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A BRIEF ORIGINAL CONTRIBUTION

Seven-year Longitudinal Population Study of Change in Gamma-glutamyltransferase: The Tromsø Study

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The determinants of individual changes in gamma-glutamyltransferase (GGT) were examined in 1,171 males and 1,267 females in Tromsø, Norway, according to a 7-year longitudinal design. The basis for the study was two comprehensive population surveys in 1979–1980 and 1986–1987. In both sexes, increase in GGT displayed a strong association with increase in body mass index and hours fasting. In males, increase in GGT also showed a strong association with increase in frequency of inebriation and with decrease in physical activity. In females, increased systolic blood pressure, starting to use oral contraceptives, the occurrence of menopause, and decrease in consumption of boiled coffee were associated with increase in enzyme levels. The strengths of the associations were considerably greater in this longitudinal design compared with earlier cross-sectional studies. *Am J Epidemiol* 1994;139:787–92.

alcohol drinking; blood pressure; body mass index; coffee; gamma-glutamyltransferase; lipids

Despite its well-established clinical use as an indicator of hepatobiliary diseases and drug- and alcohol-induced liver damage (1, 2), gamma-glutamyltransferase (GGT) is, in the normal population, influenced by many other factors. This was the conclusion of two cross-sectional population studies from Tromsø (3, 4). The most striking findings from these studies were a positive association with body mass index, high alcohol intake, serum lipids, numbers of hours fasting, blood pressure, heart rate, smoking, and use of analgesics, and a negative association with coffee intake and physical activity. There was a marked sex difference in GGT level, with higher values observed for males. To further explore these associations, longitudinal or experimental studies are needed.

The objective of the present study was to confirm the status of the cross-sectional determinants in a longitudinal design. Our study population consisted of the subsample of the survey population (n = 2,438) in which GGT was measured twice with a 7-year interval.

MATERIALS AND METHODS

The basis for the present study was two population surveys carried out in the municipality of Tromsø, northern Norway, in 1979–1980 and 1986–1987. The 1979–1980 survey comprised 16,621 subjects, i.e., 78 percent of the total eligible population aged 20–54 years. In these persons, GGT was measured in a random subsample of 3,233 (3). In the 1986–1987 survey, GGT was de-

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Abbreviation: GGT, gamma-glutamyltransferase.

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termined in all 21,782 subjects examined, i.e., 81 percent of the total population aged 20–62 years (4). GGT was measured in both studies in 2,438 subjects, who constituted the basis for the present analysis.

The methods and the questionnaires used in the two surveys were nearly identical and are described in detail elsewhere (5, 6). The measurement of GGT was performed by the Division of Clinical Chemistry, University Teaching Hospital of Tromsø, according to the recommendations of the Scandinavian Enzymes Committee (7). The serum samples were kept at 4°C and analyzed within 48 hours. The coefficients of variation in the two studies were 5.0 and 2.8 percent, respectively.

To explain the change in GGT between the two surveys, a multiple linear regression model was analyzed separately for each sex using the *SPSS-X User's Guide* (8). In the model, all variables were recoded to delta-variables (Δ-variables), i.e., actual individual change between the two screenings (value at study entry subtracted from that measured at follow-up).

Only the variables that were statistically significant in at least one sex in either of the two cross-sectional studies were included in the initial analyses. The model was further elaborated using backward elimination with a 5 percent level of statistical significance as the criterion for staying in the equation. The following independent Δ-variables remained in the final regression model: systolic blood pressure (mmHg), body mass index (g/cm^2), number of hours fasting ahead of the examination, physical activity at work (graded as 1, mostly sedentary; 2, a lot of walking; 3, a lot of walking and lifting; 4, heavy manual labor), frequency of inebriation, i.e., alcohol intake on one occasion corresponding to the amount in one bottle of wine (graded as 1, not last year; 2, a few times last year; 3, 1–2 times a month; 4, ≥3 times a week); cups of boiled coffee per day (graded as 1, <1; 2, 1–4; 3, 5–8; 4, ≥9); and, for females, also use of oral contraceptives (no/yes) and menopause (no/yes).

RESULTS

Table 1 gives the mean GGT with standard deviation for the different age group cohorts at study entry and at follow-up. The average increase in GGT was 22.6 and 23.1 percent for males and females, respectively. The correlation coefficients varied in males between 0.55 and 0.73. In females, the correlation coefficients were somewhat lower.

The results of the initial regression runs are given in table 2. The proportion of explained variance was small, only 9.1 and 5.1 percent for males and females, respectively.

TABLE 1. Number examined both in 1979–1980 and in 1986–1987, according to age and sex, corresponding mean gamma-glutamyltransferase (SD*) (U/liter), and simple correlations between individual measurements: The Tromsø Study, 1979–1980 and 1986–1987

Age (years) in 1979–1980	No.	1979–1980		1986–1987		Correlation coefficient
		Mean	(SD)	Mean	(SD)	
			Males			
20–29	271	17.00	(12.28)	21.00	(15.09)	0.654
30–39	481	19.01	(19.67)	23.93	(20.81)	0.553
40–49	286	19.64	(17.82)	22.35	(19.79)	0.732
50–54	133	19.49	(16.33)	25.02	(36.10)	0.711
			Females			
20–29	421	10.80	(6.65)	13.07	(10.58)	0.532
30–39	524	11.20	(9.89)	14.27	(22.28)	0.200
40–49	322	13.44	(14.86)	16.08	(13.00)	0.448
50–54						

* SD, standard deviation.

TABLE 2. Sex-specific multiple linear regression analysis of 7-year change in gamma-glutamyltransferase (U/liter) with changes between entry into study and follow-up as independent variables: The Tromsø Study, 1979–1980 and 1986–1987

Change in:	Males (n = 1,023)		Females (n = 1,086)	
	β	t	β	t
Body mass index (g/cm^2)	23.661	6.42	5.443	2.26
Triglycerides (mmol/liter)	−0.501	−1.06	0.907	1.38
Total serum cholesterol (mmol/liter)	0.643	1.05	−0.476	−0.92
High density lipoprotein cholesterol (mmol/liter)	2.271	2.00	−0.772	−0.67
Systolic blood pressure (mmHg)	0.024	0.66	0.077	2.24
Hours fasting before examination	0.155	0.22	0.493	2.32
Coffee consumption (1–4)*	−0.253	−0.46	−1.116	−0.76
Boiled coffee consumption (1–4)*	−0.549	−0.68	−1.682	−2.41
Drinking status (0, 1)†	1.174	0.46	−0.180	−0.11
Frequency of beer intake (1–5)†	−0.389	−0.72	0.049	0.10
Frequency of wine intake (1–5)†	−0.308	−0.47	0.448	0.82
Frequency of liquor intake (1–5)†	0.307	0.49	0.207	0.33
Frequency of inebriation (1–4)‡	3.000	4.64	0.231	0.42
No. of cigarettes per day	0.057	0.75	−0.022	−0.25
Physical activity at leisure (1–4)	0.852	1.46	−0.171	−0.32
Physical activity at work (1–4)	−0.595	−1.06	−0.302	−0.57
Bread consumption (no. of slices per day)	−0.810	−1.23	−0.022	−0.03
Use of analgesics (no/yes)	−0.117	−0.18	0.041	0.08
Rheumatoid arthritis (no/yes)	0.386	0.52	0.000	0.00
Use of oral contraceptives (no/yes)			4.811	3.67
Menopause occurred (no/yes)			2.100	1.86
R^2	0.091		0.051	
F	4.764		2.484	

* Coffee consumption and boiled coffee consumption are defined as cups of coffee or boiled coffee per day and are graded as 1, <1 cup/day; 2, 1–4; 3, 5–8; 4, ≥9 cups/day.

† Drinking status (0–1) is defined by answer to the question, "Are you a teetotaler?" (no/yes, or 0–1). For wine, beer, and liquor intake, the categories are: 1, never or a few times a year; 2, 1–2 times a month; 3, once a week; 4, 2–3 times a week; 5, approximately daily. Examples of "change" in alcohol intake are given below.

Example 1
Drinking category in 1986–1987: 5 (approximately daily)
Drinking category in 1979–1980: 3 (once a week)
"Change" from 1980 to 1987: 2 (increase in drinking)
Example 2
Drinking category in 1986–1987: 2 (1–2 times a month)
Drinking category in 1979–1980: 5 (approximately daily)
"Change" from 1980 to 1987: −3 (decrease in drinking)

Note: calculations of change in numbers of hours fasting and of change in numbers of cups of coffee per day were made in the same way as for change in alcohol intake.

‡ Frequency of inebriation is defined as alcohol intake on one occasion, corresponding to the amount in one bottle of wine, and is graded as 1, not last year; 2, a few times last year; 3, 1–2 times a month; 4, ≥3 times a week.

In males, increase in body mass index was by far the strongest predictor for increase in GGT, although high density lipoprotein cholesterol and frequency of inebriation also increased in association with increases in GGT level. In females, increases in body mass index, systolic blood pressure, hours fasting, and use of oral contraceptives were associated with increases in GGT, whereas boiled coffee consumption displayed a negative association.

The final regression analysis (table 3) includes only those variables that reached statistical significance in either sex after backward elimination. Included were additional subjects, 121 more men and 104 more women, reflecting missing values for some of the excluded variables. In both sexes, body mass index again was the most important determinant of change in GGT, but hours fasting also increased in association with increase in GGT. In males, GGT increased by increasing frequency of inebriation and decrease in physical activity at work. In females, increase in systolic blood pressure, decrease in boiled coffee intake,

TABLE 3. Sex-specific multiple linear regression analysis of 7-year change in gamma-glutamyltransferase (U/liter) with changes between entry into study and follow-up as independent variables*: The Tromsø Study, 1979–1980 and 1986–1987

Change in:	Males (n = 1,144)		Females (n = 1,190)	
	β	t	β	t
Body mass index (g/cm^2)	21.591	5.79	6.332	2.97
Systolic blood pressure (mmHg)	0.060	1.51	0.063	2.04
Hours fasting before examination	0.746	3.06	0.402	2.11
Boiled coffee consumption (1–4)†	−1.307	−1.48	−1.565	−2.47
Frequency of inebriation (1–4)‡	2.278	4.47	0.379	0.95
Physical activity at work (1–4)§	−2.116	−3.51	−0.321	−0.67
Use of oral contraceptives (no/yes)			5.069	4.25
Menopause occurred (no/yes)			1.942	1.97
R^2	0.078		0.058	
F	12.470		5.808	

* Only independent variables reaching significance in either sex after backward elimination are included. See table 2 for examples of "change."

† Boiled coffee consumption is defined as cups of boiled coffee per day and is graded as 1, <1 cup/day; 2, 1–4; 3, 5–8; 4, ≥9 cups/day.

‡ Frequency of inebriation is defined as alcohol intake on one occasion, corresponding to the amount in one bottle of wine, and is graded as 1, not last year; 2, a few times last year; 3, 1–2 times a month, 4, ≥3 times a week.

§ Physical activity at work is graded as 1, mostly sedentary; 2, a lot of walking; 3, a lot of walking and lifting; 4, heavy manual labor.

beginning to use oral contraceptives, and the occurrence of menopause were associated with increase in GGT.

DISCUSSION

The present longitudinal study confirmed the status of those determinants that displayed the strongest cross-sectional relations with GGT (3, 4). Changes over time in body mass index, numbers of hours fasting, frequency of inebriation, blood pressure, physical activity, boiled coffee consumption, and, in females, occurrence of menopause and beginning to use oral contraceptives were related to a marked change in GGT. The associations, measured by the size of the regression coefficients, were, however, stronger in this longitudinal perspective than in the cross-sectional studies. This was not unexpected, because analysis of change over time within the same subjects reduces possible confounding effects and it removes interpersonal variance and the effect of genetic factors.

Given this background, it is surprising that the proportion of variance explained in the longitudinal analysis, reflected by R^2, was relatively small and at best was less than half of that in each cross-sectional analysis (3, 4). This is even more remarkable, as GGT displayed a considerable intraindividual stability or strong "tracking" pattern. The probable explanation is that, in the present study, the variance caused by random errors in measurement, both of the dependent and independent variables, together with day-to-day fluctuations for some of the independent variables, increases relative to the variance caused by true changes over time.

An increase in GGT of approximately 23 percent was observed in the cohort during the 7-year period. Some of this can be ascribed to changes in the determinants of GGT, i.e., the subjects are 7 years older, have put on weight, etc. Nevertheless, an age- and sex-specific comparison of the population level indicated a laboratory drift probably caused by replacement of an autoanalyzer. An increase of fixed magnitude would not affect our analysis. A relative drift, for instance, related to baseline level of GGT, could however invalidate our findings. Therefore, in an alternative analysis, baseline level of GGT was introduced to adjust for a potential bias, but this did not affect our findings in any substantial way. An enhanced increase in high baseline subjects, caused by a relative laboratory drift, is adjusted for in such an analysis.

Some of the associations observed in the cross-sectional studies could not be verified in the present longitudinal analysis, e.g., the association with smoking, bread consumption, heart rate, hour of day for examination, physical activity at leisure, sleeplessness, and use of analgesics. A common characteristic for all these variables is that their associations with GGT were only observed in one of the cross-sectional studies or were present only in one sex. Possible explanations for this are that they have been observed by chance, that they reflect indirect associations, or that in our longitudinal model, which has a lower power due to a reduced sample size, we failed to assess changes over time with sufficient precision. This last explanation is the most likely for variables that are particularly prone to errors when measured by questionnaire.

In both sexes, change in body mass index was the single strongest determinant for change in GGT. The regression coefficients were more than twice those found in the 1986–1987 survey (4). A 10-kg increase in weight (from 80 to 90 kg) in a male with a height of 180 cm indicated an increase in GGT of 2.7 U/liter (an increase of 14.5 percent over the initial value) in the cross-sectional analysis (4), whereas in this study the increase was 6.7 U/liter (an increase of 35.6 percent). This strong effect of body mass index on GGT, which confirms previous studies (3, 4, 9), most probably reflects a causal relation.

Increase in frequency of inebriation resulted in an increase in GGT only in males. In females, none of the alcohol variables were significantly associated with change in GGT. When inebriation was removed from the regression model, the effect of change in use of liquor was strengthened, but was still nonsignificant. The surprisingly weak effect of the alcohol variables may reflect the imprecision of our alcohol questions, which may have introduced random measurement errors that overshadow the true changes in alcohol consumption.

In both cross-sectional studies (3, 4), coffee consumption was negatively associated with GGT. In the 1986–1987 survey, the effect was predominantly linked to consumption of boiled coffee. In this study, we found a corresponding significantly negative association between change in intake of boiled coffee and GGT in females, but not in males. The association between increase in intake of boiled coffee and decrease in GGT was nearly twice as strong as that found in the 1986–1987 cross-sectional study, which supports the hypothesis that boiled coffee is a determinant of GGT. It is also worthwhile to mention that a similar strong inverse relation has been observed between coffee consumption and liver cirrhosis (10).

Increased number of hours fasting was associated with increase in GGT. Two earlier studies have examined this association (11, 12), and the authors postulated that "fasting and postprandial serum showed approximately the same activity" (11) and that "the same activity was found before and after a meal" (12). Our cross-sectional studies as well as this study contradict those findings.

Despite certain differences, the consistency between the two cross-sectional studies and the present longitudinal analysis is noteworthy. Although the longitudinal associations displayed in the present analysis still do not establish proof of causal relations, we are reminded that strong and consistent cross-sectional associations often reflect true or causal relations, especially when observed in populations of the present size.

REFERENCES

1. Kristenson H, Trell E, Fex B, et al. Serum γ-glutamyltransferase: statistical distribution in a middle-aged male population and evaluation of alcohol habits in individuals with elevated levels. Prev Med 1980;9:108–19.
2. Peterson B, Trell E, Kristenson H, et al. Comparison of gamma-glutamyltransferase and other health screening tests in average middle-aged males, heavy drinkers and alcohol non-users. Scand J Clin Lab Invest 1983;43:141–9.
3. Arnesen E, Huseby NE, Brenn T, et al. The Tromsø Heart Study: distribution of, and determinants for, gamma-glutamyltransferase in a

free-living population. Scand J Clin Lab Invest 1986;46:63–70.
4. Nilssen O, Førde OH, Brenn T. The Tromsø Study: distribution and population determinants of gamma-glutamyltransferase. Am J Epidemiol 1990;132:318–26.
5. Thelle DS, Førde OH, Try K, et al. The Tromsø Heart Study: methods and main results of a cross-sectional study. Acta Med Scand 1976; 200:107–18.
6. Bjartveit K, Foss OP, Gjervig T, et al. The cardiovascular disease study in Norwegian counties. Background and organization. Acta Med Scand 1979;Suppl 634:1–70.
7. The Committee on Enzymes of the Scandinavian Society for Chemistry and Clinical Physiology. Recommended method for the determination of γ-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119–25.
8. SPSS Inc Staff. SPSS-X user's guide. 3rd ed. New York: McGraw-Hill Book Co, 1988.
9. Schiele F, Guilmin A-M, Detienne H, et al. Gamma-glutamyltransferase activity in plasma: statistical distributions, individual variations, and reference intervals. Clin Chem 1977;23:1023–8.
10. Klatsky AL, Armstrong MA. Alcohol, smoking, coffee, and cirrhosis. Am J Epidemiol 1992;136: 1248–57.
11. Goldbarg JA, Pineda EP, Smith EE, et al. A method for colorimetric determination of γ-glutamyl transpeptidase in human serum; enzymatic activity in health and disease. Gastroenterology 1963;44:127–33.
12. Szczeklik E, Orlowski M, Szewczuk A. Serum γ-glutamyl transpeptidase activity in liver disease. Gastroenterology 1961;41:353–9.