diabetes in men and women. This association was independent of other predictors of type 2 diabetes, including alcohol intake and BMI. Furthermore, the effect of obesity on the risk of type 2 diabetes was apparent amongst those with low GGT (<median) and with high GGT (≥median), respectively, in both sexes. However, obesity appeared to be more strongly associated with type 2 diabetes in women with GGT equal or greater than the median compared to women with GGT below the median, whereas in men the association between obesity and type 2 diabetes was almost identical in the two groups.

So far, there are several prospective studies that examined serum GGT levels and incidence of type 2 diabetes [3, 7, 9, 12–14]. Most of these studies were limited to employed men [3, 7, 12]. In a cohort study of Japanese male office workers aged 35–59 years, elevated, although still normal, serum GGT was a significant risk factor for the risk of type 2 diabetes [3, 12]. The RR of type 2 diabetes for the top quintile versus bottom quintile was 2.44 (95% CI: 1.34–4.46) [3]. Furthermore, in a cohort of 4088 healthy men working in a steel manufacturing company, there was also a strong dose–response relationship between serum GGT concentrations at baseline and the incidence of type 2 diabetes. In comparison with the group whose GGT concentration was <9 U L^{-1}, the adjusted-RRs for incident diabetes amongst those with GGT concentrations of 10–19, 20–29, 30–39, 40–49, and over 50 U L^{-1} were 8.0, 13.3, 12.6, 19.6, and 25.8, respectively [7]. Results from the Coronary Artery Risk Development in Young Adults (CARDIA) Study suggested that serum GGT concentrations at ages 18–30 years and mostly within the reference interval predicted the development of diabetes during 15 years of follow-up in a dose–response relationship. The association was not confounded by lifestyle factors examined and did not differ materially by race or sex [9]. Perry *et al.* [14] demonstrated a strong, independent and graded association between serum GGT levels at baseline and the incidence of type 2 diabetes in a cohort of middle-aged men from the general population during a mean follow-up period of 12.8 years. The association was independent of serum glucose and BMI and of other predictors of type 2 diabetes, which are associated with GGT, including alcohol intake and physical activity level (adjusted-RR for highest versus lowest quintile: 4.8, 95% CI: 2.0–11.8). Recently, a prospective cohort study of 20 158 Finnish men and women aged 25–64 years reported a RR for diabetes incidence across GGT categories (25th, 50th, 75th and 90th percentiles) of 1.0, 1.2, 2.3, 3.1 and 3.9 amongst men and 1.0, 0.8, 1.7, 3.5 and 6.4 amongst women after adjustment for known risk factors for type 2 diabetes [13]. The findings from the present study confirm the results of prior studies suggesting that serum GGT is associated with an increase in risk of type 2 diabetes in both sexes. Furthermore, in agreement with Lee *et al.* [13] obesity appeared to be more strongly associated with type 2 diabetes in women with GGT equal to or greater than the median (≥10 units L^{-1}) in comparison to women with GGT below the median. However, contrary to other studies [7, 13] in the present study the association of obesity with the development of diabetes was slightly stronger amongst men with low normal GGT (<20 units L^{-1}) than amongst men with high normal or abnormal GGT.

Several possible mechanisms how serum GGT increases the risk of type 2 diabetes should be taken into consideration. Elevation of serum GGT could be the expression of an excess deposition of fat in the liver, termed nonalcoholic fatty liver disease [5]. Fatty liver is thought to cause hepatic insulin resistance and to contribute to the development of systemic insulin resistance and hyperinsulinaemia [5, 17]. Thus, GGT could serve as a marker of the insulin resistance syndrome in the pathogenesis of diabetes. Another possible mechanism is that GGT plays an important role in antioxidant systems. Experimental studies have reported that GGT has a central role in the maintenance of intracellular antioxidant defences through its mediation of extracellular glutathione transport into most types of cells [6]. Hence, raised GGT concentrations could be a marker of oxidative stress, which might also play a role in the cause and development of diabetes [6, 7]. Other studies suggested that elevated serum GGT could be the expression of subclinical inflammation [18, 19], which also contributes to the development of type 2 diabetes [20].

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.

Because diabetic patients have an increased risk of dying of a cardiovascular disease [21] they could also be lost by selective mortality during follow-up. Furthermore, response bias cannot be excluded in our study. Although we adjusted for a variety of confounders, in the present study no glucose data and no data on waist circumference were available. Some studies showed that waist circumference is more strongly associated with insulin resistance and that this measure predicts diabetes better than BMI [22]. Therefore, the associations observed in this study could be due to a confounding by unmeasured variables. Finally, in the present study only self-reported information on diabetes status of the subjects or use of antidiabetic medication were available. Although this information was validated with medical records, it is likely that the group of nondiabetic persons may include subjects with undetected diabetes mellitus. The strengths of the MONICA/KORA Augsburg Cohort Study are primarily its prospective design, the representativeness of the cohort, based on a random sample of the general population and the availability of data on lifestyle and multiple cardiovascular risk factors. Furthermore, in contrast to most other prospective studies of this kind in which diagnosis of diabetes was based upon self-report, diabetes diagnosis in the present study was based on doctor-validated diagnosis of type 2 diabetes.

In conclusion, the present study suggests that GGT is associated with an increased risk of type 2 diabetes in men and women from the general population. So far, the underlying pathophysiological mechanisms are not entirely clear. It seems that insulin resistance, oxidative stress and chronic low-grade systemic inflammation may be involved. Further studies are needed to investigate the biological mechanisms underlying this association.

Conflict of interest statement

No conflict of interest was declared.

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