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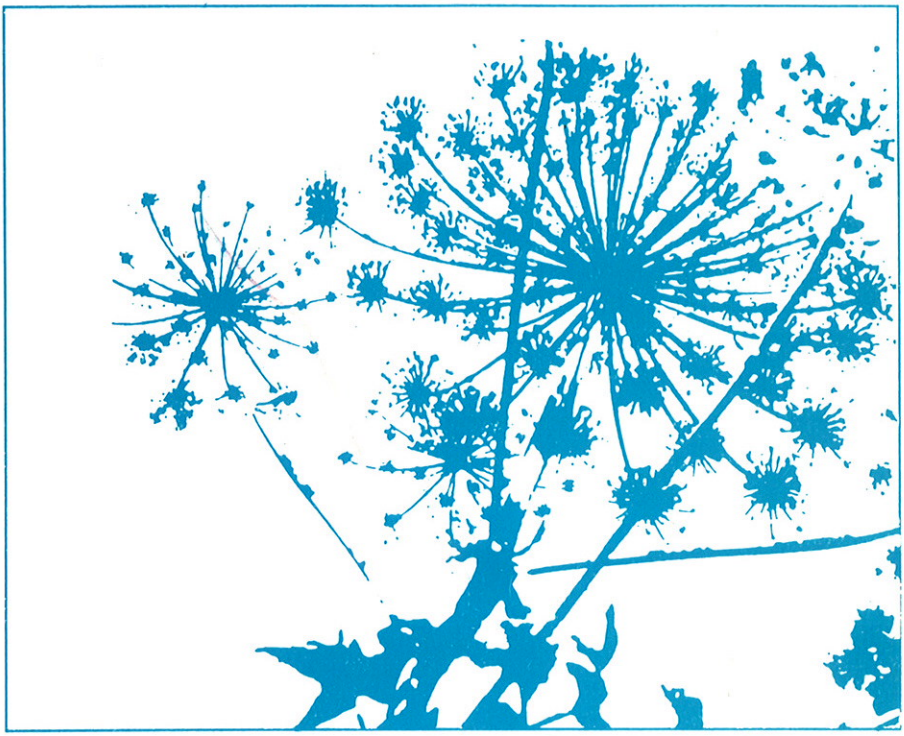

SERUM GAMMA-GLUTAMYLTRANSFERASE: POPULATION DETERMINANTS AND DIAGNOSTIC CHARACTERISTICS IN RELATION TO INTERVENTION ON RISK DRINKERS.

by
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Institute of Community Medicine

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UNIVERSITY OF TROMSØ, NORWAY

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PREFACE

The present study was carried out at the Institute of Community Medicine, University of Tromsø during the years 1987-1991. The study is based on data from three population studies: The Second (1979-1980) and Third (1986-1987) Healt Survey in the municipality of Tromsø, and the Svalbard Stud (1988-1989).
The institute of Community Medicine was responsible for all three surveys. They were carried out in co-operation with t National Health Screening Services, Oslo, and, for the Svalbard Study, also in co-operation with Longyearbyen Hospital.

In all three screenings, the participants were asked about their alcohol consumption. The answers were given in terms frequency of intake of beer, wine, liquor and frequency of inebriation. At Svalbard, the participants additionally wer asked about their actual alcohol intake (in units=15 g) the last week.

Gamma-glutamyltransferase (GGT) were measured in all subjec (except for the second health screening in Tromsø where GGT only was determined in a subsample of 3233 subjects). At Svalbard, the serum activity of mitochondrial isoenzyme of aspartate aminotransferase (mAST) and carbohydrate-deficien transferrin (CDT) were also determined.
The above mentioned questions and measurements constitute t

LISTS OF PAPERS INCLUDED

1. NILSSEN O, FØRDE OH, BRENN T. The Tromsø Study: Distribution and Population Determinants of Gamma-glutamyltransferase. Am J Epidemiol 1990;132:318-26.
2. NILSSEN O, FØRDE OH. The Tromsø Study: A Seven-year Longitudinal Population Study of Change in Gamma-glutamyltransferase. Submitted.
3. NILSSEN O, FØRDE OH. The Tromsø Study: The Positive Predictive Value of Gamma-glutamyltransferase and an Alcohol Questionnaire in the Detection of Early Stage Risk Drinkers. J Intern Med 1991;229:497-500.
4. NILSSEN O, HUSEBY NE, HØYER G, BRENN T, FØRDE OH, SCHIRMER H. New Alcohol Markers. How Useful are they in Population Studies. The Svalbard Study 1988-89. Accepted for publication in Alcoholism (NY) 1991;
5. NILSSEN O. The Tromsø Study: Identification of and a Controlled Intervention on a Population of Early Stage Ris Drinkers. Prev Med 1991;4:518-28.

Background and general objectives.

The treatment of alcoholics in the Norwegian society has mainly been organized by private institutions and religious organisations.

In their general perspective alcoholism is a moral problem, contrast to some other medical problems. Strategies for treatment of alcohol dependent individuals thereby have remained uninfluenced by the developments that has taken pla in medicine and community health (1).

In this respect a change has emerged in recent years. As alcoholism and alcohol related problems has become one of th most threatening health hazards of Western society (2), more attention has been paid to alcoholism and the consequences o alcohol consumption. Surveys have indicated that between 30 and 70 percent of hospital patients have harmful levels of alcohol intake (3,4). Further, for about one-half of those surveyed, the patient's illness is directly related to alcoh use. Scandinavian studies have estimated the proportion of alcohol-related somatic hospitalizations to be between 15 an 20 percent (5-7), and even mounting to 40 percent in psychiatric hospitals (8). Several reports have indicated a relation between alcohol consumption and primary hypertensio (9-11). In addition, and probably even more serious, the psychological and social burden and consequences of alcohol abuse are considerable.

Consequently, different aspects of alcohol abuse have become of major interest for medical researchers, and the increasing number of reports reflect a growing activity in the field.

In a WHO-report from 1987, Aasland and Saunders (12) state:

> "Alcohol-related disabilities are being seen with increasing frequency in both the developed and developing world. The health and social cost to individuals, to families and to national economies are considerable. There is widespread dissatisfaction with current treatment options. By the time persons present spontaneously to health and welfare agencies dependence is often entrenched and disability severe. The prognosis of those with advanced problems is generally unfavourable. The traditional therapeutic response to such problems has been to establish in-patient programs and yet evidence for their efficacy is lacking."

New initiatives have been called for in helping people who misuse alcohol (13). The strategy of early detection of alcohol abuse has received increased recognition and research support (14-17). The basic objective is to take action before the patient has developed major symptoms of alcohol dependence (18,19), since the prognosis is better for socially stable individuals at earlier stages of problem drinking (20).

The broad spectre of terms used to typify alcohol drinking, do

"hazardous", "excessive or "problem" drinking do not always seem to mean the same. Early stage risk drinkers are, in th study, meant to be individuals "potentially at risk of developing major symptoms of alcohol dependence". The most commonly used diagnostic systems (DSM-III-R, and ICD-9) request detailed personal information about actual drinking habits and symptoms. As no such information, for methodological reasons, could be collected in this study, early sta risk drinkers are defined as those with GGT higher than 50 U (45 U/l for females) with an alcohol intake more frequent th once a week.

The general practitioner and industrial physicians should theoretically be in a good position to intervene on patients who drink too much but who do not consider themselves as alcoholics. But first two essential questions have to be answered. The first is; how can alcohol misusers be identifi at an early stage? The second is; how, and with what presumable outcome, can intervention at early stages be carried out?

From a population perspective we have tried to focus these t questions. Firstly by scrutinizing the population determinan and diagnostic characteristics of the most generally accepte alcohol marker, gamma-glutamyltransferase. The performance o two "new" alcohol markers, carbohydrate-deficient transferri (CDT) and mitochondrial aspartate aminotransferase (mAST), h also been examined and compared with GGT. Secondly by

segment of subjects with high GGT levels.

Identification of elevated alcohol intake

Essential in the early identification of problem drinkers is the tools used for the detection. Although biological markers (21,22) constitute the most frequently used tool, also questionnaires (23-25), clinical symptoms (17,26) or combinations (27-30) of these are used. No single biological test has so far proved to have the properties necessary to separate problem drinkers from no-problem drinkers, although GGT represents the most frequently used.

The two new biological markers, CDT and mAST, have been looke upon with great expectation. Reports (31-45) have indicated that the sensitivity and specificity of these markers are close to 100 percent. On the other side, the majority of this data stems from studies on selected populations, only one study (46) has tested out mAST in an unselected population, and concluded that mAST is "not useful as a screening procedure in an unselected population".

The setting, where early identification takes place, differs from one study to another. The literature, most often, report from general practice, from in-hospital patients, or from health screening programs. Especially the setting in general practice and industrial health care, but also in hospital,

Although many of the alcohol-induced symptoms, clinical sign and abnormal laboratory findings are nonspecific, the "doctor patient situation" might legitimize further questions or tes to reach a correct diagnosis.

Screening for alcohol drinking is essentially different from most other population screenings. While population screening generally search for risk factors unknown to the participant the extent of alcohol consumption is well-known to, although not always internalized by, the participants in alcohol screenings. Further, while for instance high serum cholester and blood pressure are looked upon as harmful and unwanted, alcohol drinking is a more inherent part of our culture and self-inflicted by the individuals. This makes special demand on the tools used for identification and motivation in alcoh intervention programs.

Intervention strategies

Intervention on problem drinkers has been recommended on the assumption that intervention will be more effective at an earlier stage in the illness (47). In this respect, two studies of great importance have recently been published, The Malmö Study (48) and The Edinburgh Study (49). Through a brief, structured interview, together with simple laboratory tests, the problem drinkers were identified, and subsequently intervened on. In Malmö, the intervention group were regularl

in a letter were informed that they had an impaired liver test, and told to live as usual. In Edinburgh, the intervention group received one single counselling from a nurse with experience in treating alcoholism. The control group received no advice, but was informed that they would be interviewed again 12 months later.

Both studies demonstrated reduction in alcohol intake for both groups, but the treatment groups had a significantly better outcome than the control groups.

These two studies have shown how early identification of problem drinkers can easily be done. Further, they have demonstrated how "low time-consuming interventions" have imposed important changes in problem drinking. Most of all, they have encouraged further studies in this field.

The aim of this study

The aims of this study have been to describe and test some of the identification tools used for the detection of alcohol drinking, and, on the other hand, to demonstrate how intervention on "early state risk drinkers" could be done and with what outcome.

The most used biological alcohol marker, GGT, has been fairly well described (50-61) as a diagnostic tool in a clinical setting. As a screening instrument in the general population however, its scientific basis is far more shaky, and when it comes to other potential population determinants than alcoho

Our first aim therefore was to identify and describe other possible determinants, for GGT. Based on the third Tromsø Study (1986-87), a community-based, comprehensive health survey with more than 20,000 participants, the determinants for GGT within its normal range, have been described (paper I). To confirm the findings in this cross-sectional study, t determinants for change in GGT was explored in a seven-year longitudinal design in a subsample of 2438 individuals (pape II).

The second aim was to describe the diagnostic properties of three alcohol markers and one alcohol questionnaire, the fir one (paper III) in terms of positive predictive value (PPV), the second one (paper IV) in terms of sensitivity, specificity, PPV and likelihood-ratio (LR), with alcohol consumption, obtained through a structured interview, as "go standard".

The third and last aim was to measure and describe the effect of two short-term, low-cost, intervention procedures on a population of early stage risk drinkers, using GGT and self-reported alcohol consumption as effect measures.(paper V).

A short description of biological alcohol markers

Besides alcohol questionnaires and physical and clinical symptoms, specific biological markers are used in the

marker is GGT, although many other markers have been introduced in the literature in the last years. Two of these, CDT and mAST, have been described as "very promising".

Gamma-glutamyltransferase (GGT) catalyses the first step in a degradation of glutathione and other gamma-glutamyl compounds The highest activity is found in the kidney, but measurable levels are also found in the pancreas, epididymis, seminal vesicle, jejunum, liver and spleen (50). The liver has been identified as the main source of the serum enzyme (51,52). In clinical studies GGT is elevated in alcoholism and heavy drinking (53,54). The mechanism of this enhancement of serum GGT activity is still a matter of controversy, although microsomal enzyme induction (55-57) and liver cell damage (58 60) after alcohol intake have been suggested. GGT have therefore, in recent years, served as an indicator of both acute and chronic ethanol ingestion (61).

Carbohydrate-deficient transferrin (CDT). Human transferrin, a protein for binding and transport of human iron, is a heterogeneous glucoprotein with an isoelectric point (pI) ranging from 5.2 to 5.7. One of the isotypes of the most common transferrin genetic variant, type C, is referred to as carbohydrate-deficient transferrin (CDT) or desialylated transferrin (dTF). CDT, which contain less cyalic acid, represent a fraction of the totally circulating transferrin. It has been detected at higher levels in subjects with high alcohol intake, and such reported to be associated with high

suggested as a sensitive and specific marker of alcoholism.

Mitochondrial aspartate aminotransferase (mAST). Aspartate aminotransferase (AST) is present in human serum as two enzyme-forms, one cytoplasmic (cAST), the other mitochondria (mAST), described in this thesis as the third alcohol marker mAST is an iso-enzym of AST, and is found in almost all huma cells. It transfers aminogroups from acid- to ketoform, and increases in serum by various conditions, especially in connection with necrosis (liver cirrhosis, heart infarction, pancreas damages, ect).

Serum mAST activity is reported much higher in alcoholic hepatitis than expected judging from the total AST (tAST) activity (39). Moreover, mAST and its ratio to tAST are considered as one of the most promising new biological marke of alcoholism (40-45).

SUMMARY AND MAIN CONCLUSIONS OF THE PAPERS

The present papers are, with the exception of paper IV, base on the third Tromsø Study (1986-87). Paper II have in additio data from the second Tromsø Study (1979/80), whereas paper IV has its data from the Svalbard Study (1988/89).

The papers deal with three main topics:

1. What are the determinants of GGT, in a normal population (paper I), and how do changes in the determinants over time influence the GGT-level (paper II)?

2. The diagnostic characteristics of GGT when used for identification of alcohol risk drinkers (papers III and IV).

3. Early intervention on alcohol risk drinkers; how could it be done, and what is the effect of such intervention (paper V)?.

1. The population determinants of GGT.

The first paper describes the distribution and the determinants of GGT, in a cross-sectional study (the third Tromsø Study, 1986-87) with more than 20,000 participants. Most striking was the marked, consistent sex-difference in GGT which most probably is physiologic. In both sexes, GGT displayed a strong positive association with body mass index, alcohol use and total serum cholesterol, and a somewhat weaker positive association with serum triglycerides, HDL-cholesterol, blood pressure, heart rate, use of analgesics, and time since last meal. Strong negative associations were in both sexes found for coffee consumption, hour of the day for the examination, and, in males, physical activity. Strong

impact on GGT in females was also found for oral contraceptives, pregnancy and menopause.

To explore the status of the determinants found in the cross sectional study, the determinants for change in GGT were analyzed in a subsample of 2438 individuals, in a longitudin design (paper II). The previous findings were in general confirmed, and we concluded that within its normal range, GG has many other and even stronger determinants than alcohol consumption.

2. The diagnostic characteristics of GGT when used in screening for alcohol risk drinkers.

In a selected population of 225 individuals with elevated GG values (paper III), the positive predictive value (PPV) of GG in different combinations with a questionnaire on frequency c alcohol intake, were calculated. "True" daily alcohol consumption, obtained through a structured interview, served as our gold standard. PPV for GGT was generally disappointingly low in women, but ranged in men from .33 to .88 according to cutoff points, frequency and levels of alcohol intake. The alcohol questionnaire appeared to have an equally strong predictive power, and more predictive value appeared to be gained by increasing the questionnaire criteria than by increasing the GGT level.

One objection against GGT has been its low sensitivity and specificity. In the search for new and better alcohol markers, two biological markers, CDT (31-38) and mAST (38-45), have been described as "very promising".

The second paper (paper IV) has evaluated the diagnostic characteristics of GGT, CDT, and mAST. In an unselected population (n=481), sensitivity, specificity, PPV and likelihood-ratio (LR) were determined for different levels of alcohol intake and different cutoff levels of the tests. In males, GGT showed the best discriminatory power at higher levels of alcohol intake, with LR's up to 6.1. CDT discriminated best at lower levels (LR's up to 4.5), whereas mAST was judged not usable as a marker for alcohol intake in this unselected population. None of the tests seemed suitable in females.

Although the relation between alcohol consumption and raised serum levels of GGT have been demonstrated by numerous studies (53,54,58,62-70), its use as a diagnostic marker of alcohol abuse have certain limitations (71-73).

3. Early intervention on alcohol risk drinkers.

Paper V describes a randomized (using tables of random permutations, 74) controlled trial of two short term, low-cost intervention procedures on a population subsample of 338 subjects with elevated GGT-values (>45 and 50 U/L for women and men, respectively), and alcohol intake more frequent than

once a week. The first one, in this study designated as the "minor" intervention, consisted of a single consultation fo 15-20 minutes where the participants subsequently were aske to consider possible reasons for own elevated GGT-value.
The second one, named the "major" intervention, also starte with a 15-20 minutes consultation, but ended up with the conclusion that a "too high" alcohol consumption probably h caused the elevated GGT-level. The participants in this gro were offered monthly consultations, of 15 minutes length, w blood control until normalization of GGT.
All subjects in the intervention groups were handed a folde with general advice on changes in drinking habits.
The third group served as control group and remained "untouched" until follow-up.
At the follow-up one year later, both intervention groups showed significant decrease in GGT-level, and both groups reported to have reduced their alcohol intake with more tha 50 percent. The control group demonstrated an increase in b GGT-level and alcohol intake for the same period.

In conclusion, the applied interventions proved to be a feasible alternative in preventive alcohol programs both in primary practice and in industrial health care.

Study populations; representativity and suitability.

The attendance rates in all three screenings, Tromsø II 78 percent, Tromsø III 81 percent, and Svalbard 75 percent, were in accordance with similar studies in Norwegian counties (75 This acceptable attendance rate must be ascribed to the long experience of The National Health Screening Services' and the tradition in Norway. In fact, a fair share of the non-responders is individuals who are unable to meet at the screening because of temporary absence from their homeplace. This particularly affects the attendance rate in the younges age groups, and the somewhat lower attendance at Svalbard may to a great extent be explained by its over-representation of young men, who have the lowest attendance rate in all Norwegian population surveys.

In the Svalbard Study, which had the most translucent study population, we have no factual evidence in support of any alcohol related non-response bias. On the contrary, the local health workers, who monitored the screening, reported that th "non-responders" were evenly recruited from all social groups of the Svalbard society.

For all three study populations, the GGT-levels were in general low. Only 2.4 percent of the subsample in the second Tromsø Study had GGT-values exceeding our upper reference

limit (50 U/l for males and 45 U/l for females). The corresponding values for the Tromsø-III and the Svalbard population were 3.7 percent and 5.9 percent, respectively. T portion of subjects with elevated GGT in an international perspective were low (48,49), and even in discrepancy with a estimated prevalence (76) of about 10 percent problem drinke in the Norwegian society. The low sensitivity of GGT (77,78) may to some degree explain this last difference, but the possibility can, on the other hand, not be excluded that the non-response in the Tromsø studies to some extent may have reduced the number of subjects with high GGT levels, as there in other studies have been observed an over-representation of problem drinkers among the "non-responders" (79-81). In a paper from Jacobsen and Thelle (82), the responders and the non-responders to the second Tromsø Study were compared on a variety of background and lifestyle factors.They concluded that there were no substantial differences between the two populations. The findings of Tverdal (83) in a study from the cardiovascular disease screenings in Norwegian counties, that non-responders have a six times increased rate of death from liver cirrhosis, however, indicates that at least heavy drinkers and alcoholics are in overweight among non-responders.

In more than one aspect the Svalbard population differs from the general Norwegian population. The Svalbard population is younger (no one are allowed to stay there after they have reached retirement), and females only account for 35 percent

of the total population. In addition to a high "tax-free" consumption and the typical Scandinavian drinking pattern (heavy consumption at each occasion, but seldom) (84), the inhabitants also seemingly have adapted a "continental" drinking pattern (i.e daily intake, small amount). Further, subjects with alcohol problems to an extent that affects the individual's work, are sent back to the Norwegian mainland. Despite its peculiarities, the Svalbard population should be well suited for evaluating the diagnostic characteristics of the alcohol markers.

With exception for the Norwegians living at Svalbard, the average alcohol consumption in the Norwegian population is lo compared with most other European countries (85). This is probably also one of the main reasons for the low GGT level compared with other studies. It might therefore be argued tha our findings are not representative in an international perspective.

On the other side, the low prevalence of non-alcohol induced liver diseases in Norway (86) makes our populations especiall suitable for the study of determinants for GGT.

Our relatively low number of misusers has obviously reduced the eligible population for the intervention study (paper III and paper V). Our "target group", however, was the socially well-integrated risk drinkers, and subjects with known alcoho dependence and high GGT levels were excluded before intervention.

All in all, our study populations seems representative and

well suited for the objective, although findings on determinants of a physiologic measure, diagnostic characteristics, and effect and acceptability of preventive intervention nearly always will vary among populations.

The determinants of Gamma-glutamyltransferase.

The problems of causal inference

The "determinant" concept does not necessarily imply any causal relationship. It is merely a description of a consistent association between a factor, variable or attribute, and a physical measure. The strength, consistenc and plausibility of the association may indicate the probability that the association reflects a causal relationship.

It is well known that the associations displayed in multiple regression analyses in cross-sectional studies may well be t result of relation and confounding. Although confirmed in a longitudinal design, most of the observed determinants only reach the level of being candidates for hypotheses and furth studies preferrably with an experimental design.

Two of the relationships, however, emerge as strong candidat for causal relationships: the association with gender and relative weight. The gender-association can hardly be confirmed in an experimental design, but further studies on

the relationship with hormonal status, menopause and substitutional hormone treatment seem justified. Whatever this may bring, it seems improper to keep the same "normal" or reference values for GGT for the two sexes. Also, the relationship to body mass index was strong and consistent in both the cross-sectional and the longitudinal analysis. Here, an experimental confirmation appears feasible for instance by monitoring GGT in weight reduction programs. Still, we believe the observed association reflects physiologic mechanisms, and the concomitant association to cholesterol, although disappearing in the longitudinal analysis, and coffee consumption, suggest a link to the lipid metabolism.

Gamma-glutamyltransferase as a marker of alcohol risk consumption.

The effectiveness of a test, expressing its ability to discriminate between subjects with and subjects without a given state or given disease, most commonly is given in terms of sensitivity and specificity. Other parameters used are likelihood-ratio, positive and negative predictive value, validity score and accuracy score.

All these measures require a "gold-standard" to compare a tests performance with. When evaluating alcohol markers, no

ideal and generally accepted gold-standard exists. We have chosen, as many others (24,27,28,32,35,44,46,87), a standardized interview or alcohol questionnaire on average amount of alcohol consumed.

The main methodological fallacy with this gold standard is under-reporting or denial (88,89). The report bias tends to reduce the estimates of specificity. On the other hand, the sensitivity figures will be overestimated since the true number of high consumers is greater than the gold standard denotes. This means that the often crucial, and in the pres study disappointingly low sensitivities, probably is even lower.The effect of this bias on the likelihood-ratios is generally smaller, and depends on the relative size of its effect in sensitivity and specificity and can not be predic without assessment of the un-obtainable true consumption.

Comparing the positive predictive values of GGT in Tromsø (paper III) and Svalbard (paper IV), reveals higher values Tromsø, which hardly could be expected since this populatio has a lower prevalence of high consumers. The explanation probably lies in the two different gold standards, an interview and a self-administered questionnaire, where the assessments of the interviews come closer to the true consumption than the questionnaire.

The relatively low sensitivity of GGT as a marker of even higher levels of alcohol consumption, may seemingly undermin

its position as an efficient screening tool. In any screening GGT would pick out only a minority of the high consumers. On the other hand, however, in most community surveys the false positives is a greater concern, both because of the work load and for the fear of stigmatisation. Handled with care, knowing that a normal GGT is no assurance of a low risk consumption, it still may be an applicable screening tool.

One may question the rationale behind the use of a biologic screening test that probably is no better than the traditional clinical history, standardized interview or questionnaire. Its strength, however, lies in its motivational abilities in prevention programs aiming at behavioral changes as shown in the intervention trial (paper V). Combination of biological test and clinical history, however, is better than either alone.

The search for other and better biologic alcohol markers is therefor appropriate, but so far no real alternative has appeared. mAST seems useless in a population setting, and CDT displays the same weaknesses as GGT although it may have some advantages in marking subjects with lower consumption. The combination of GGT and CDT also seems to have limited benefit, although the tests appear independent. If any association appeared in the present study, it was a negative association, i.e. the sensitivity of CDT was higher in "positives" with negative GGT, and vice versa. This may indicate that some subjects respond on an elevated alcohol

consumption with an elevated CDT others with increase in GG
The response may be constitutionally determined.

Anyhow, the refinement of the present alcohol markers is required, especially since none of the existing seems usefu in women. It is tempting to suggest, in line with findings from the studies on determinants (paper I and II), that the genders differ both with respect to basic GGT level and GGT response on alcohol intake (90-92).

Intervention on alcohol risk consumers.

The randomized controlled intervention study (paper V) show that it is possible, with a minimal use of resources, to reduce the alcohol intake in a population segment with high GGT. The intervention aimed at a group of early risk drinke and the impression from the consultations was that this was socially well integrated population with a high motivation behavioral change.

The attendance and compliance in the study were impressive. Our explanation for this is first and foremost the constitution of the target group. Thereafter, the setting o the trial as a part of a general health survey with close links to the health care system in Tromsø. This may have increased the acceptability and reduced the potential

stigmatization effect of the participants.

The way the consultations were carried out, the arrangement and the open "climate", turned out to be highly acceptable, without a single incident with an offended participant leavi in a fury. This came as a surprise even to us.
This must be viewed in the light of the way the participants were presented with their problem, in essence: "Your liver has, with an early and not dangerous sign, reacted to something, possibly to alcohol intake. This does not mean tha you drink more than others, but may reflect a higher susceptibility of your liver". Avoidance of any form of moralization were emphasized, and the practical implications in terms of decisions on changes in drinking behaviour, were the responsibility of the individual.

The acceptability of the intervention was also confirmed by the way the participants, sometimes with great personal effort, kept the appointments, by their eagerness to keep up the contact after the trial, and by their recommendation to friends and family outside the trial.

We are, however, well aware of the general popularity of programs that intend to supervise people's health with medica diagnostics. Despite the popularity of these programs, increasing concern is felt about their "hidden" side-effects in terms of increased anxiety, illness preoccupation, test dependency and medicalization.

Any preventive high risk strategy must anticipate such side-effects, and we have no reason to believe that they are avoided in the trial. Still, in light of the sensitivity of the topic, we believe that the damage done has been modest.

One might speculate if the risk of side-effects could have been additionally reduced by decreasing the focus on GGT. Th must be considered when the practical implications are drawn and in individual counselling. If it would be possible to induce life-style changes without testing, this might be preferrable. Our experience, however, is that the elevated G value was a great help in the de-sensitivitation of the situation and in avoiding moralization. In addition it was f many of the participants of great motivational importance. In the trial, the monitoring of the GGT values was of fundamental importance as documentation of intervention effect. Without backing in decreased GGT levels, the reporte reduction in alcohol intake could have been written off as a report bias, reflecting an "eager to please" effect.

As it stands, it documents that it is possible, even with us of less resources than in the Edinburgh and Malmö studies (48,49), to reduce risk drinking. The comparation of the two intervention procedures also indicates that a strategy which almost totally leaves the responsibility to the individual, as effective as a somewhat more longterm follow-up with testing. This is encouraging in light of the concern with side-effects of intervention, and should trigger an even over

loaded primary health care to use the experiences from the trial and take their responsibility on risk drinking as a health problem seriously.

A long-time follow-up of the groups would of course be of greate importance. As the control-group also was included in the one-year follow-up, one have to find other methods for evaluation. Several end-points seem actual in this connection, for instance hospitalization, sickness- or disability allowance, and death rate. Such follow-up are already planned.

FINAL REMARKS

The population perspective has obvious advantages, but also some weaknesses. The weaknesses are primarily associated with the study design, including the practical organization beside the established health services. Some of the conclusions may therefor indicate solutions somewhat "distanced" from the existing health services.

On the other hand, the same perspective contains indisputable scientific benefits. It has enabled us to document the sex difference of GGT, which might led to changes in the actual laboratory reference values of GGT.

It has also been possible, through this perspective, to document the diagnostic characteristics of GGT and the two ne biological alcohol markers (CDT and mAST), a documentation which indicate the need for further search after new and better alcohol markers.

We also hope to have demonstrated the possibility for intervention, by simple means, on individuals with an alcohol risk consumption. We therefor allow us to express a modest hope that we, through this study, may have inspired other researchers for further work on this field, a field where Norwegian colleagues not have been heavy represented.

APPENDIX.

10 POINTS OF ADVICE CONCERNING THE USE OF ALCOHOL*

1. Register how much alcohol you drink over a period, e.g. 2 weeks. Calculate the average per day. Remember that "home-made" drinks are normally larger than "bardrinks".

2. If you are a **man**, try reducing to 30 g per day (or less). If you are a **woman**, try reducing to 15 g per day (or less)

3. Plan your drinking. decide ahead of time **when** and **how much** you will drink.

4. Leave off drinking for two days running. "**A hair of the dog**" is often the quick way to alcohol dependency.

5. If you drink liquor, mix your drinks with wather (soda- or mineral water). Put your glas down between each sip. By taking non-alcoholic drinks (e.g soda water) between each drink, you can reduce your alcohol intake.

6. If you feel you drink too much, it may help if you change your drinking situations (drink with other people, other places, other times, openly instead of secretly), or type of drink (from liquor to beer or wine, from beer to light beer).

7. Never use alcohol as medicine. Alcohol is a **very bad** nerv medicine, a **very bad** sleeping drug, and is absolutely useless as a "problem solving medicine"

8. Alcohol is best used when you are in a good mood. Avoid alcohol when you are low. Alcohol often increases the moo you are in when you start drinking.

9. If you think you drink too much, see your doctor and ask have your liver checked with the bloodtest GAMMA-GT.

10. See that you have an alternative to alcohol in the house Many people appreciate a cup of coffee or tea, or a fizz non-alcoholic drink instead of alcohol. Try yourself too "You will never regret the drink you did not take".

* From the pamphlet given to the participants in the intervention trial.

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PAPER I

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THE TROMSØ STUDY

DISTRIBUTION AND POPULATION DETERMINANTS OF GAMMA-GLUTAMYLTRANSFERASE

ODD NILSSEN, OLAV HELGE FØRDE, AND TORMOD BRENN

Nilssen, O. (Inst. of Community Medicine, U. of Tromsø, N-9000 Tromsø, Norway), O. H. Førde, and T. Brenn. The Tromsø Study: distribution and population determinants of gamma-glutamyltransferase. *Am J Epidemiol* 1990;132:318–26.

Gamma-glutamyltransferase was measured in 10,942 males aged 12–62 years and 10,840 females aged 12–59 years screened in a health survey program. The distribution was right-skewed, with medians of 17 and 12 units/liter for males and females, respectively. Fewer than 5.5% of the males and 1.5% of the females had values exceeding 50 units/liter, reflecting the modest use of alcohol in Norway. In sex-specific multiple regression analyses, gamma-glutamyltransferase showed a strong positive association with body mass index, alcohol use, and total serum cholesterol and a somewhat weaker positive association with serum triglycerides, high density lipoprotein cholesterol, heart rate, blood pressure, use of analgesics, and time since last meal. Strong negative associations were found for coffee consumption, hour of the day at which the examination was performed and, in males, physical activity. In females, use of oral contraceptives and menopause were positively associated with gamma-glutamyltransferase, whereas pregnant females had lower values. In conclusion, the gamma-glutamyltransferase level in the Tromsø population was low, with marked and consistent sex differences which probably are physiologic. Within its normal range, gamma-glutamyltransferase has many other, even stronger determinants than alcohol consumption.

alcohol drinking; blood pressure; body weight; coffee; gamma-glutamyltransferase; health surveys; lipids; smoking

In Norway and in many other occidental countries, gamma-glutamyltransferase (GGT) has been used as the best single marker of alcohol intake (1–8). Several studies dealing with this topic (9–14) have evaluated the use of GGT in identifying high-risk alcohol consumers, described the association between drinking habits and GGT, and considered GGT a beneficial tool in monitoring treatment of heavy drinkers. Others (15–19) have associated GGT with stroke, hepatobiliary diseases, and premature death, using GGT as an indicator of alcohol consumption.

In spite of the wide use of GGT in clinical practice, knowledge concerning the distribution and the determinants of this risk factor in the normal population is sparse.

The Second Tromsø Study, conducted in 1979–1980, examined the distribution of

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Abbreviations: GGT, gamma-glutamyltransferase; HDL cholesterol, high density lipoprotein cholesterol.

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nants in a subsample of 3,233 subjects screened for coronary risk factors (20).

The Third Tromsø Study, carried out in 1986–1987, gave us the opportunity to study the population distribution of GGT as well as its relation with a wide variety of possible determinants in a total population of more than 20,000 middle-aged males and females.

Materials and methods

The total population of males aged 20–62 and females aged 20–59 in the municipality of Tromsø was invited to participate in the Third Tromsø Study. In addition, a sample of males and females aged 12–19 was invited. The total number examined was 21,782, 81.3 percent of the eligible population.

The examination included a questionnaire identical with that used in the two previous studies in Tromsø (20, 21) and in the cardiovascular studies in Norwegian counties (22). In addition, a second questionnaire, given to subjects at the end of the examination, was to be returned by mail. Altogether 20,025 (92 percent) participants returned this questionnaire on education, previous and present diseases, dietary habits, alcohol, use of drugs, and mental and sleeping problems. For females, some items on menstruation and contraception were also included.

The physical examination comprised collection of venous nonfasting blood samples for measurements of serum lipids and GGT; measurement of weight, height, and blood pressure; and a one-channel electrocardiogram. Systolic and diastolic blood pressures were recorded with an automatic device (DINAMAP R, Critikon, Tampa, Florida) and measured three times at intervals of 2 minutes on the right upper arm while the subject was in a sitting position. Total serum cholesterol was measured directly by the enzymatic oxidase method using a commercial kit (Boehringer Mannheim, Mannheim, Federal Republic of Ger-

(HDL cholesterol) was assayed by the s
procedure after precipitation with hep
and manganese chloride. Triglycerides w
enzymatically determined as glyc
(Boehringer Mannheim). The meas
ments of GGT were performed at 3
according to the recommendations of
Scandinavian Enzymes Committee (
The serum samples were kept at 4°C
analyzed within 48 hours. The coeffici
of variation was 2.8 percent for a comm
cial control serum (Precinorm, Boehrin
Mannheim) during the study period.

All laboratory assessments were p
formed by the Division of Clinical Che
istry, University Teaching Hospital
Tromsø.

Multiple regression analyses were p
formed separately for each sex using
Statistical Package for the Social Scien
(24). Since the distribution of GGT
skewed to the right, all GGT values w
logarithmically transformed and hence
placed by $\log_{10}$ (GGT) when used as
dependent variable.

Initial regression procedures were
complished by introducing the independ
variables in subsets, i.e., blocks compris
demographic variables, alcohol consun
tion, other life-style variables (coffee a
tobacco consumption), medication, sym
toms, and physical measurements (ser
lipids, blood pressure, body mass, and he
rate). When introduced as first block,
association was not adjusted for other va
ables, but when introduced as last block
was adjusted for all other variables. T
blocks were tested independently of ea
other, and the analyses were done w
forced forward entry and backward elir
nation using a 5 percent level of sign
cance as criterion.

The following independent variables
mained in the regression model in one
both of the sexes: teetotaler (no/yes), be
and liquor consumption (graded as 1, nev
or a few times a year; 2, 1 to 2 times
month; 3, once a week; 4, 2 to 3 times

quency of 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 to 2 times a month; 4, three or more times a week), daily smoking (no/yes), cups of coffee per day (graded as 1, less than 1; 2, 1–4; 3, 5–8; or 4, eight or more), boiled, filter, and instant coffee (no/yes), use of analgesics during the last 2 weeks (no/yes), bothered by sleeplessness (no/yes), suffering from headache (graded as 1, seldom or never; 2, one time or more per month; 3, one time or more per week; or 4, daily), hour of day of the examination (8 a.m. to 9 p.m.), time since last meal (in hours), age (in 5-year age groups), physical activity at work (graded as 1, mostly sedentary; 2, a lot of walking; 3, a lot of walking and lifting, or 4, heavy manual labor), leisure time physical activity (graded as 1, seldom or never; 2, weekly; 3, several times per week; or 4, daily), total and HDL cholesterol (mmol/liter), triglycerides (mmol/liter), body mass index (g/cm^2), systolic pressure (mmHg), and heart rate (frequency/minute). For women, use of oral contraceptives (no/yes), current pregnancy (no/yes), and menopause (no/yes) were also included. These variables were included in the final standard multiple regression analyses.

Multiple classification analysis was performed in order to display the association between each independent variable and GGT adjusted for other variables (24).

Results

Table 1 shows the percentile distributions and some descriptive measures of GGT for each sex. That some individuals had high GGT values was demonstrated by the positive coefficients of skewness. The medians varied with age from 11 to 19 in males and from 9 to 13 in females. The means and standard deviations increased by age in males up to age 50–54 years followed by a decrease, while in women the increase was almost linear for all ages.

The skewness and kurtosis values in table 2 show that the logarithmically transformed GGT had a shape close to the normal distribution. In addition to the variables displayed in table 2, the following variables did not reach the level of statistical significance ($p > 0.05$) in either sex in our initial analyses and were subsequently not considered: marital state; daily breakfast; wine consumption; indicators of salt

TABLE 1

Percentiles and some descriptive measures of gamma-glutamyltransferase (units/liter) by sex and age, Tromsø, Norway, 1986–1987

Percentiles	Age groups (years)											
	Males											
	12–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–62	12–62
2.5	3	4	6	6	6	7	8	6	8	6	7	6
5.0	4	6	8	8	8	8	9	8	9	8	9	8
10.0	7	8	9	9	9	10	11	11	11	11	11	10
25.0	9	11	12	13	13	13	14	14	14	13	14	13
50.0	11	13	15	16	17	18	18	19	18	18	18	17
75.0	14	16	21	22	23	25	28	29	28	28	27	24
90.0	17	21	29	33	37	39	43	45	45	43	39	38
95.0	20	26	34	44	49	55	60	66	60	65	55	52
97.5	21	37	42	58	68	74	83	94	91	97	78	70
99.0	44	48	56	84	99	101	109	126	136	175	195	103
No.	179	367	1,158	1,313	1,578	1,708	1,485	1,074	891	835	354	10,942
Mean	11.8	14.3	17.9	19.9	21.2	22.8	24.5	26.1	27.1	25.7	24.8	22.4
Standard deviation	5.3	7.3	11.8	15.5	17.8	22.8	21.4	30.4	47.4	27.8	28.6	24.6

intake; use of vegetables; low back pain; neck pain; mental depression; coping problems; sickness, disability, or unemployment allowances; and use of the antihypertensives, hypnotics, heart medication, antipyretics, migraine drugs, antiepileptics, tranquilizers, antiallergica, and eczema ointment.

In the final regression analysis, displayed in table 2, the independent variables explained 23.4 percent of the total variance in males and 12.5 percent in females. The lower number for explained variance in females may to some extent reflect a possible low analytical precision by measurements at low levels of GGT.

In both sexes, body mass index, serum lipids, heart rate, blood pressure, time since last meal, sleeplessness, headache, and use of analgesics were positively associated ($p < 0.05$) with GGT. Both the frequency of one-occasion intake of alcohol corresponding to one bottle of wine and use of beer raised the GGT level in both sexes, whereas being a teetotaler was associated with a lower GGT level. Use of liquor reached statistically positive significance only in males.

The number of cups of coffee per day, the hour of day of examination, and physical activity at leisure and at work (in males) showed a strong negative association with GGT. With the methods of br ing taken into consideration, the asso tion of coffee with GGT was predominar linked to the intake of boiled cof whereas the two other coffee types (fi and instant) displayed a positive asso tion with GGT.

In women, use of oral contraceptives menopause also showed a positive asso tion, whereas pregnant women displaye lower GGT level.

The different subsets of variables c tributed, when introduced are as first bl and last block (in parentheses) in ma and females, respectively, as follows: al hol consumption, 20(12) and 10(8) perce other life-style variables, 5(6) and 13(percent; physical measurements, 63(and 37(28) percent; and demographic va ables, 22(3) and 18(3) percent. The sub of variables specific for women contribut 28 percent as first block and 13 percent last block. Figure 1 displays sex-speci means of GGT for each category or p centile for some of the strongest deter nants. The means were mutually adjust for all other determinants in the figure analysis of covariance (multiple classifi tion analysis) (24). In addition, all mea are adjusted for age, time since the l meal, hour of day of the examination, a heart rate.

TABLE 1—*Continued*

Age groups (years)										
Females										
12–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	12–59
3	4	4	4	4	4	4	5	5	5	4
4	6	5	5	5	6	6	6	7	8	6
6	7	7	7	7	7	7	8	8	9	7
8	8	9	8	8	9	9	9	10	11	9
9	11	12	11	11	12	12	12	13	13	12
11	14	15	14	14	14	15	16	18	18	15
13	18	20	18	19	19	20	23	27	28	20
16	22	25	23	25	25	29	32	45	43	27
18	27	34	29	34	34	43	55	60	61	38
24	34	45	41	51	57	67	74	90	92	63
193	389	1,299	1,568	1,845	1,678	1,524	1,058	871	381	10,840
9.6	12.0	13.2	12.3	13.1	13.5	14.3	15.0	17.1	18.3	13.8
3.8	5.8	8.4	7.0	11.4	14.6	18.0	13.8	17.7	23.5	13.6

TABLE 2

Regression coefficients (b) with t values (t) in multiple regression analysis of transformed gamma-glutamyltransferase with a dependent variable of $\log_{10}$ (gamma-glutamyltransferase), Tromsø, Norway, 1986–1987

	Males (n = 9,943)*		Females (n = 9,830)†	
	b	t	b	t
Body mass index	0.1901	22.32	0.0809	12.07
Serum lipids				
Total cholesterol	0.0285	12.76	0.0092	4.14
HDL cholesterol	0.0402	5.37	0.0157	2.53
Triglycerides	0.0158	5.78	0.0156	3.95
Hour of day of the examination	−0.0115	−11.41	−0.0079	−8.96
Coffee (cups/day)	−0.0308	−9.88	−0.0253	−8.22
Boiled	−0.0171	−2.84	−0.0262	−4.63
Filter	0.0282	5.03	0.0294	5.28
Instant	0.0189	2.09	0.0235	2.65
Heart rate	0.0014	7.83	0.0004	2.22
Physical activity at work	−0.0182	−7.75	−0.0042	−1.50
Systolic blood pressure	0.0012	6.90	0.0010	6.18
Time since last meal	0.0069	6.50	0.0054	4.98
Frequency of alcohol use				
Beer	0.0162	6.00	0.0114	4.03
Liquor	0.0201	6.38	0.0055	1.60
Intake corresponding to 1 bottle of wine	0.0233	6.58	0.0206	6.37
Teetotaler	−0.0441	−5.31	−0.0341	−4.54
Leisure time physical activity	−0.0151	−5.07	−0.0064	−1.91
Use of analgesics	0.0184	5.02	0.0147	4.59
Sleeplessness	0.0207	4.74	0.0096	2.46
Headaches	0.0093	2.72	0.0122	4.52
Age (group)	0.0016	1.32	0.0084	5.76
Daily smoking	−0.0060	−1.16	0.0224	4.68
Use of oral contraceptive			0.0561	7.70
Current pregnancy			−0.1158	−9.16
Menopause started			0.0248	3.45

* Mean, 1.258; standard deviation, 0.258; skewness, 0.562; kurtosis, 2.553; R^2, 0.234.

† Mean, 1.073; standard deviation, 0.219; skewness, 0.608; kurtosis, 4.281; R^2, 0.125.

For coffee consumption, only subjects predominantly drinking a particular type of coffee were included: for boiled coffee, 6,568 and 6,557 males and females, respectively, and for filter coffee, 3,513 and 2,832, respectively. As seen in figure 1, the negative association was stronger for boiled coffee than for filter coffee in both sexes. In men, the negative association seemed to level out in the highest consumption groups.

The alcohol variables showed a modest and almost linear increase up to the most frequent drinkers, for whom the increase also seen for body mass index in females. In males, on the other hand, the positive association seemed to cover the whole range of body mass, although it was steeper in the higher percentiles.

A somewhat weaker, but positive association was found between GGT and total cholesterol. In the same way as demonstrated for body mass index, the relation was stronger in males than in females, but was almost linear in both sexes. A similar pattern was observed for systolic pressure.

DISCUSSION

GGT has been widely used in connection

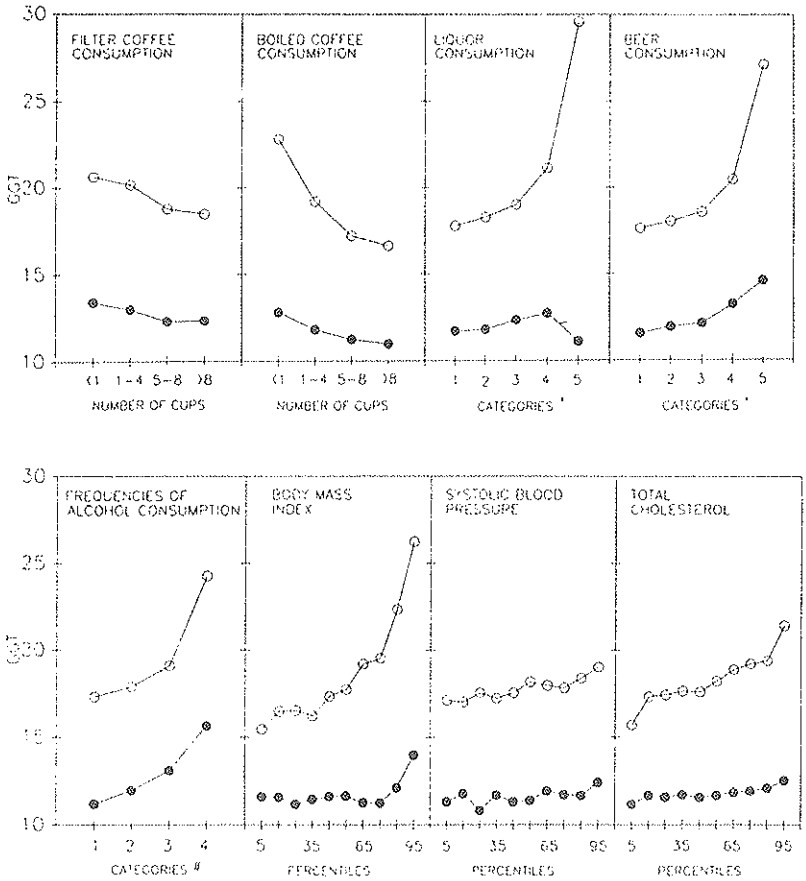

FIGURE 1. Mean values of gamma-glutamyltransferase, mutually adjusted by analysis of covariance fo other variables in the figure and for age, time since last meal, hour of the day of the examination, and rate, according to the level of some of the strongest determinants. Liquor and beer consumption categori never or a few times a year; 2, 1–2 times a month; 3, once a week; 4, 2–3 times a week; 5, about daily. Freque of alcohol consumption categories: 1, not last year; 2, a few times last year; 3, 1–2 times a month; 4, thr more times a week. O, male; ●, female.

drinkers. In this setting, it is crucial to be aware of other possible determinants which can influence GGT over time. To our knowledge, no other study of comparable size has explored the relation between GGT and a broad spectrum of demographic, physical, and life-style variables in a representative normal population. The size of the data set also allowed a separate analysis of teetotalers which revealed an impact as strong and even stronger of these determinants.

Since the study took place over a period of 9 months (August 1986 to April 1987) one might expect our findings to be so what biased by seasonal and geograp variations. Separate analyses of seas and weekday variations were perfor and the most consistent finding wa higher GGT level in both sexes in Dec ber. This probably reflects life-s changes, including an increased alc consumption during this month. Adj ment for these possible confounders weekday variation did not, however, a any of our conclusions.

The sex difference in GGT level i accordance with other studies (25).

determinants and is most likely physiologic. Use of oral contraceptives increased the GGT level by 15 percent and pregnancy lowered the GGT level by 25 percent, whereas postmenopausal state was associated with a 7 percent increase. These significant effects may suggest an association between hormonal state and GGT.

A noticeable increase of approximately 10 percent in the GGT levels was observed when we compared our results with the findings of the Second Tromsø Study (20). This increase seems uniform with regard to age and sex, which may point toward a change at laboratory level, although the methods used in the two studies were basically the same. The distribution of the present study, however, was noticeably more right-skewed, with a marked increase in the number of high values. This may indicate change in one or more of the strong determinants of GGT. Correspondingly, an increase in the frequency of alcohol intake both for beer and wine was observed between the surveys, together with a reduction in coffee consumption.

Irrespective of the observed increase, the levels of GGT were still low in this population. This may reflect the fact that the alcohol consumption and the prevalence of hepatobiliary diseases in Norway are low compared with other occidental countries (26). To what extent this reduces the generalizability of our findings is difficult to predict. It probably affects the relative impact of alcohol and diseases as predictors rather than the association with other variables.

As expected, the use of alcohol was an important predictor for elevated GGT in both sexes (1–3). Although highly intercorrelated, each of our alcohol variables contained separate information about the use of alcohol. However, only use of beer and the frequency of high one-occasion alcohol intake together with being a teetotaler were significantly associated in both sexes. Use of wine displayed a positive association in icant. This may reflect the lack of a wine-drinking tradition, with a low intake in our population. Correspondingly, the low liquor intake in females yielded nonsignificance, whereas liquor use in males was a strong predictor of GGT. Of the total variance explained, the alcohol variables contributed about 20 and 10 percent in males and females, respectively.

Several recent reports (27–29) have suggested an association between high alcohol consumption and primary hypertension. In our study, increasing GGT was associated with increasing blood pressure and heart rate. On the other hand, blood pressure and heart rate, as well as body mass index, showed the same or stronger independent association with GGT in teetotalers (data not shown). These associations, therefore, seemed not to be mediated through alcohol consumption in our study.

The strong impact of coffee drinking on GGT was the most unexpected finding, although indicated in the Second Tromsø Study (20). The regression coefficients displayed that nine or more cups of coffee a day compared with one or less cup a day gave 19.4 percent lower GGT for males and 16.6 percent lower for females. The strong negative correlation, predominantly linked to boiled coffee, suggests an important influence of the brewing method, as was observed in the association between coffee consumption and serum cholesterol (30, 31). When the amount of coffee consumed was excluded from the regression model, the explanatory value of boiled coffee more than doubled, whereas the two other types of coffee (filter and instant) were of reduced importance and did not reach the conventional level of statistical significance.

Body mass index was the single most important determinant of GGT in both sexes in this study. The impact of body mass has also been shown in other studies (20, 32), but to our knowledge, no biological mechanism has been suggested. Its association pattern was almost similar to that for

centiles. This may point in the direction of a link between GGT and the lipid metabolism. That there is a positive association between coffee consumption, again mainly boiled coffee, and serum cholesterol, together with the opposite effect of both on GGT, may suggest a competitive mechanism connected to liver/lipid metabolism. Special attention should be paid to exploring these possible mechanisms.

The most common findings in other studies concerning the serum GGT are the elevated GGT in populations with hepatobiliary diseases and among high consumers of alcohol (9–14). This study confirms the importance of GGT as a strong biological marker for frequent alcohol consumption. Within the normal range of GGT, however, its contribution as indicator of alcohol consumption is modest. The determinants of GGT within its normal range, are many and varied, covering a field from life-style habits to biological and possibly genetic characteristics.

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PAPER II

THE TROMSØ STUDY: A SEVEN-YEAR LONGITUDINAL POPULATION STUDY OF CHANGE IN GAMMA-GLUTAMYLTRANSFERASE.

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Key words: Gamma-glutamyltransferase, human.

SUMMARY.

Study Objective: To explore the determinants of gamma-glutamyltransferase over time.

Design: A population cohort were followed for seven years.

Setting: Community based health survey.

Participants: Random sample of 1171 males and 1267 females, aged 20-54 years, examined in 1979-80 and re-examined 7 yea later.

Measurements and Main Results: Three different multiple regression models of change in gamma-glutamyltransferase we compared with independent variables from: 1) first examination, 2) re-examination, and 3) changes between 1 and 2. Al three models displayed low explanatory value (2-9 percent), but changes in determinants (model 3) were in general superi in predicting change in gamma-glutamyltransferase over time. In both sexes, change in gamma-glutamyltransferase showed a strong positive association with change in body mass index a hours fasting. In males, increased frequency of inebriation was positively, increased physical activity negatively associated with change in gamma-glutamyltransferase. In females, increased systolic blood pressure, starting use of oral contraceptives, the occurrence of menopause, and decrea in consumption of boiled coffee increased gamma-glutamyltransferase.

The regression coefficients for the significant variables we considerably stronger in this study compared with those in t cross-sectional studies.

Conclusion: In a longitudinal design changes in the

determinants are superior to determinant values at start or at follow-up in explaining changes in gamma-glutamyltransferase over time. Our findings support previous assumptions, that within the normal range, gamma-glutamyltransferase has other and even stronger determinants than alcohol consumption.

Key words: alcohol drinking; blood pressure; body weight; coffee; gamma-glutamyltransferase; health survey; human; lipids; physical activity; smoking.

INTRODUCTION.

Despite its well established clinical use as an indicator o hepato-biliary diseases and drug- and alcohol-induced liver damage (1,2), gamma-glutamyltrasferase (GGT) is, in the norr 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, besides a marked sex difference in GGT, a positive association with body mass index, serum lipids, and blood pressure, and a negative association with coffee intake. Association with alcohol intake was strong and consistent or for the highest categories of consumption. Although some of these determinants of GGT have also been observed by others (5), associations observed in cross-sectional studies do not allow conclusions on causal relationships.

Longitudinal or experimental studies is therefore called for and in the present study we have tried to confirm the status of the cross-sectional determinants in a longitudinal design and to compare the predictive power of the determinants, measured at start, at follow up, and as changes in between. The subsample of the Tromsø population (n=2438) in which GGT was measured twice with a seven-year interval, constitutes c study population.

MATERIALS AND METHODS.

The basis for the present study is two population surveys in the municipality of Tromsø, Northern Norway, the second (1979-80) and the third (1986-87) Tromsø Study. The second Tromsø Study comprised 16621 subjects, i.e 78 per cent of the total eligible population aged 20-54 years, of whom GGT was measured in a random subsample of 3233 (3).
In the third Tromsø Study GGT was determined in all 21782 subjects examined, i.e 81 per cent of the total population aged 20-62 years (4). Measurements of GGT in both studies were done in 2438 subjects, which constitute the basis for the present analysis.

The methods of the two surveys were identical if nothing else is stated, and they included a questionnaire nearly identical to that used in the first Tromsø Study (6) and in the cardiovascular studies in Norwegian counties (7). In addition a second questionnaire on education, previous and present diseases, dietary habits including coffee and alcohol, use of drugs, and mental and sleeping problems, were handed out at the end of the examinations, and returned by mail.
The physical examinations comprised measurement of weight, height, and blood pressure, and a venous nonfasting blood sample for measurements of serum lipids and GGT. In the second Tromsø Study blood pressure was measured with a sphygmomanometer, in the third with a semiautomatic device (DINAMAP R). Total serum cholesterol was measured directly by the enzymatic

oxidase method using a commercial kit (Boehringer Mannheim, Germany). High density lipoprotein cholesterol (HDL) was assayed by the same procedure after precipitation with hepa and manganese chloride. Triglycerides were enzymatically determined as glycerol (Boehringer).

The measurements of GGT was performed at 37°C according to t recommendations of the Scandinavian Enzymes Committee (8). serum samples were kept at 4°C and analyzed within 48 hours. The coefficients of variation (CV) in the two studies were and 2.8 percent, respectively, for a commercial control ser (Precinorm, Boehringer Mannheim, Germany) during the study period.

All laboratory assessments were performed by the Division of Clinical Chemistry, University Teaching Hospital of Tromsø.

To explain the change in GGT between the two surveys, three different multiple regression models were analyzed separatel for each sex using the Statistical Package for the Social Sciences (10). The three models used the same set of indepen dent variables measured 1. at start (1979-80), 2. at follow- (1986-87), and 3. as changes in the same in between. In the last model all variables were recoded to "delta"-variables (-variables), i.e. actual individual change between the two screenings (Tromsø III - Tromsø II).

The second Tromsø Study contained no information on type of coffee consumed. A "boiled coffee" variable therefore were constructed by difference in coffee consumption for those wh

drank boiled coffee in the third Tromsø Study.

The following independent variables, all statistically significant in one or both sexes in either of the two cross-sectional studies, were introduced in the initial analyses: teetotaller, frequency of beer, wine or liquor consumption, frequency of inebriation, coffee consumption, boiled coffee consumption, bread consumption, number of cigarettes a day, physical activity at work and at leisure, rheumatoid arthritis, use of analgetics, body mass index, total and HDL-cholesterol, triglycerides, systolic blood pressure and time since last meal. For women menopause and use of p-pills were also included.

The "change" model was further elaborated using backwards elimination with a 5 percent level of statistical significance as criterion for staying in the equation. The following independent -variables remained in the final regression model in either sex: systolic blood pressure (mmHg), body mass index (g/cm^2), time since last meal (in hours), physical activity at work (graded as 1, mostly sedentary; 2, a lot of walking; 3, a lot of walking and lifting; 4, heavy manual labour), 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 to 2 times a month; 4, three or more times a week), cups of boiled coffee per day (graded as 1, less than 1; 2, 1-4; 3, 5-8; 4, nine or more), and, for females, also use of oral contraceptives (no/yes) and menopause (no/yes).

To compensate for the difference in measurement of blood pressure (sphygmomanometer versus DINAMAP-R), adjustments o the "DINAMAP-pressure" were done according to standard proc dures (9). When introduced in the regression model, this adjustment did not alter the regression coefficients or the values, and was therefore removed and replaced by the un-adjusted values.

The difference between logarithmically transformed GGT-valu was also attempted as dependent variable, but subsequently replaced by -GGT as the effect of the transformation was negligible.

RESULTS

Table 1 gives the mean GGT with standard deviation for the different age-group-cohorts in the second and the third Tro Study. The average increase in GGT was 4.24 U/l and 2.69 U/l for males and females, respectively. In percent the increase was 22.6 for males, and 23.1 for females. For the total population the increase was 22.9 percent.

The correlation coefficients between individual measurements varied in males between 0.55 and 0.73, in females the correl tions were somewhat lower.

The results of the initial three regression models are given in table 2 (males) and table 3 (females). The numbers (n) differ in the models, indicating "missing values" for some o the variables, especially in the "start" model. The amount o

explained variance were small for all six equations, and model 1 ("start model") in males were non-significant.
Overall the "change" model were superior in both sexes, but with some consistency with the "follow up" model.

In males, in both the significant models, change in GGT displayed positive associations with HDL cholesterol and frequency of inebriation. In the "change" model, change in body mass index was by far the strongest predictor for change in GGT.
In females, all three models reached statistically significance in the initial analysis. In the "change" model, change in body mass index, systolic blood pressure, time since last meal, and use of p-pills were positively associated with change in GGT, whereas change in boiled coffee consumption displayed a negative association.

The final regression analysis (table 4 and table 5) includes only those variables which reached statistically significant in either sex after backwards elimination in the "change" model. The numbers (n) increased with about 100 in each sex, reflecting missing values in some of the excluded variables. In both sexes, change in body mass index and time since last meal were positively associated with change in GGT. A regression coefficient of 21.59 for body mass index in males, indicate that an increase in body mass index with 0.309 (i.e a man of 180 cm height increasing his weight from 80 to 90 kg) rise the GGT-value with 6.7 U/l, whereas a regression coefficient

of 6.33 in females indicate an increase in GGT with 2.5 U/l a woman of 160 cm height gains weight from 55 to 65 kg. In males, increasing the frequency of inebriation increased the GGT level, whereas decrease in physical activity at work was associated with an increase in GGT. In females an increasing systolic blood pressure, decrease in boiled coffee intake, starting use of p-pills and the occurrence of menopaus increased GGT. An increase in blood pressure of 10 mmHg increased the GGT-level with 0.6 U/l in both sexes, whereas starting use of p-pills increased the GGT-level with 5 U/l.

DISCUSSION.

The present study supports the main findings from the previo cross-sectional studies from Tromsø. Change over time in the strongest cross-sectional determinants of GGT, i.e time sinc last meal, body mass index, frequency of inebriation, blood pressure, physical activity, boiled coffee consumption, occu rence of menopause and starting use of p-pills, results in a correspondingly marked change in GGT. The associations measu ed by the size of the regression coefficient were, however, stronger in the longitudinal "change" model. This is hardly unexpected since an analysis of change over time within subjects, reduce possible confounding and removes inter-persona variance from uncontrolled genetic and physiological sources

It may on this background be unexpected that the proportion variance explained in the "change" model, reflected by the

relatively small R^2, was small and only half that from the cross-sectional analysis (3,4). This is even more so as GGT displayed a considerable intra-individual 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 increases relatively to the variance caused by true changes over time.

The comparison of the three models with three different sets of independent variables, clearly favour the change model. This is not intuitively obvious so for all potential predictors of change in GGT. For instance it could easily be hypothesized that a high alcohol consumption at the start best would predict subsequent increase in GGT. This was not so, even for this variable the "change"-model was superior.

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

An increase of approximately 10 percent in GGT in the total population, was observed between the two surveys. The increase was uniform with regard to age, sex, and GGT-level. This

suggests, despite identical method, a change in laboratory level, probably caused by replacement of autoanalyzer. This systematic bias, affecting the dependent variable, does not affect our analysis.

In contrast, measurements of blood pressure were done with different methods and different devices in the two surveys. These differences may represent a bias for persons with extremely high or low blood pressures (9). The introduction o an "adjusted" change in blood pressure in the regression model, did not noticeably influence the results.

In both sexes, change in body mass index was the single str gest determinant for change in GGT. The regression coeffi- cients were more than twice as strong as in the third Troms Study (4). A 10 kg increase in weight (from 80 to 90 kg) i male with a height of 180 cm, indicated an increase in GGT 2.7 U/l (14.5 percent) in the cross-sectional analysis (4), whereas the increase was 6.7 U/l (35.6 percent) in this stu This strong effect of body mass index on GGT, which confirm previous studies (3-5), most probably reflects a causal relationship.

Several reports (11,13-15) have suggested an association between alcohol consumption and essential hypertension. In cross-sectional study (4), we demonstrated an association between GGT and blood pressure, irrespective of alcohol intake. In this study, an increase in systolic blood pressure

10 mmHg corresponds to an increase of 0.6 U/l in GGT in both sexes. The increase in GGT is not impressive, but still stronger than in both cross-sectional studies.

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 still insignificant. The surprisingly weak effect of the alcohol variables may reflect the imprecision of our alcohol questions introducing random measurement errors which overshadow the true changes in alcohol consumption.

In both cross-sectional studies (3,4) coffee consumption was negatively associated with GGT. The effect turned out, in the third Tromsø Study, to be predominantly linked to consumption of boiled coffee. A corresponding significantly negative association between change in intake of boiled coffee and GGT was found in females, but not in males. A change from 1 or less cups a day to 9 cups or more, reduced GGT with 4.7 U/l (31.2 percent) and 3.9 U/l (20.9 percent) in females and males respectively. The association between change in intake of boiled coffee and change in GGT was nearly twice as strong as found in the last cross-sectional study, supporting the position of boiled coffee as a determinant of GGT.

Fasting showed a significant influence on -GGT. Two earlier

studies have examined this association (16,17), postulating that "fasting and postprandial serum showed approximately th same activity" (16), and "the same activity was found before and after a meal" (17). Our cross-sectional studies as well this study contrast these findings. The present data show 27 and 18.7 percent higher GGT-values for those males and femal who had their last meal eight hours before the screening, compared to those who had their last meal less than one hour before the screening, i.e. an increase with increased fastin

In females starting use of oral contraceptives and occurrenc of menopause increased the GGT values with 33.7 percent and 12.9 percent, respectively. This indicates an association between hormonal state and GGT.

In conclusion, the present study indicate that "change" in life-style variables and background characteristics between start and follow-up values better predict change in a biological variable as GGT than the level of the corresponding variables at start and at follow up. The findings in this study confirm our earlier suggestions that the determinants gamma-glutamyltransferase within its normal range, are far more than alcohol consumption, and predominantly found in li style and biological markers.

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Table 1. Number examined both in 1979/80 and in 1986/87, according to age and sex, corresponding mean GGT (SD) in U/l, and simple correlation between individual measurements. The Tromsø Study 1979-80 and 1986-87.

	MALES				
	n	1979/80		1986/87	Correlation
Age in 1979/80		$\bar{X}$	SD	$\bar{X}$ SD	r
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				
	n	1979/80		1986/87	Correlation
Age in 1979/80		$\bar{X}$	SD	$\bar{X}$ SD	r
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

Table 2. Multiple regression analysis of a seven-years change in gamma-glutamyltransferase (U/l) males, with independent variable set taken from start (Tromsø 2), follow up (Tromsø 3) and chang between start and follow up (Tromsø 3 - Tromsø 2). Dependent variable is change in gamma-glutamyltransferase. The Tromsø Study 1979-80 and 1986-87.

	Males					
	Tromsø 2 (1979-1980)		Tromsø 3 (1986-1987)		Difference (Tromsø 3 - Tromsø	
	b	t	b	t	b	t
Body mass index (g/cm²)	0.648	0.28	1.790	0.88	23.661	6.42
Triglycerides (mmol/l)	-1.354	-2.19	0.150	0.27	-0.501	-1.06
Total serum cholesterol (mmol/l)	0.503	1.02	0.223	0.49	0.643	1.05
HDL cholesterol (mmol/l)	0.247	0.20	4.396	2.73	2.271	2.00
Systolic blood pressure (mmHg)	-0.027	-0.62	0.127	3.71	0.024	0.66
Time since last meal (hours)	-0.434	-0.82	0.469	1.75	0.155	0.22
Coffee consumption (1-4)	0.246	0.33	-0.637	-0.93	-0.253	-0.46
Boiled coffee consumption (1-4)	-	-	0.476	0.41	-0.549	-0.68
Teetotaler (yes/no)	-4.656	-0.83	-3.748	-1.92	1.174	0.46
Frequency of beer intake (1-5)	0.394	0.62	-0.046	-0.08	-0.389	-0.72
Frequency of wine intake (1-5)	0.844	0.97	-0.174	-0.25	-0.308	-0.47
Frequency of liquor intake (1-5)	1.064	1.32	0.847	1.23	0.307	0.49
Frequency of inebriation (1-5)	-1.384	-1.57	2.429	3.17	3.000	4.64
Numbers of cigarettes a day	0.320	0.25	0.667	0.59	0.057	0.75
Physical activity at leisure (1-4)	-0.783	-1.11	-0.967	-1.37	0.852	1.46
Physical activity at work (1-4)	1.008	1.77	-0.301	-0.56	-0.595	-1.06
Bread consumption	-0.786	-0.72	-0.927	-1.41	-0.810	-1.23
Use of analgesics (no/yes)	1.799	1.53	0.725	0.86	-0.117	-0.18
Rheumatoid arthritis (no/yes)	1.272	0.25	0.008	0.01	0.386	0.52
n:	1027		1096		1023	
R^2:	0.021		0.064		0.091	
F :	1.105		3.846		4.764	

Table 3. Multiple regression analysis of a seven-years change in gamma-glutamyltransferase (U/l females, with independent variable set taken from start (Tromsø 2), follow up (Tromsø 3) and ch between start and follow up (Tromsø 3 - Tromsø 2). Dependent variable is change in gamma-glutamyltransferase. The Tromsø Study 1979-80 and 1986-87.

	Females					
	Tromsø 2 (1979-1980)		Tromsø 3 (1986-1987)		Difference (Tromsø 3 - Tromsø	
	b	t	b	t	b	t
Body mass index (g/cm²)	0.329	0.19	1.030	0.86	5.443	2.26
Triglycerides (mmol/l)	0.045	0.05	0.961	1.36	0.907	1.38
Total serum cholesterol (mmol/l)	0.461	1.04	0.105	0.30	-0.476	-0.92
HDL cholesterol (mmol/l)	0.552	0.50	0.463	0.48	-0.772	-0.67
Systolic blood pressure (mmHg)	0.058	1.65	0.075	3.04	0.077	2.24
Time since last meal (hours)	-0.296	-0.65	0.262	1.30	0.493	2.32
Coffee consumption	0.776	1.28	0.644	1.30	-1.116	-0.76
Boiled coffee consumption	-	-	-3.036	-3.82	-1.682	-2.41
Teetotaler	3.079	0.58	-0.228	-0.18	-0.180	-0.11
Frequency of beer intake	0.075	0.12	-0.369	-0.76	0.049	0.10
Frequency of wine intake	-0.903	-1.29	-0.516	-1.05	0.448	0.82
Frequency of liquor intake	0.210	0.29	0.494	0.93	0.207	0.33
Frequency of inebriation	0.282	0.36	0.853	1.59	0.231	0.42
Numbers of cigarettes a day	-0.643	-0.67	-0.062	-0.08	-0.022	-0.25
Physical activity at leisure	-0.055	-0.08	0.342	0.59	-0.171	-0.32
Physical activity at work	-0.199	-0.32	-0.374	-0.82	-0.302	-0.57
Bread consumption	-0.888	-0.74	-0.412	-0.73	-0.022	-0.03
Use of analgesics	-0.260	-0.37	-0.929	-1.70	0.041	0.08
Rheumatoid arthritis	6.360	1.68	0.265	0.57	0.000	0.00
Use of p-pills	-4.705	-3.08	3.025	1.67	4.811	3.67
Menopause occurred	-7.154	-2.91	0.131	0.13	2.100	1.86
n:	1092		1182		1086	
R^2:	0.036		0.041		0.051	
F :	1.716		2.327		2.484	

Table 4. Result of multiple regression analysis of individual change in gamma-glutamyltransferas (U/l) in males, with independent variable set taken from start (Tromsø 2), follow up (Tromsø 3), and change between start and follow up (Tromsø 3 - Tromsø 2). Only independent variables reachin significance in either sex after backwards elimination in the "change" model are included. Depen variable is change in gamma-glutamyltransferase. The Tromsø Study 1979-80 and 1986-87.

	Males					
	Tromsø 2 (1979-1980)		Tromsø 3 (1986-1987)		Difference (Tromsø 3 - Tromsø	
	b	t	b	t	b	t
Body mass index (g/cm²)	-3.040	-1.46	1.877	1.04	21.591	5.79
Systolic blood pressure (mm Hg)	0.067	1.59	0.141	4.16	0.060	1.51
Time since last meal (in hours)	-0.599	-1.16	0.532	2.02	0.746	3.06
Boiled coffee consumption (1-4)			-0.474	-0.42	-1.307	-1.48
Frequency of inebriation (1-5)	0.326	0.46	2.930	4.90	2.278	4.47
Physical activity at work (1-4)	1.181	2.17	-0.455	-0.88	-2.116	-3.51
n:	1150		1173		1144	
R^2:	0.011		0.046		0.078	
F:	1.866		7.476		12.470	

Table 5. Result of multiple regression analysis of individual change in gamma-glutamyltransfera (U/l) in females, with independent variable set taken from start (Tromsø 2), follow up (Tromsø and change between start and follow up (Tromsø 3 - Tromsø 2). Only independent variables reachi significance in either sex after backwards elimination in the "change" model are included. Depe variable is change in gamma-glutamyltransferase. The Tromsø Study 1979-80 and 1986-87.

	Females					
	Tromsø 2 (1979-1980)		Tromsø 3 (1986-1987)		Difference (Tromsø 3 - Tromsø	
	b	t	b	t	b	t
Body mass index (g/cm²)	0.946	0.73	1.632	1.48	6.332	2.97
Systolic blood pressure (mm Hg)	0.038	1.33	0.077	3.18	0.063	2.04
Time since last meal (in hours)	-0.294	-0.76	0.275	1.41	0.402	2.11
Boiled coffee consumption (1-4)	-	-	-2.837	-3.64	-1.565	-2.47
Frequency of inebriation (1-5)	0.192	0.38	0.677	1.43	0.379	0.95
Physical activity at work (1-4)	-0.074	-0.14	-0.330	-0.73	-0.321	-0.67
Use of oral contraceptives (no/yes)	-4.355	-3.31	3.314	1.86	5.069	4.25
Menopause occurred (no/yes)	-4.371	-2.37	0.734	0.81	1.942	1.97
n:	1191		1271		1190	
R^2:	0.023		0.034		0.058	
F:	3.140		4.381		5.808	

PAPER III

The Tromsø Study: the positive predictive value of gamma–glutamyltransferase and an alcohol questionnaire in the detection of early-stage risk drinkers

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Abstract. Nilssen O, Førde OH (Institute of Community Medicine, University of Tromsø, Tromsø, Norway). The Tromsø Study: the positive predictive value of gamma–glutamyltransferase and an alcohol questionnaire in the detection of early-stage risk drinkers. *Journal of Internal Medicine* 1991; 229: 497–500.

Based on the measurement of gamma–glutamyltransferase and a questionnaire on frequency of alcohol intake, 338 early-stage risk drinkers were identified from more than 20000 participants in a health survey programme. Two-thirds (225) of these subjects were questioned regarding their 'true' alcohol intake at the first consultation. Positive predictive values were calculated for true daily intake of 30 and 40 g alcohol d^{-1} for men (20 and 30 g alcohol d^{-1} for women) on the basis of gamma–glutamyltransferase activity and the response to a questionnaire. The positive predictive values for a risk intake of 30 g d^{-1} in men increased from 0.49 to 0.88, with increasing values for gamma–glutamyltransferase activity and increasing frequency of alcohol intake. The corresponding values for a risk intake of 40 g d^{-1} were 0.34–0.75. In women, increasing gamma–glutamyltransferase activity gave no increase in positive predictive values. The estimates for increasing frequency of alcohol intake were unreliable due to small numbers.

Keywords: alcohol, gamma–glutamyltransferase, health survey.

Introduction

The methods used to identify harmful levels of alcohol consumption are many and varied [1], and are often combined in order to increase the level of accuracy [1, 2]. Gamma–glutamyltransferase (GGT) is still the most commonly used marker [3–5], its effects are well documented and it is readily available. A single 'perfect' marker has not yet been found, although several new and promising markers have recently been reported in the literature [6, 7]. On the other hand, it is crucial to discuss the desired properties of a potential tool for identification. Should it reflect the exact intake of alcohol per day, or should it detect early somatic, psychological or even social damage? For instance, assuming that liver damage mirrors the degree of alcohol addiction, should such a marker measure possible liver damage? As identification is usually followed by intervention in order to reduce alcohol intake, should an ideal marker also constitute an instrument for intervention?

In the third Tromsø Study, conducted in 1986–1987, an alcohol risk population, identified on the basis of GGT and a questionnaire on frequency of alcohol consumption, was identified from a group of more than 20000 participants. These methods of identification were selected because we believed that those individuals who responded to the questionnaire would probably also participate in an intervention trial. Furthermore, we considered that GGT would constitute an effective means of monitoring the intervention. Based on a subsample of 225 subjects (191 men and 34 women), this paper describes and discusses the accuracy of a combined GGT and questionnaire response in terms of positive predictive value (PPV), taking an extensive interview on 'true' alcohol intake to be the gold standard.

Subjects and methods

The total population of men aged 20–62 years and women aged 20–56 years in the municipality of

Table 1. Number of men and predictive values for 'true' daily alcohol intake of ≥ 30 g and < 30 g d^{-1}, various combinations of GG ($U\ l^{-1}$) and questionnaire response: Tromso 1986–1988

	Total risk population			Questionnaire-reported frequency of intake of alcoholic beverages*								
				B ≥ 4 W ≥ 4 L ≥ 4 I ≥ 3			B ≥ 4 W ≥ 4 L ≥ 4 I = 4			B = 5 W = 5 L = 5 I = 4		
	True daily intake ≥ 30 g < 30 g			True daily intake ≥ 30 g < 30 g			True daily intake ≥ 30 g < 30 g			True daily intake ≥ 30 g < 30 g		
GGT	N	*n*	PV	N	*n*	PV	N	*n*	PV	N	*n*	PV
≥ 50	94	97	0.49	81	74	0.52	59	32	0.65	31	8	0.80
≥ 55	76	79	0.49	66	60	0.52	46	28	0.62	22	7	0.76
≥ 60	63	60	0.51	55	48	0.53	38	25	0.60	18	7	0.72
≥ 65	54	45	0.55	47	35	0.57	33	20	0.62	16	5	0.76
≥ 70	44	36	0.55	39	26	0.60	28	14	0.67	16	4	0.80
≥ 75	36	32	0.53	32	23	0.58	24	13	0.65	15	4	0.79
≥ 80	35	27	0.57	31	20	0.61	23	11	0.68	14	2	0.88

* B = beer, W = wine, L = liquor (4 = 2–3 times per week, 5 = approximately daily), I = inebriation (3 = 1–2 times per month, 4 = or more times per week).
PV = predictive value.

Tromso were invited to participate in the third Tromso Study. In addition, a sample of men aged 12–19 years and women aged 12–19 and 57–62 years were invited to participate. The total number of subjects examined was 21647, i.e. 81.3% of those invited. The measurement of GGT was performed at 37 °C according to the recommendations of the Scandinavian Enzymes Committee [8]. The serum samples were stored at 4 °C and analysed within 48 h. The coefficient of variation was 2.8% for a commercial control serum (Precinorm, Boehringer) during the study period. A questionnaire consisting of the following five questions on frequency of alcohol intake was answered by the participants: (a) are you a teetotaller (no/yes); (b, c, d) intake of beer, wine, liquor, graded 1–5 (never or only a few times a year, 1–2 times per month, once a week, 2–3 times a week, approximately daily); (e) frequency of inebriation, i.e. alcohol intake on one occasion corresponding to the amount contained in one bottle of wine, graded 1–4 (not last year, a few times last year, 1–2 times per month, 3 or more times a week).

On the basis of the measured GGT and the responses to the alcohol questionnaire, a population of 338 early-stage risk drinkers was identified and intervention initiated. Inclusion criteria were a GGT value in the range 50–200 $U\ l^{-1}$ (45–200 $U\ l^{-1}$ for women), and at least a weekly intake of alcohol. The medical records for all subjects were checked, and diagnosed alcoholics ($n = 43$) and psychiatric patients were excluded. Subjects with GGT values of > 200 $U\ l^{-1}$ ($n = 32$) were also excluded. The iden ified population was randomized into two inte vention groups and one control group. The true dai intake of alcohol was determined by a structure interview, conducted by one of the authors (O.N following a standardized WHO questionnaire [9]. F methodological reasons only two groups (22 subjects) were interviewed about their true dai intake prior to intervention. These individuals cor stitute the analysed population. Detailed descriptio of the screening methods [10] and the procedure f selection of the intervention population [11] a given elsewhere. Using a GGT scale ranging from 5 (45 for women) to 80 $U\ l^{-1}$, together with increasin questionnaire-reported frequency of alcohol intak or inebriation, PPV was estimated for different 'true consumption levels.

Results

Tables 1 and 2 show PPV data for male subject Using values of 30 g or more (Table 1) and 40 g c more (Table 2) as cut-off points for 'true' cor sumption. PPVs are given for various combination of GGT values and questionnaire responses. A PPV c 0.49 indicates that 49% of the population with GGT value of ≥ 50 $U\ l^{-1}$ have an alcohol intake c ≥ 30 g per day. Table 1 indicates that there is a tren towards increasing PPV with increasing GGT in th first and second blocks. With increasing alcoh intake reported in the questionnaire (blocks 3 and 4

Table 2. Number of men and predictive values for 'true' daily alcohol intake of ⩾ 40 g and < 40 g d^{-1}, for various combinations of GGT (U l^{-1}) and questionnaire response: Tromsø 1986–1988

				Questionnaire-reported frequency of intake of alcoholic beverages*								
	Total risk population			B ⩾ 4 W ⩾ 4 L ⩾ 4 I ⩾ 3			B ⩾ 4 W ⩾ 4 L ⩾ 4 I = 4			B = 5 W = 5 L = 5 I = 4		
	True daily intake ⩾ 40 g < 40 g			True daily intake ⩾ 40 g < 40 g			True daily intake ⩾ 40 g < 40 g			True daily intake ⩾ 40 g < 40 g		
GGT	N	n	PV	N	n	PV	N	n	PV	N	n	PV
⩾ 50	64	127	0.34	56	99	0.36	41	50	0.45	24	15	0.62
⩾ 55	51	104	0.33	46	80	0.37	31	43	0.42	18	11	0.62
⩾ 60	43	80	0.35	39	64	0.38	27	36	0.43	16	9	0.64
⩾ 65	37	62	0.37	33	49	0.40	24	29	0.45	14	7	0.67
⩾ 70	35	45	0.44	31	34	0.48	22	20	0.52	14	6	0.70
⩾ 75	30	38	0.44	27	28	0.49	20	17	0.54	13	6	0.68
⩾ 80	29	33	0.47	26	25	0.51	19	15	0.56	12	4	0.75

* B = beer, W = wine, L = liquor (4 = 2–3 times per week, 5 = about daily), I = inebriation (3 = 1–2 times per month, 4 = 3 or more times per week).
PV = predictive value.

this trend disappears. However, PPV increased with increasing questionnaire-reported intake in all blocks. When the 'true' intake was increased to ⩾ 40 g per day (Table 2), a general reduction in PPV was observed. There is little difference for GGT values of 50, 55 and 60. At higher values there is a clear increase in the PPV trend, with a gradient almost twofold steeper than that for a daily intake of 30 g alcohol. As shown for a daily intake of 30 g alcohol, a consistent trend towards higher PPVs was found with increasing questionnaire-reported frequency of alcohol intake.

In female subjects, PPVs were estimated for true daily alcohol consumption of ⩾ 20 g and ⩾ 30 g, according to different levels of GGT (data now shown). The PPVs ranged from 0.28–0.39, with no consistent difference in trend between intake of 20 and 30 g, or for increasing GGT levels.

Discussion

The lack of data on daily volume of alcohol intake in subjects with normal GGT values is a drawback of the present study. As a result, this investigation could not provide estimates of the sensitivity and specificity of GGT as a screening instrument. However, this is compensated for by a population-based sample with estimates of predictive power, which often represents the crucial parameter in preventive programmes.

Our study has confirmed the validity of GGT, in combination with reports on the frequency of alcoho intake, as a basis for identification of male risk alcohol drinkers. More surprising was its lack o discriminatory power in women.

In other similar studies [3, 12–14] on indicators o alcohol drinking, the basis for identification has varied, including self-reports on frequency or volume of intake, clinical findings, biological markers or social and psychological effects. In addition, terms such as 'risk', 'high risk', 'hazardous', 'excessive' 'problem' and 'heavy' drinking, and phrases such as 'abuse' and 'alcoholism' do not always have the same meaning. In this study we have selected as our 'gold standard' daily intake of alcohol measured by a standardized and well-documented interview [9]. The cut-off points, 20 and 30 g daily for women, and 30 and 40 g daily for men, appear to reflect the limits for more detectable effects of alcohol drinking [9]. The combination of GGT and questionnaire responses in men gives estimates of positive predictive values for risk consumptions increasing from 0.34–0.88 with increasing GGT level and frequency o questionnaire-reported intake. Even the lower o these estimates which, in the light of the relatively low prevalence of risk drinking in the Tromsø popu lation, must be regarded as a minimum value compares favourably with other screening tests However, it might be argued that the risk o stigmatization in alcohol intervention is high, and

the stringency of identification tools should be correspondingly higher. Even so, as was shown in a previous paper [11], our experience from the Tromsø Study indicates that it is possible to handle the false positive group in a way that results in minimal damage. The alternative, which is to increase the stringency of the positive criterion, would reduce the sensitivity. But this would also imply a reduction of the true-positive group which, together with some of the 'false positive', would benefit from intervention [11].

In women no increase in positive predictive value could be observed with increasing GGT levels. The relatively low number of female subjects calls for caution, but it is still tempting to suggest, in line with the findings of our earlier study [10], that the sexes differ with regard to both GGT level and GGT response to alcohol intake.

The questionnaire appears to have an equally strong predictive power, and more predictive value appears to be gained by increasing the questionnaire criteria than by increasing the GGT level. Caution should be exercised, however, when drawing any conclusion on the performance of these two markers used independently. First, the strong positive correlation between the self-administered questionnaire and the structured interview may reflect a common recall-bias. Secondly, by omitting the GGT level as a tool of identification, an important part of the risk population might be lost, i.e. those individuals who exhibit a GGT increase on alcohol intake, or who under-report their intake. In addition, an important motivation 'factor' in intervention is also lost [15]. We are aware of the ongoing search for single biochemical markers with improved diagnostic accuracy [6, 7]. However, until such markers are available for population studies, identification of alcohol abuse must be based on combinations of the existing diagnostic tools. For population studies such as the present one, where our aim was to identify subjects with a risk intake of alcohol, and to intervene in order to reduce their daily intake of alcohol, we consider that the combination of GGT and a questionnaire on drinking habits constitutes an effective alternative instrument for this task.

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PAPER IV

NEW ALCOHOL MARKERS: HOW USEFUL ARE THEY IN POPULATION STUDIES. THE SVALBARD STUDY 1988-89.

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Regular high consumption of alcohol in selected populations, ha
with high precision, been identified by two new alcohol markers
carbohydrate-deficient transferrin and mitochondrial aspartate
aminotransferase. To test this markers in an unselected
population, gamma-glutamyltransferase (GGT), carbohydrate-
deficient transferrin (CDT), and mitochondrial aspartate
aminotransferase (mAST) were measured in the Norwegian populatic
310 males and 171 females, aged 18-60 years, living at Svalbard.
Using self-reported alcohol intake as gold standard, sensitivity
specificity, positive predictive value, and likelihood-ratio wer
estimated according to different cutoff-points for alcohol intak
and for the tests.

In contrast to earlier studies, the sensitivity was in general
low. With a specificity of 90 percent or higher, the sensitivity
did not exceed 26 percent for any of the tests. Whereas CDT show
its best discriminatory power at lower intake of alcohol, GGT
discriminated best at higher levels. Parallel and serial analysi
of CDT and GGT, indicated a conditional independence between the
tests, as well at higher as at lower levels of alcohol
consumption.

mAST was judged as not suitable in population studies.

INTRODUCTION

Besides specific alcohol questionnaires and the use of clinical symptoms, biological markers constitute the most used tools for identification of alcohol drinking (1-4). Despite low sensitivity and specificity, gamma-glutamyltransferase (GGT) has served as the single best marker (5,6).

Two new markers for high alcohol consumption have recently been introduced in the literature. The serum concentration of carbohydrate-deficient transferrin (CDT) has been reported to be associated with high regular intake of alcohol, and presented as a marker with high sensitivity and specificity for high alcohol consumption (7-14). Correspondingly, the serum activity of mitochondrial isoenzyme of aspartate aminotransferase (mAST), has been detected at higher levels than expected in alcoholics, compared to the total AST activity, and the mAST : AST ratio has been proposed as a parameter to distinguish alcoholic hepatitis from other liver diseases (15). Moreover, mAST has been proposed as a sensitive marker of alcoholism (14,16-20). As the studies mostly are based on regular high alcohol consumers and alcoholics, we know little about how suitable these tests may be in population studies. Although one recent report has concluded that mAST is not useful as a marker for excessive alcohol consumption in unselected populations (21), the need for further studies is obvious.

The Svalbard Study (1988-89) gave us the opportunity to explore the sensitivity and the specificity of GGT, CDT and mAST, compared to questionnaire responses on total alcohol intake last week as gold standard.

Of the total Norwegian population (barely 1100 individuals) livi at Svalbard, 818 persons aged 18 years or more, were invited to health screening launched in October 1988. Of these, 612 persons met, i.e. 74.8 percent of the invited population.

The examination comprised administration of a questionnaire identical to that used in the cardiovascular studies in Norwegia counties (22); collection of nonfasting blood samples for measurements of serum lipids, glucose level and alcohol markers; weight, height and blood pressure measurements. In addition all participants were given a second questionnaire on dietary habits alcohol and coffee consumption, use of drugs and previous and present diseases. Altogether 515 persons returned the questionnaires, i.e 84.1 percent of those who attended the screening. Of these, 481 persons answered the alcohol questions.

Enzyme activities of AST and GGT were measured at 37°C in Hitachi 737 Automatic Analyzer using commercial kits (Boehringer Manheim, Germany), in accordance with the recommendations of the Scandinavian Enzymes Committee (23,24). The measurements were performed by the Division of Clinical Chemistry, University Teaching Hospital of Tromsø.

For GGT, the serum samples were kept at 4°C and analyzed within 4 hours. The samples were subsequently frozen at -70°C, and thawed once or twice during February/March 1991 for analysis of mAST and CDT.

of the cytoplasmic AST (cAST) as described by Rej (20). The same batch of antibodies was used throughout the study. After centrifugation of precipitated cAST, the residual mAST activity was determined with the same procedure as described above (20).
CDT was determined using commercial kits (Pharmacia, Uppsala, Sweden, newest version), in accordance with the manufacturer's instructions. The kit included minicolumns for separation of CDT from other transferrin isoforms, and the amount of eluted CDT were quantitated using a radioimmunological determination of transferrin. Values are given as U/l. Counting of radioactivity was performed with a LKB Wallac 1260 Multigamma 11 (Uppsala, Sweden). The analysis was performed in duple, and the difference between parallels was less than 10 percent when values were less than 18 U/l, and less than 7 percent with higher values.
A sample of normal serum and the commercial kit control were used for the estimation of CDT precision. For both, a coefficient of variation (CV) less than 9 percent were found (mean value 14 and 16 U/l, respectively).
The CV for GGT and AST were less than 3.0 and 1.5 percent, respectively, using commercial lyophilized control sera. The precision of mAST was determined with a pooled normal serum and a control with purified mAST. The CV for day-to-day variation of the normal serum was 28 percent (mean 3 U/l), and for the control 5 percent (mean 44 U/l).

The response on the following question on alcohol intake was used as our gold standard:

questionnaire as a bottle of beer, a glass of wine and a drink
liquor) did you drink last week before the screening?
Using the 90 and the 95 percentile of weekly alcohol intake as
limit for high alcohol consumption, and the 80 percentile as li
for a "risk" intake, sensitivity, specificity, positive predict
value (PPV) and likelihood-ratio (LR) were calculated for
different cutoff-points (50, 60, 70, 80, 90 and 95 percentiles
the tests) for GGT, CDT and mAST. The 95 percent confidence
intervals for the LR's were test based (25).

RESULTS

Mean self-reported intake of alcohol was 14.6 g/day for the tota
population, with 18.6 g/day and 7.2 g/day for males and females,
respectively. The equivalents in litres of pure alcohol/year wer
6.7, 8.6 and 3.3, which are approximately 30 percent higher than
the average consumption on the Norwegian mainland. Self-reported
consumption on the other hand, only accounted for 40 percent of
the total consumption according to the local statistics for sale
(data not shown).
Tables 1, 2, and 3 give sensitivity, specificity, PPV and LR for
the three tests. PPVs for all three tests were highest with the
lowest cutoff-point for alcohol intake. At the lower levels of a
three tests, the sensitivity was reasonable, but the specificity
low. At higher levels, increase in specificity was observed but
with a simultaneous decrease in sensitivity.
In females, the LR-values were generally low for all three tests

In males, CDT displayed the best diagnostic properties, expressed in terms of LR, with the lower cutoff-point in alcohol intake of 30 g/day. The test value 19, 22 and 28 U/l (table 1) achieved corresponding point estimates for LR (with 95% CL) of 2.0 (1.3-3.0), 3.0 (1.8-5.4) and 4.5 (1.9-10.9). The highest LR-values for GGT (table 2) were observed at the higher cutoff-point of 52 g/day and with test values of 43 U/l or higher, achieving point estimates of LR of 3.1 (1.2-8.0) and 6.1 (2.3-16.1). Irrespective of cutoff-point for daily intake of alcohol, the highest LR for mAST in males did not exceed 1.1 (table 3).

A parallel analysis of CDT and GGT in combination (table 4) increased the sensitivity for all levels of the tests and for all levels of alcohol intake, but reduced the specificity and the PPV accordingly. The LR's for the combined test did consequently not achieve the size of the best of the corresponding single tests. When the analysis were done serial (cutoffs were the 90 and 95 percentiles for both tests and the 90 percentile for alcohol intake), none of the high consumers had both tests positive, and neither had any of the moderate or low consumers. This indicate conditional independence of the two tests both among drinkers and none-drinkers.

DISCUSSION

Alcohol markers in clinical practice mainly are used for an early detection of alcohol abuse, the verification of alcoholism, and

ability for each marker to distinguish alcoholics from abstaine and light drinkers, are usually given in terms of sensitivity a specificity, calculated in selected clinical samples of known alcoholics and abstainers. Although sensitivity, specificity an thereby LR principally are independent of prevalence, the "case mix" in these samples are so different from the population in general that an evaluation of the diagnostic properties in unselected populations is necessary before any conclusions can drawn regarding the properties of these markers as screening instruments. For early identification of misusers, as in screen programs, it is essential to test out the markers in unselected populations.

There were no difference in GGT, total serum cholesterol and triglycerides between responders and non-responders, and the loc health workers, who monitored the screening, reported there were no social difference between responders and non-responders. Further, there were no age-specific differences when the markers were analyzed in age-groups.

The level for alcohol intake in Norway is low compared to other European countries (26), and does hardly exceed 5 litres of pure alcohol per year per inhabitant 15 years or more. At Svalbard, t statistics of sales indicate an average yearly intake of more th 16 litres of pure alcohol. The reliability of this statistic is high, with precise registration of sales, and, due to very low prices, no illegal sales, no smuggling and no moonshining. Self-

paper, accounts for only 40 percent of the actual consumption, compared with the sales-statistic. This underreporting, which is in accordance with other Scandinavian studies (27,28), probably represents a systematic bias in our study, and can not explain the relatively poor performance of the markers. Even if the reporting bias to some degree is differential, it would not, if eliminated through a more thorough assessment of the gold standard, improve the sensitivity of the tests, which seem to be the crucial parameter as they at their best only identifies one third of those who admit a high alcohol intake. The specificity, on the other hand, may be somewhat better than observed in our study.

The limit between abusing and none-abusing alcohol consumption is rather unclear (29), and differs from one study to another. Most frequently, the cutoff-points are estimated as mean value of daily intake of alcohol +2 standard deviations.
In this study we have used the percentiles of self-reported daily consumption as our cutoffs. As the estimated prevalence of problem drinkers in the Norwegian society represents about 10 percent of the adult population (30), we have chosen the 90 percentile (41 and 15 g/day in males and females, respectively) and the 95 percentile (52 and 22 g/day) as cutoff-point for "problem drinking". In addition we have introduced the 80 percentile (30 and 13 g/day for males and females, respectively) as cutoff for "risk drinking".

Similar considerations were used to define the cutoff-points for

intervals (and thereby the upper reference limits as a possible cutoff-point), differ from study to study. To illustrate the importance of the test cut-off level, we have used the percenti between 50 and 95 with the corresponding values in U/l as our cutoff-points for all three tests, and sensitivity, specificity PPV and LR were calculated for all levels.

Our study does not confirm the high sensitivity and specificity for CDT found in other studies (7-14). Where the specificity in males was higher than 90 percent, the sensitivity did not excee 26 percent. The highest PPV and LR in males were found with cut 30 g alcohol/day. When the cutoff-point for alcohol intake was increased, both PPV and LR were considerably reduced. LR for CD in females was low for all levels of intake, whereas PPV gave t highest values for a cutoff-point at 13 g/day.

Whereas CDT showed the best discriminatory power at lower level of intake, the results was the opposite for GGT. The highest LR was found when the cutoff-point was 52 g/day. Only 16 males had intake higher than 52 g/day, of which 4 had positive GGT (≥60 U, but only 2 had CDT values higher than 28 U/l. This indicate tha CDT has its best diagnostic performance at lower levels of intal and that GGT better discriminate at higher levels of consumptio This was in fact unexpected. Most studies on CDT (7-12) conclud on the contrary, that CDT is superior to the convential markers, especially for identification of regular high consumers. On the other hand, the better discriminatory power of CDT at lower leve of alcohol consumption, may be a great advantage in the identification of "risk drinkers". The low sensitivity may be

primary practice (31).

Schiele et al (21) concluded that "mAST is not particulary useful as a screening test in unselected populations". Our study confirms their findings (table 3). The highest LR (LR=2.2) for mAST was found in females, but was insignificant as the 95 percent confidence interval was 0.7-7.0.

In two earlier paper (32,33) we have described the determinants of GGT in a normal population. Our conclusion was that GGT, within its normal range, have many and other determinants than alcohol consumption. In addition a marked, and most probable, physiologic sex-difference in GGT was observed. The latter finding corresponds well with the poor diagnostic performance of GGT in women.

In conclusion none of potential markers seem usable in identifying females with high alcohol intake. Even in males the performance of the markers are poor. mAST seemed useless, and were consequently not introduced in any serial or parallel analyzes.

In screening programs, CDT and GGT might be useful in identifying males with a high probability of being high consumers of alcohol. CDT and GGT seems conditional independent both among high and low consumers.

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Table 1. Sensitivity (Sens), specificity (Spec), positive predictive value (PPV) and likelihood-ratio (LR) for carbohydrate deficient transferrin (CDT) according to sex, different levels of se reported alcohol consumption and different cutoff-points for the test. The Svalbard Study 1988-8

Cutoff-points for CDT (value and percentiles)	CUTOFF-POINTS FOR DAILY INTAKE OF ALCOHOL MALES (n=310) 80-PERCENTILE (30 g/day)				90-PERCENTILE (41 g/day)				95-PERCENTILE (52 g/		
	Sens	Spec	PPV	LR	Sens	Spec	PPV	LR	Sens	Spec	PPV
14 U/l (50)	66.2	53.3	.29	1.4	65.6	50.8	.14	1.3	68.8	50.0	.07
15 U/l (60)	55.4	62.0	.29	1.5	53.1	59.6	.14	1.3	62.5	59.4	.08
17 U/l (70)	44.6	62.0	.29	1.5	40.6	69.1	.14	1.3	50.0	69.1	.09
19 U/l (80)	38.5	80.8	.36	2.0	34.4	77.9	.16	1.6	37.5	77.3	.09
22 U/l (90)	26.2	91.3	.46	3.0	18.8	88.2	.16	1.6	18.8	87.8	.08
28 U/l (95)	13.9	96.9	.56	4.5	12.5	95.4	.25	2.7	12.5	95.0	.13
	FEMALES (n=171) 80-PERCENTILE (13 g/day)				90-PERCENTILE (15 g/day)				95-PERCENTILE (22 g/		
17 U/l (50)	60.0	43.7	.22	1.1	52.4	42.3	.11	0.9	54.6	42.8	.06
18 U/l (60)	48.6	53.3	.21	1.0	42.9	52.4	.11	0.9	45.5	52.8	.06
20 U/l (70)	40.0	71.9	.27	1.4	33.3	69.8	.13	1.1	45.5	70.4	.09
21 U/l (80)	37.1	75.6	.28	1.5	33.3	73.8	.15	1.3	45.5	74.2	.11
25 U/l (90)	11.4	89.6	.22	1.1	9.5	89.3	.11	0.9	9.1	89.3	.05
31 U/l (95)	2.9	94.1	.11	0.5	4.8	94.6	.11	0.9	0.0	94.3	-

Table 2. Sensitivity (Sens), specificity (Spec), positive predictive value (PPV) and likelihood-ratio (LR) for gamma-glutamyltransferase (GGT) according to sex, different levels of self-report alcohol intake and different cutoff-points for the test. The Svalbard Study 1988-89.

CUTOFF-POINTS FOR DAILY INTAKE OF ALCOHOL

MALES (n=310)

Cutoff-points for GGT (value and percentiles)	80-PERCENTILE (30 g/day)				90-PERCENTILE (41 g/day)				95-PERCENTILE (52 g/		
	Sens	Spec	PPV	LR	Sens	Spec	PPV	LR	Sens	Spec	PPV
18 U/l (50)	53.6	46.9	.22	1.0	63.6	48.0	.13	1.2	75.0	48.0	.07
21 U/l (60)	43.5	59.8	.24	1.1	51.5	60.3	.13	1.3	62.5	60.2	.07
25 U/l (70)	34.8	70.1	.25	1.2	39.4	70.0	.13	1.3	50.0	70.1	.08
33 U/l (80)	21.7	79.7	.23	1.1	27.3	80.1	.14	1.4	31.3	79.9	.07
43 U/l (90)	11.6	91.7	.29	1.4	18.2	92.0	.21	2.3	25.0	91.8	.14
60 U/l (95)	8.7	95.9	.38	2.1	12.1	95.7	.25	2.8	25.0	95.9	.25

FEMALES (n=171)

	80-PERCENTILE (13 g/day)				90-PERCENTILE (15 g/day)				95-PERCENTILE (22 g		
12 U/l (50)	54.3	45.6	.20	1.0	61.9	46.7	.14	1.2	63.6	46.3	.07
13 U/l (60)	48.6	55.9	.22	1.1	52.4	56.0	.14	1.2	63.6	56.3	.09
14 U/l (70)	42.9	70.6	.27	1.5	42.9	69.3	.16	1.4	54.6	69.4	.11
17 U/l (80)	22.9	80.2	.23	1.2	19.1	79.3	.11	0.9	18.2	79.4	.05
22 U/l (90)	5.7	87.5	.11	0.5	9.5	88.7	.11	0.8	9.1	88.8	.05
29 U/l (95)	2.9	92.7	.09	0.4	4.8	93.3	.09	0.7	0.0	93.1	-

Table 3. Sensitivity (Sens), specificity (Spec), positive predictive value (PPV) and likelihood-ratio (LR) for mitochondrial aspartate aminotransferase (mAST) according to sex, different level self-reported alcohol intake and different cutoff-points of the test. The Svalbard Study 1988-89

	CUTOFF-POINTS FOR DAILY INTAKE OF ALCOHOL										
	MALES (n=310)										
Cutoff-points for mAST(value and percentiles)	80-PERCENTILE (30 g/day)				90-PERCENTILE (41 g/day)				95-PERCENTILE (52 g/		
	Sens	Spec	PPV	LR	Sens	Spec	PPV	LR	Sens	Spec	PPV
3 U/l (50)	63.1	41.5	.23	1.1	59.4	40.5	.11	1.0	62.5	40.7	.05
4 U/l (90)	12.3	83.0	.17	0.7	15.6	84.0	.11	1.0	12.5	83.8	.04
5 U/l (95)	4.6	90.8	.13	0.5	3.1	91.2	.04	0.4	6.3	91.7	.04
	FEMALES (n=171)										
	80-PERCENTILE (13 g/day)				90-PERCENTILE (15 g/day)				95-PERCENTILE (22 g/		
2 U/l (50)	91.4	7.4	.20	1.0	90.5	7.4	.12	1.0	81.8	6.9	.05
3 U/l (70)	37.1	60.7	.20	1.0	19.1	58.4	.06	0.5	9.1	59.1	.02
4 U/l (95)	11.4	94.8	.36	2.2	9.5	94.0	.18	1.6	0.0	93.1	-

Table 4. Sensitivity (Sens), specificity (Spec), positive predictive value (PPV) and likelihood-ratio (LR) in males for a combination of gamma-glutamyltransferase (GGT) and carbohydrate deficient transferrin (CDT) according to different levels of self-reported alcohol consumption and different cutoff-points for the combined test. The Svalbard Study 1988-1989.

Cutoff-points for CDT and GGT (value and percentiles)		CUTOFF-POINTS FOR DAILY INTAKE OF ALCOHOL MALES (n=310)										
		80-PERCENTILE (30 g/day)				90-PERCENTILE (41 g/day)				95-PERCENTILE (52 g/		
		Sens	Spec	PPV	LR	Sens	Spec	PPV	LR	Sens	Spec	PPV
CDT	or GGT											
19 (80)	33 (80)	52.7	63.8	.29	1.4	54.6	62.0	.15	1.4	62.5	61.5	.08
19 (80)	43 (90)	44.9	74.5	.33	1.8	48.5	72.4	.17	1.8	56.3	71.6	.10
19 (80)	60 (95)	42.0	78.2	.36	1.9	42.4	75.6	.17	1.8	56.3	75.3	.11
22 (90)	33 (80)	42.0	72.0	.30	1.5	39.4	69.9	.13	1.3	43.8	69.6	.07
22 (90)	43 (90)	34.8	84.0	.38	2.2	33.3	81.4	.18	1.8	37.5	80.7	.09
22 (90)	60 (95)	31.9	88.1	.43	2.7	27.3	85.0	.18	1.8	37.5	84.8	.12

PAPER V

Intervention on a Population of Early-Stage Risk Drinkers[1,2]

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Background. In a health survey of more than 21,000 men and women ages 12–62 years, measurement of γ-glutamyltransferase (GGT) and answers on five questions on alcohol consumption were used as a basis for selecting an intervention population of early-stage risk drinkers. Altogether 290 men and 48 women met the criteria for inclusion.

Methods. The 338 subjects were randomized to a control group and two intervention groups. The minor intervention consisted of a single consultation during which possible reasons for the elevated GGT were discussed and a pamphlet with advice on changes in drinking habits was handed out. In the major intervention group the intervention was directed more specifically toward alcohol, with an extensive interview on drinking habits. In addition, the subjects in this group were offered follow-up consultations for new measurements of GGT.

Results. All three groups were examined after 1 year with GGT determination and an interview on change in drinking habits during the past year. At follow-up, significant decreases in mean GGT (26.5 U/liter) and self-reported alcohol intake (24.7 g/day) were observed in the intervention groups compared with the control group. No significant differences were, however, observed between the intervention groups.

Conclusion. The study indicates that modest and simple interventions may yield important changes in drinking habits in early-stage risk drinkers.

INTRODUCTION

Alcoholism and alcohol-related diseases have become threatening health hazards of Western societies (1). As such, the social consequences of alcoholism such as incest, child abuse, accidents, and violence seem to overshadow the wide spectrum of psychiatric and physical diseases which are known to be associated with alcohol abuse (2–4). Surveys have indicated that between 30 and 70% of hospital patients have harmful levels of alcohol intake (5, 6). Further, for about one-half of those surveyed, the patient's illness is directly related to alcohol use. Considering the limited resources available for public health care, it seems obvious that the search for effective intervention procedures in the field of alcohol prevention programs is essential.

Medical doctors generally lack the knowledge and appropriate tools to identify and help patients who are potential alcohol abusers. The strategy outlined in the literature has as its focus the early detection of alcohol abuse (7, 8) with subsequent action before the patient has developed major symptoms of alcohol depen-

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[2] This study was financially supported by the Blue Cross Center for Treatment of Alcoholics, Håkøy, Tromsø.

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intervention be implemented, and what is the effect of such an intervention'

The third Tromsø Study, a community-based, comprehensive health sur aimed primarily at cardiovascular diseases (11, 12) but also incorporating o health problems, was carried out in 1986–1987 in cooperation with the Nati Health Screening Service. This provided us with the opportunity to identi population of early-stage risk drinkers and to examine the effect of two type intervention in a controlled trial on 338 subjects. Long-term follow-up is plar in 5 years.

MATERIALS AND METHODS

Participants in the third Tromsø Study comprised the total population of ages 20–62 and women ages 20–56 in the municipality of Tromsø (Fig. 1) addition, a sample of males ages 12–19 years and females ages 12–19 and 5 years was invited to participate. The total number of subjects examined 21,647, i.e., 79.6% of the invited population.

The examination included a questionnaire identical to that used in the former studies in Tromsø (11, 12) and in the cardiovascular studies in other N wegian counties (13). A second questionnaire on education, previous and pre disease, dietary habits, alcohol and coffee consumption, drug use, and mental sleeping problems, handed out at the end of the examination, was to be filled i home and returned by mail. Completed questionnaires were returned by 92.5% those who attended the screening.

The physical examination comprised collection of venous nonfasting bl samples for measurements of serum lipids and γ-glutamyltransferase (GG weight, heights, and blood pressure measurements, and a one-channel ECG.

The measurements of GGT were performed at 37°C according to the rec mendations of the Scandinavian Enzymes Committee (14). The serum sam were kept at 4°C and analyzed within 48 hr. The coefficient of variation 2.8% for a commercial control serum (Precinorm, Boehringer-Mannheim) du the study period. All laboratory assessments were performed by the Divisio Clinical Chemistry, University Teaching Hospital of Tromsø.

Blood pressure was recorded with a semiautomatic device (DINAMAP-R) measured three times at intervals of 2 min on the right upper arm in a sit position. The same procedure was also used at the reexamination, but with other investigator and at another time of day.

The questionnaire comprised five questions on alcohol habits: teetotaller yes); beer/ wine, and liquor consumption (graded 1–5; never or a few times a y one to two times per month, once a week, two to three times a week, about da and the frequency of alcohol intake on one occasion corresponding to the amo in one bottle of wine (graded 1–4; not in the last year, a few times last year, to two times per month, three or more times a week).

The criteria for inclusion in the risk group were: (a) GGT from 50 (45 females) up to 200 U/liter, and (b) self-reported beer, wine, or liquor consump

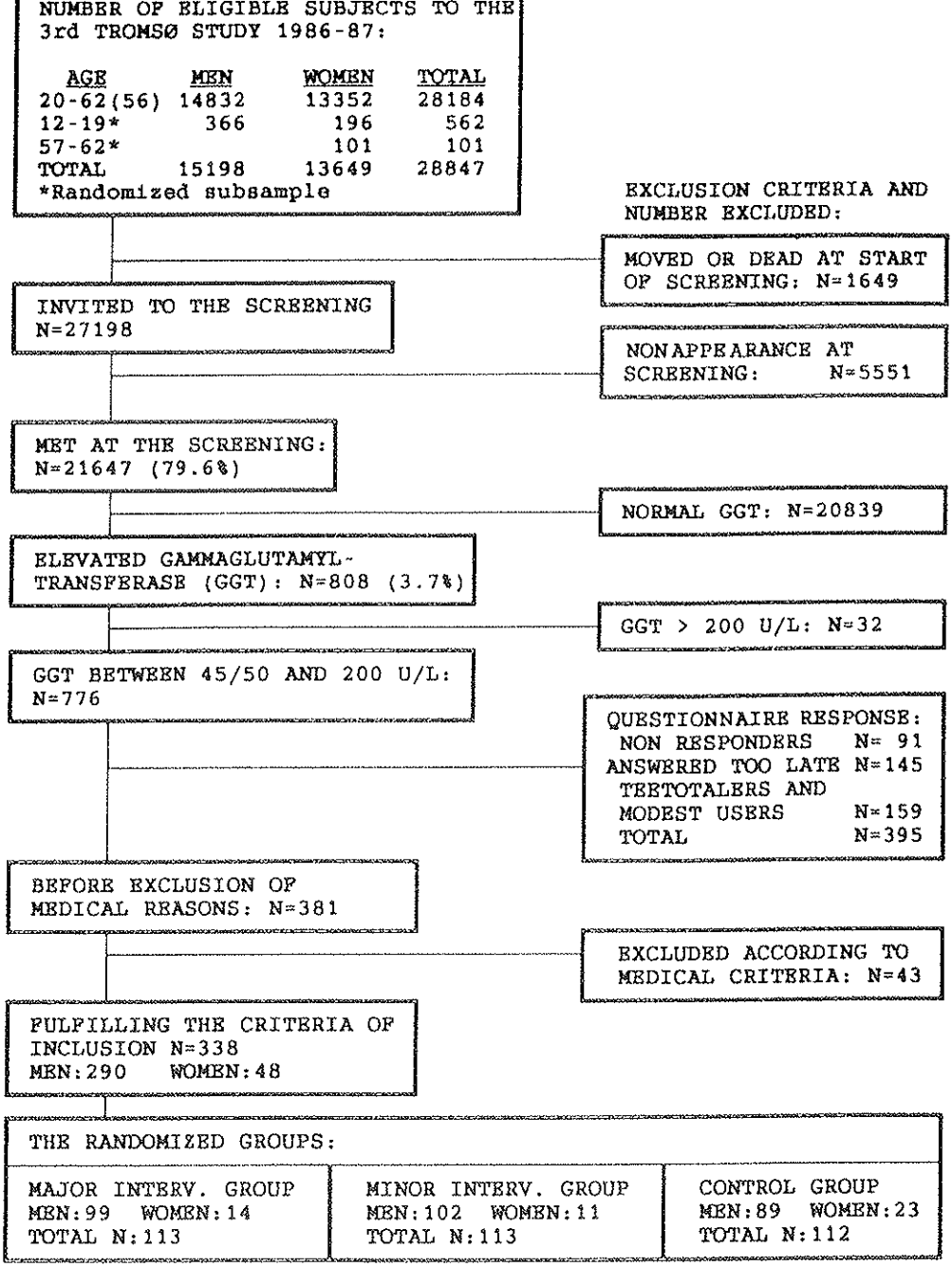

FIG. 1. Selection of participants in the risk group: The Tromsø Study 1987–1988.

at least two to three times a week or an alcohol intake on one occasion corresponding to one bottle of wine at least one to two times per month (the two upper categories).

The medical records of all subjects were checked at the University Hospital in

Tromsø. Excluded were all subjects with diagnosed alcoholism, hepato bil diseases, or major psychiatric disorders, and subjects on antiepileptic medicat

To search for contrasts between the background and the alcohol-risk pop tion, a standard multiple regression analysis was performed separately for e sex with inclusion in the risk group as dependent variable (yes/no) and a num of background characteristics as independent variables. Significant contrasts presented in a comparison of group means after adjustment by analyses of variance (multiple classification analyses) (15).

Figure 1 shows the selection of participants in the study. Of the population v attended the screening, 808 (3.7%) had GGT values exceeding the inclusion le Criteria for inclusion were fulfilled by 338 subjects (1.6%), 290 men and women. The risk population was randomized into three groups, a control gr which remained uninformed and untouched until follow-up, and two interven groups.

The Intervention Procedure

At the start of the intervention the two intervention groups (designated *minor* and the *major* intervention group) were sent a letter, which referred to elevated blood test," and were invited for a reexamination. Of the 226 invited, (99%) responded.

In the minor intervention group the participants were informed of the m common reasons for an elevated GGT value (illness, drugs, exposure to che cals, and use of alcohol), and asked to consider possible reasons for their e elevated GGT. A blood sample was drawn for a new GGT analysis, and a fol containing some advice on GGT and alcohol consumption was handed out at end of the consultation. In a follow-up letter, the subjects in this group w informed of the results of their most recent GGT analysis and an invitation to h a new GGT test within 1 year was suggested.

In the major intervention group the intervention was directed more specific toward alcohol consumption. After exclusion of other possible reasons, alco consumption was introduced as the reason for elevated GGT level. The part pants were then asked about their drinking habits, and alcohol consumption day) was registered according to the standardized WHO questionnaire (16). A r GGT test was taken, and monthly consultations with new GGT tests were offe (until normalization of GGT level). Advice on different ways of reducing alco intake was given, and a folder on alcohol consumption and GGT was handed Of the 105 participants in this group, 26 persons met only once for a GGT test met twice, and 25 persons met three times or more. This means that the former groups were left unintervened for the remaining period until follow-up

One year after the first reexamination, both intervention groups and the con group (approximately 1½ years after the screening) were invited to a follow- The letters of invitation were mailed so that they would be received 1 to 2 d ahead of the scheduled date for follow-up. Altogether 320 subjects (95%) m Blood pressure and GGT levels were measured, and all participants were in viewed about their present alcohol habits, including daily consumption (g/da Changes in alcohol intake during the past year and corresponding reasons for su

changes were recorded. Analyses of variance were used to test differences in GGT, heart rate, alcohol consumption, and blood pressure levels between groups and within groups during the intervention.

RESULTS

Table 1 shows the adjusted sex-specific difference in characteristics at the screening between the alcohol-risk group and the background population. The risk group, which had somewhat higher education, displayed higher blood pressure, heart rate, total cholesterol, and high-density lipoprotein cholesterol levels, and was more obese. Subjects in the risk population also reported more smoking, more sleeplessness, and using more hypnotics and antihypertensives. There was no significant difference in the rate of sickness, unemployment, or disability allowance between the groups (data not given). The same contrasts appeared in both sexes, and as they also showed a homogenous response to intervention, the sexes were pooled in the following analysis.

Figure 2 displays the mean change in GGT from baseline values at screening, at the start of intervention, and at follow-up. Table 2 shows the corresponding means with standard deviations for GGT along with blood pressure, heart rate, and daily consumption of alcohol in the different groups.

At screening, the mean GGT was significantly ($P = 0.028$) lower in the major invention group than in the two other groups. This difference was reduced and no

TABLE 1
SEX-SPECIFIC COMPARISON OF DIFFERENT CHARACTERISTICS AT SCREENING IN THE ALCOHOL-RISK GROUP AND THE BACKGROUND POPULATION: TROMSØ 1987–1988

	Men		Women		
	Risk group ($n = 288$)	Background population ($n = 8876$)	Risk group ($n = 48$)	Background population ($n = 9041$)	Adjusted for
Age (years)	41.0	38.7	42.7	36.5	
Body mass index (g/cm^2)	2.69	2.45	2.46	2.31	Age, smoking
Education (years)	12.11	11.43	12.29	11.25	Age
Coffee consumption (cups)	2.50	2.65	2.01	2.45	Age
Systolic blood pressure (mm Hg)	138.48	134.94	133.73	125.05	Age, BMI
Heart rate (frequency/min)	74.55	70.43	84.07	76.15	Age, BMI
Total cholesterol (mmol/liter)	6.15	5.82	6.00	5.59	Age, BMI
HDL-cholesterol (mmol/liter)	1.47	1.36	1.72	1.64	Age, BMI
Triglycerides (mmol/liter)	1.89	1.59	1.62	1.13	Age, BMI
Smoking (%)	54.1	45.8	58.2	45.0	Age, education
Antihypertensive (%)	4.94	2.77	13.13	1.91	Age
Hypnotica (%)	6.40	1.96	8.82	3.38	Age
Sleeplessness (%)	40.78	27.72	55.98	40.49	Age

Note. BMI, body mass index; HDL, high-density lipoprotein.

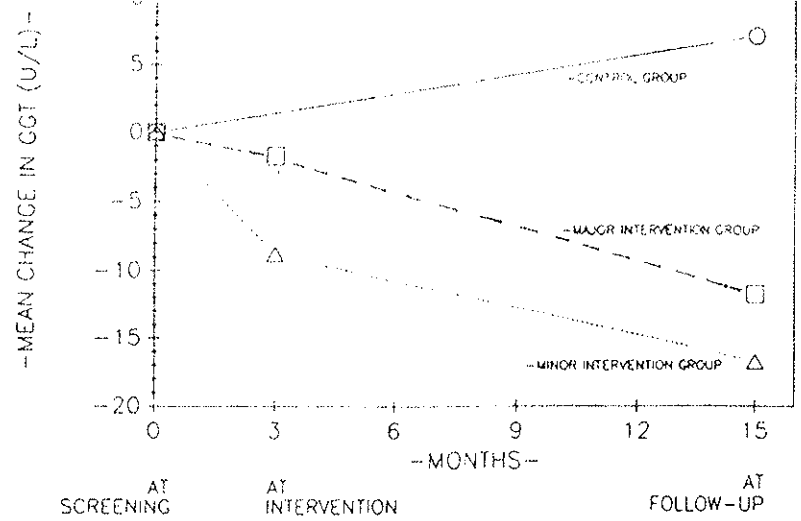

FIG. 2. Mean change in GGT from baseline values to intervention and follow-up: The Tromsø S 1987–1988.

longer significant at the start of the intervention. At follow-up, a strong signifi difference ($P < 0.001$) in mean GGT levels was found between the control gr and the two intervention groups. In the control group, the mean GGT was and 47.3% higher than that in the minor and major intervention groups, resp tively. There was no significant difference between the two intervention group $= 0.544$), even though the major intervention group displayed a lower mean va than the minor intervention group.

The within-group analyses showed a nonsignificant increase in mean GGT 7.1 U/liter for the control group from screening to follow-up. Both interven groups showed a decrease in mean GGT during the same period, significant f the baseline values ($P < 0.001$) as well as from start of the intervention ($P = 0.$ and $P < 0.001$ for the minor and the major intervention groups, respectively

Only subjects in the major intervention group were asked about their d

TABLE 2

MEAN GGT, BLOOD PRESSURE (BP), HEART RATE (HR), AND DAILY ALCOHOL CONSUMPTIO (DAC) WITH STANDARD DEVIATION (SD) AT SCREENING, AT START OF INTERVENTION, AND AT FOLLOW-UP: TROMSØ 1987–1988

	At screening			At intervention			At follow-up		
Groups:	Control	Minor	Major	Control	Minor	Major	Control	Minor	
N:	(112)	(113)	(113)	—	(111)	(112)	(108)	(107)	
GGT (U/liter)	79.2	78.4	70.1	—	69.6	68.3	86.5	61.1	
SD	31.5	30.0	22.1	—	38.1	30.4	55.1	30.7	
BP (mm HG)	137.6	139.0	137.9	—	—	—	145.9	143.2	1
SD	17.3	16.3	18.7	—	—	—	17.5	17.7	
HR (frequency/min)	78.7	77.6	78.6	—	—	—	80.2	77.1	
SD	13.7	16.4	14.9	—	—	—	13.8	14.6	
DAC (g/day)	—	—	—	—	—	32.6	39.2	15.6	
SD	—	—	—	—	—	24.0	35.9	16.3	

intake of alcohol at the start of the intervention. At follow-up, the mean daily alcohol consumption in the control group was more than double that in the two intervention groups. This difference was highly significant ($P < 0.001$). The subjects in the major intervention group reported a nonsignificantly lower daily intake of alcohol than the minor intervention group. Assuming the same (as the major intervention group) level of alcohol intake after randomization, there was a highly significant decrease in intake in both intervention groups at follow-up ($P < 0.001$). The increase in alcohol intake in the control group for the same period was marked but not significant.

The values for blood pressure and heart rate at follow-up were higher than the screening values, in all three groups. The increase was, however, highest in the control group.

Table 3 shows the mean difference in GGT between screening and follow-up according to self-reported change in alcohol intake. Irrespective of reported change in alcohol intake, the control group displayed an increase in GGT, with the highest increase among those who reported lower intake. Both intervention groups showed a significant decrease in GGT, in accordance with reported changes.

DISCUSSION

The results from the present population-based, controlled intervention study indicate that modest and simple intervention may yield important changes in drinking habits in early-stage risk drinkers.

Comparable intervention studies (17, 18) have recruited their participants mainly through clinical practice and thereby embraced a population characterized by more developed and serious alcohol-related problems or even manifest alcoholism. In our study, subjects with known alcoholism and markedly elevated GGT values were excluded.

The study therefore was designed to comprise a sample of "early-stage problem drinkers," who over time might be at high risk for developing more manifest symptoms of alcoholism. Although certain contrasts in background characteristics were observed, most of them were well known and expected (19). Our study

TABLE 3

MEAN CHANGE ($\bar{x}$) IN GGT (U/LITER) WITH STANDARD DEVIATION (SD) OF DIFFERENCE FROM SCREENING TO FOLLOW-UP ACCORDING TO SELF-REPORTED CHANGE IN ALCOHOL INTAKE: TROMSØ 1987–1988

	Changes in reported alcohol intake last year											
	Increased			Unchanged			Decreased			Total		
	n	$\bar{x}$	SD	*n*	$\bar{x}$	SD	*n*	$\bar{x}$	SD	*n*	$\bar{x}$	SD
Control group	12	3.2	42.0	81	6.7	34.7	15	12.5	91.7	108	7.1	46.8
Minor intervention group	1	—	—	17	−6.7	21.2	89	−18.7	34.3	107	−16.8	32.7
Major intervention group	0	—	—	16	−5.0	20.2	89	−13.1	29.3	105	−11.8	28.1

population was socially well integrated and had the same employment rate; same rate of receiving sickness, unemployment, and disability allowance; and even higher education level than the background population.

Compared with an estimated prevalence of "problem drinkers" in the Norwegian society of about 10% (9), our population may seem highly selective. Most this selection, in our opinion, stems from a low sensitivity of GGT as a screen test (21, 22). There is on the other hand no reason to believe that "probl drinkers" with normal GGT differ from those with elevated values. The select from nonattendance (23, 24), questionnaire nonresponse, and underreporting alcohol intake, however, may to some extent have given us a population es cially susceptible to intervention. Still, we believe that this population is fa representative for an undetected "alcohol-risk population."

The major intervention group showed a lower mean GGT, technically sign cant, after the screening. This difference leveled off at the start of the intervent and may be considered random. The decrease in GGT from this point to follow- is almost identical for the two intervention groups. In the control group there v a nonsignificant increase in mean GGT at follow-up. This group remained un formed and, in contrast to the Malmö Study group (18, 25), also untouched u follow-up. Our assumption is that the change in GGT in this group, with a m erate increase which overcompensated the expected regression toward the me is fairly representative for an untouched risk population. The increased standa deviation in this group at follow-up also displays the marked rise in GGT in so individuals, indicating loss of control of drinking habits.

In an open study such as the present one, one always runs the risk of eliciti an "eager to please" bias, with changes in drinking habits immediately bef follow-up and an underreporting of alcohol consumption at follow-up as an eff of the intervention. To minimize this, all participants received the invitation o 1–2 days prior to follow-up. Self-reported alcohol consumption (Table 2) is g erally underreported. Scandinavian studies (26–28) on this topic conclude t self-reporting reveals only about 50% of the total intake. On the other han self-reported alcohol consumption is useful in separating consumption groups a in studying time trends in consumption. Despite the lack of accuracy in se reported volume, we believe that the differences between the intervention grou and the control group mainly reflect the effect of the intervention. This is su ported by the results of the GGT analysis.

Only one of the participants in the intervention groups reported an increase alcohol intake; 83% reported a decrease. In the control group, about 75% of t subjects reported unchanged intake of alcohol, whereas 11% reported an increas The participants were asked about the motivation for their changes. In the int vention groups, 98% of the subjects linked it directly to the intervention. The fe other reasons given were overweight, economic problems, or social changes.

Several recent reports (29–31) have indicated a relation between high alcoh consumption and elevated blood pressure. They conclude that in subjects wi high blood pressure and high alcohol intake, a reduction in blood pressure is se after a corresponding decrease in alcohol intake. This study does not confirm su findings. This may be explained by differences in procedures for measurements

blood pressure at screening and at follow-up, differences in time of day for the examination (screening at daytime, follow-up at afternoon/evening), and changes in staff performing the measurements.

On the other hand, the identified risk population showed at screening significantly higher blood pressure and heart rate than the background population. Further, a trend toward lower values for blood pressure and heart rate was found in the two intervention groups compared with the control group, at follow-up. This may indicate an effect of alcohol intake on these variables.

One of the more surprising experiences from this study was the high response to the invitation to participate and the high rate of compliance. The dropouts were few, only 1% at the start and 5% at follow-up. It was feared that many participants would drop out due to the touchy topic and "misclassification" of subjects as risk drinkers. On the contrary, the response was generally very positive and many of the participants requested further controls after the end of the study. This may also indicate that the combination of GGT values and questions about alcohol provides an acceptable specificity. Further, to initiate change in drinking habits for persons below the level of risk consumption is hardly harmful, although markers of greater accuracy are required.

In the Malmö Study (18, 25) GGT values from a population study were used as a basis for intervention. The investigators concluded that GGT provided a useful tool both in identification and in motivating and monitoring treatment of heavy drinkers. Our study has many similarities to the Malmö Study, but our population includes both sexes, is younger with a broader age span, and excludes known alcoholics and subjects with GGT values above 200 U/liter. The GGT level of the intervention population in Malmö was considerable higher.

CONCLUSION

This study establishes that GGT is a powerful motivating factor for changes in drinking habits among early-stage risk drinkers. There are arguments against the use of a biological marker as motivation for lifestyle changes. Side effects such as "medicalization," needless fear, and excessive test preoccupation are probably more frequent than usually reported from such programs. On the other hand, there are obvious advantages connected with such use in a field where denial and lack of objective measurement of "exposure" are recurring problems.

Compared to the Malmö Study, where a separate outpatient clinic was set up for a long-term intervention, both of our intervention procedures seem very cost-effective. The minor intervention in our study, with a single consultation leaving the responsibility to the individuals themselves, proved as effective as the more time-consuming, and potentially more stigmatizing, major intervention. We, therefore, consider this approach a feasible alternative in preventive alcohol programs both in primary practice and in industrial health care.

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