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The alcohol marker phosphatidylethanol is closely related to AST, GGT, ferritin and HDL-C

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Abstract

Background: The aim of this study was to evaluate the quantitative relation between common clinical chemical analyses and ethanol use, measured by a combination of the two alcohol markers phosphatidylethanol (PEth) and carbohydrate-deficient transferrin (CDT).

Methods: Results of PEth and CDT in whole blood and serum, respectively, were included, together with information on 10 different commonly measured clinical chemical analytes, as well as age and sex. PEth was analysed by UPC^2-MS/MS and CDT was measured by capillary electrophoresis.

Results: Samples from 4873 patients were included. The strongest relation to alcohol consumption as measured by PEth, when correcting for age and sex, was found for HDL-C (standardized $\beta = 0.472$, $p < 0.001$), AST (standardized $\beta = 0.372$, $p < 0.001$), ferritin (standardized $\beta = 0.332$, $p < 0.001$) and GGT (standardized $\beta = 0.325$, $p < 0.001$). The relation to PEth was weak for total cholesterol, TG and ALP. No relation was found for Hb and LDL-C.

Conclusions: When using PEth as a marker for alcohol consumption, this study demonstrated the quantitative relation to commonly used test as AST or GGT, but also an important relation to ferritin or HDL-C. In clinical practice, elevated levels of these clinical chemical analytes should initiate further work-up on possibly harmful alcohol use.

KEYWORDS
alcohol biomarker, carbohydrate-deficient transferrin, clinical chemical analytes, phosphatidylethanol

1 | INTRODUCTION

Clinical chemical analyses are widely performed in clinical practice and are of great importance being able to provide each patient correct diagnosis. A wide range of indications are present for each analysis. Among the most requested analyses are haemoglobin (Hb), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C) and liver tests like aminotransferases (AST and ALT) and gamma-glutamyl transpeptidase (GGT). As the number of conditions and pathophysiological changes affecting each of

the analyses is large, the complex relationship between environmental factors, diseases and clinical chemical results is important to understand.

Alcohol consumption is one of the factors possibly leading to changes in clinical chemical results. As the concentration of AST, ALT and GGT increase as a result of acute alcoholic hepatitis, increased levels are expected in continuously heavy alcohol consumers. This relation to alcohol consumption is well known and also sometimes the indication for performing analyses like AST, ALT and GGT.[1,2] However, as a marker of alcohol consumption, AST, ALT and GGT show a low sensitivity and specificity.[3,4]

For clinical chemical analyses like lipids and ferritin, the relation to alcohol consumption is less obvious.[5,6] There are, however, publications showing the relation between HDL-C and alcohol use on an epidemiological level,[7] and this relation is also documented by experimental studies.[8,9] Also for ferritin, this relation is previously addressed,[10,11] but some publications discuss the relation between high levels of ferritin and cardiac diseases like atrial fibrillation, without including the possible moderating role of alcohol consumption.[12–14]

A diagnosis of harmful alcohol use has traditionally been difficult using objective markers, but lately the introduction of the direct alcohol marker phosphatidylethanol (PEth) has improved this diagnostics.[15] If PEth is used in combination with the more traditional alcohol marker carbohydrate-deficient transferrin (CDT),[16] the diagnostic accuracy, sensitivity and specificity to detect heavy alcohol consumption are high.[3]

It is important for physicians to be aware of which clinical chemical analytes that show a close relation to alcohol consumption. A deviant result from routine analyses which cannot be explained by the most common medical conditions might be related to excessive alcohol consumption. In this way, alcohol-related problems might be suspected at an earlier stage, and sensitive and specific alcohol markers can be requested and analysed for confirmation. The aim of this study was therefore to compare the results of the common clinical analyses such as AST, ALT, GGT, alkaline phosphatase (ALP), total cholesterol, LDL-C, HDL-C, triglycerides (TG), ferritin or Hb to the use of ethanol, as measured by a combination of the two alcohol markers PEth and CDT.

2 | MATERIAL AND METHODS

2.1 | Data collection

Results from PEth and CDT analysed at the Fürst Medical Laboratory were used for the present study together with results from AST, ALT, GGT, ALP, total cholesterol, LDL-C, HDL-C, TG, ferritin and Hb as well as age and sex. All samples analysed from September 2016 to April 2018 were included if results were available for both PEth and CDT, combined with one or more of the clinical chemical analytes. Analyses were made according to the requisitions from the doctors, and only the results from the routine handling of the case are included in this study.

The study database contained anonymous and encrypted information on age and sex in addition to analytical results. Samples were mostly collected from primary care physicians (97.4%) in addition to some from social care institutions (2.6%). However, further medical information about the study population could not be obtained.

2.2 | Analysis of PEth and CDT

PEth and CDT were analysed as described thoroughly in a previous publication.[17] In brief, PEth was analysed in whole blood using a Waters Acquity UPC2 (TM) Ultra Performance Convergence chromatography system connected to Waters TQ-S triple quadrupole mass-spectrometer (UPC2-MS/MS) (Waters, Milford, MA, USA). Serum CDT was quantified by electrophoretic separation of the transferrin fractions using a classic Sebia Capillarys 2 (Lisses, France) without CDT-IFCC standardization. The limit of quantification was 0.015 μmol/L (10.5 ng/ml) for PEth and 0.4% units for CDT.

PEth was related to alcohol consumption according to previously published results and clinical practice. Values of PEth > 0.30 μmol/L[18] and CDT ≥ 1.7% units[19] were considered to represent harmful alcohol consumption. PEth levels of 0.30 μmol/L corresponds to approximately 210 ng/ml (exactly 210.9 ng/ml), but as the limit of 0.30 μmol/L is commonly reported, this unit is further used in the present article.

2.3 | Analysis of clinical chemical tests

Blood Hb was analysed using Sysmex XN-9000 (Sysmex Corporation, Kobe, Japan), and the other clinical chemical tests were analysed in non-fasting serum samples using Advia Chemistry XPT (Siemens Healthineers, Erlangen, Germany). Reference levels were set according to the Nordic Reference Interval Project.[20]

2.4 | Statistics

SPSS IBM SPSS® Software Version 25.0 was used for statistical calculation of the data. Mean and standard deviation were reported for continuous variables. For examining the relation between PEth and CDT, respectively, to each of the clinical chemical analytes, 10 separate linear regression analyses were performed (one for each clinical chemical analyte) using the clinical chemical analyte as the dependent variable and PEth or CDT, respectively, together with age and sex as independent variables. Note that more than one clinical chemical analysis were often present in each patient (analysed in the same serum sample), making many patients included in more than one of the statistical models. To compare levels between two different groups, Student's *t*-tests were used.

Figures were made using Statistica (v. 12, Tibco, CA) and Canvas Draw 3.0.

2.5 | Ethics

Ethical approval was obtained from Regional Committee for Medical and Health Research Ethics, Region South-East, Norway (2018/1041). Due to the large size of the data material and the anonymous handling of the data, the study was approved to be performed without informed consent from each of the participants.

3 | RESULTS

In total, 4873 patients had valid results of both PEth and CDT, together with one or more results of the clinical chemical analyses (AST, ALT, GGT, ALP, total cholesterol, LDL-C, HDL-C, TG, ferritin or Hb). Only the first sample was chosen if the patient had measurements at different occasions.

The median age was 55.5 years; 66% were males and 34% females. In the total cohort, 2448 (50%) had PEth values > 0.30 μmol/L (~210 ng/ml). The number of patients with valid results for each clinical chemical analyte is seen in Table 1, together with the reference values, the mean values in the present population and the PEth levels for each group.

In multiple regression analyses, correcting for age and sex, the association to PEth was strongest for HDL-C (standardized $\beta = 0.472$, $p < 0.001$), AST (standardized $\beta = 0.372$, $p < 0.001$), ferritin (standardized $\beta = 0.332$, $p < 0.001$) and GGT (standardized $\beta = 0.325$, $p < 0.001$). No association to PEth was seen for LDL-C (standardized $\beta = -0.026$, $p = 0.219$) and Hb (standardized $\beta = 0.023$, $p = 0.144$). This is seen in Table 2. Figure 1 shows the relation between PEth and AST, the ratio AST/ALT, GGT, HDL-C and ferritin.

For CDT, the relations were generally weaker, except for HDL-C (standardized $\beta = 0.453$, $p < 0.001$), which showed a similar relation as PEth. A positive association between CDT and AST (standardized $\beta = 0.168$, $p < 0.001$) and ferritin (standardized $\beta = 0.097$, $p < 0.001$) was also seen. For CDT, a significant negative relation was seen to LDL-C (standardized $\beta = -0.170$, $p < 0.001$). This is seen in Table 3.

The measured values of the different clinical chemical analyses were divided into those above or below the mean values, respectively (as reported in Table 1). The proportion of subjects with PEth values > 0.30 μmol/L (indicating excessive alcohol consumption) having a concentration above the mean value of the clinical chemical results was highest for AST (73.0%), GGT (72.9%) and HDL-C (67.1%) (Table 4). The largest differences to those with clinical chemical values below the mean value was seen for AST, GGT, HDL-C and ferritin (Table 4).

When a combination of more than one of the analytes AST, GGT, HDL-C and ferritin was above the mean value, the percentage of subjects showing high PEth values was even higher. In patients where both ferritin and HDL-C were measured ($n = 1748$), 254 subjects had the combination of high values of both ferritin and HDL-C, and 83.5% of these had high levels of PEth. Correspondingly, in cases where all the analyses AST, GGT, HDL-C and ferritin were measured ($n = 1048$), only 63 subjects showed high values of all of them, but 96.9% of these showed high levels of PEth.

If studying the patients showing high PEth values (>0.30 μmol/L), the concentrations of AST, GGT and ferritin were more than 50% higher compared to the patients showing normal PEth values (≤0.30 μmol/L). For ALP, total cholesterol, LDL-C and Hb, this difference was below 10% (Table 5).

HDL-C levels in men were on average 1.25 mmol/L (SD 0.34) in those with normal PEth levels (≤0.30 μmol/L), compared to 1.62 mmol/L (SD 0.54) in those showing high PEth levels (>0.30 μmol/L). In men with the highest PEth-values (>2.5 μmol/L), the mean HDL-C concentration was 2.14 mmol/L.

Among patients showing high PEth (>0.30 μmol/L), only 27% of women and 18% of men showed ALT above the reference range. For AST, the same numbers were 33% of women and 27% of men, while for ferritin they were 36% for women and 34% for men.

TABLE 1 Number of cases analysed for each clinical chemical analyte, the mean values with standard deviation and the reference range used by the laboratory

	N	Mean value (SD)	Reference range	PEth value (mean, SD) μmol/L
Liver tests				
ALT (U/L)	4436	43.9 (88.0)	<70 U/L (males), <45 U/L (females)	0.68 (0.95)
AST (U/L)	3042	37.5 (55.6)	<45 U/L (males), <35 U/L (females)	0.69 (0.97)
GGT (U/L)	3861	110.1 (224.8)	Below 40 years: <80 U/L (males), <45 U/L (females) 40 years and above: <115 U/L (males), <5 U/L (females)	0.70 (0.97)
ALP (U/L)	2680	83.5 (48.9)	≤105 U/L	0.72 (1.00)
Lipids				
Total cholesterol (mmol/L)	2343	5.5 (1.3)	3.9–7.8 mmol/L[a]	0.65 (0.91)
TG (mmol/L)	809	2.2 (3.5)	≤2.60 mmol/L (fasting)	0.62 (0.94)
LDL-C (mmol/L)	2146	3.4 (1.1)	1.95–5.34 mmol/L[a]	0.64 (0.90)
HDL-C (mmol/L)	2103	1.5 (0.5)	0.75–2.14 mmol/L (males) 0.95–2.74 mmol/L (females)	0.64 (0.90)
Ferritin (μg/L)	3362	229.3 (276.2)	20–300 μg/L (males) 15–200 μg/L (females)	0.69 (0.97)
Hb (g/dl)	3350	14.6 (1.6)	13.4–17.0 g/dl (males) 11.7–15.3 g/dl (females)	0.69 (0.98)

Note: The mean (SD) PEth values within the cases analysed for each clinical chemical analysis are reported.
[a]For age less than 50 years: lower reference values.

TABLE 2 The multiple regression unstandardized and standardized β-coefficients and *P*-values for a relation between different clinical chemical analyses (liver tests, lipids, ferritin or Hb) (dependent variable) and PEth values (independent variable)

PEth			
	Unstandardized β	Standardized β	*P*
Liver tests			
ALT	12.4	0.133	<0.001
AST	21.6	0.372	<0.001
GGT	75.6	0.325	<0.001
ALP	3.57	0.073	<0.001
Lipids			
Total cholesterol	0.248	0.174	<0.001
TG	0.406	0.108	0.002
LDL-C	−0.033	−0.026	0.219
HDL-C	0.280	0.472	<0.001
Ferritin	94.0	0.332	<0.001
Hb	0.037	0.023	0.144

Note: Age and sex were inserted to the model as independent variables.

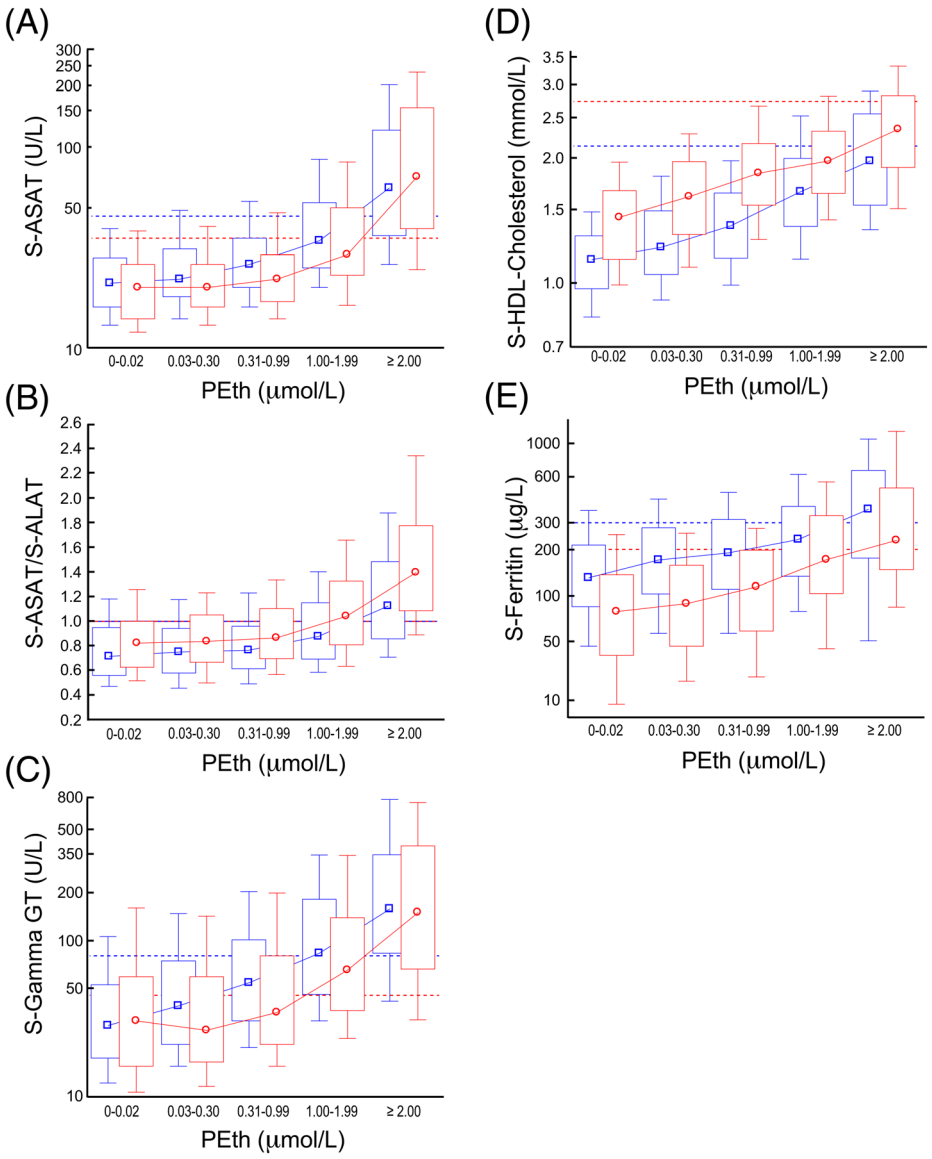

FIGURE 1 The distribution of AST, the ratio AST/ALT and GGT (A-C left panel) and HDL-C and ferritin (D-E right panel) grouped according to PEth level for males (blue squares) and females (red circles). The horizontal dotted lines represent the reference limits for men and females (highest for males, except from HDL-C). For GGT, the upper reference limit is shown only for persons below 40 years

4 | DISCUSSION

This study examined quantitatively the known relation between alcohol consumption and levels of liver enzymes, especially AST. The relation to HDL-C and ferritin, however, is of the same order of magnitude, although less appreciated. For analytes like LDL-C and Hb, there was no association to alcohol consumption. The knowledge of which clinical chemical analytes that are related to alcohol consumption might lead to earlier detection of alcohol-related problems, because a suspicion could be made from routine analyses performed in everyday clinic. This suspicion could then be confirmed or refuted by the analyses of specific alcohol biomarkers like PEth.

Alcohol consumption in the present study was defined according to levels of the direct alcohol marker PEth and the more traditional, indirect alcohol marker CDT. Self-reported consumption might be an appropriate gold standard, but numerous previous studies have shown substantial under-reporting of alcohol intake.[21,22] According to a relatively large body of evidence, both PEth and CDT have a high specificity for excessive alcohol intake.[23] PEth levels above 0.30 µmol/L are very likely to represent harmful consumption, either by episodic heavy drinking or persisting overuse. This may also apply for CDT concentration above 1.7-unit %. In addition, PEth, unlike CDT, has a high sensitivity detecting any alcohol use.[3,23]

Of the present results, the association between alcohol consumption and ferritin levels may be one that is less appreciated in clinical practice.[11] Elevated ferritin levels are seen in many conditions affecting the liver including haemochromatosis, viral hepatitis, metabolic syndrome and overweight and in hematologic and inflammatory diseases. The present finding is, however,

TABLE 3 The multiple regression unstandardized and standardized β-coefficients and *P*-values for a relation between different clinical chemical analyses (liver tests, lipids, ferritin or Hb) (dependent variable) and CDT values (independent variable)

CDT			
	Unstandardized β	**Standardized β**	***P***
Liver tests			
ALT	1.70	0.047	0.002
AST	3.83	0.168	<0.001
GGT	2.40	0.026	0.106
ALP	−0.883	−0.045	0.021
Lipids			
Total cholesterol	0.005	0.009	0.677
TG	−0.140	−0.080	0.024
LDL-C	−0.085	−0.170	<0.001
HDL-C	0.105	0.453	<0.001
Ferritin	10.8	0.097	<0.001
Hb	−0.023	−0.036	0.026

Note: Age and sex were inserted to the model as independent variables.

TABLE 4 Percent of patients showing PEth levels > 0.30 μmol/L (~210 ng/ml) among those having low (low group) and high (high group) values of each clinical chemical analysis (liver tests, lipids, ferritin or Hb), respectively

	% PEth >0.3 μmol/L in low group	***N***	**% PEth >0.3 μmol/L in high group**	***N***	***P***	**Difference in % high PEth**
Liver tests						
ALT	45.3	3145	63.9	1291	<0.001	18.6
AST	43.7	2301	73.0	741	<0.001	29.3
GGT	45.0	2943	72.9	918	<0.001	27.9
ALP	51.9	1733	51.6	947	0.883	−0.3
Lipids						
Total cholesterol	45.2	1290	56.2	1053	<0.001	11
TG	46.7	600	52.2	209	0.172	5.5
LDL-C	50.4	1146	49.1	1100	0.537	−1.3
HDL-C	36.6	1178	67.1	925	<0.001	30.5
Ferritin	44.0	2262	64.1	1100	<0.001	20.1
Hb	49.0	1632	52.3	1718	0.056	3.3

Notes: Low and high values of each clinical chemical analysis are defined as below and above the mean values, respectively (reported in Table 1). A *P*-value for a difference in % of cases with high PEth levels is also reported.

expected, given the relation between ferritin levels and liver damage.[24,25] Increased serum iron levels are also seen in heavy alcohol consumption, as this may lead to iron deposition in the liver.[26]

A small number of previous studies have addressed the relation between alcohol consumption and levels of ferritin. In one previous study of 148 patients (only published in Polish), a relation between AST, ALT, GGT, CDT and ferritin was seen,[27] and another study found a relation between AST/ALT and ferritin in 136 subjects with both alcoholic hepatitis and hepatitis C or B.[28] Two other studies examined 111 and 91 heavy drinkers, respectively, and found elevated ferritin levels in 58% and 67% of these.[10,29] A large previous study showed that moderate alcohol intake was not accompanied by increased ferritin levels, but increased levels were seen with high intakes.[30] The present study, which included a large number of patients, added knowledge to this field and showed gradually increasing levels of ferritin in all PEth groups, although most patients showed values below the

TABLE 5 Values for the different clinical chemical analyses (liver tests, lipids, ferritin or Hb) among patients showing PEth ≤ 0.30 μmol/L (~210 ng/ml) and PEth >0.30 μmol/L (~210 ng/ml), respectively

	PEth ≤0.30 μmol/L	*N*	PEth >0.30 μmol/L	*N*	*P*	% difference in mean value
Liver tests						
ALT (U/L)	37.9 (61.2)	2185	49.7 (107.5)	2251	<0.001	31
AST (U/L)	27.9 (57.0)	1495	46.7 (52.7)	1547	<0.001	67
GGT (U/L)	65.7 (124.1)	1869	151.8 (282.7)	1992	<0.001	131
ALP (U/L)	83.2 (52.1)	1291	83.7 (45.2)	1389	0.810	0.6
Lipids						
Total cholesterol (mmol/L)	5.29 (1.19)	1168	5.67 (1.37)	1175	<0.001	7.2
TG (mmol/L)	2.04 (3.30)	420	2.36 (3.79)	389	0.193	16
LDL (mmol/L)	3.37 (1.10)	1077	3.39 (1.19)	1069	0.635	0.6
HDL-C males (mmol/L)	1.25 (0.34)	705	1.62 (0.54)	746	<0.001	30
HDL-C females (mmol/L)	1.57 (0.44)	346	2.02 (0.59)	306	<0.001	29
HDL-C males + females (mmol/L)	1.36 (0.41)	1051	1.73 (0.58)	1052	<0.001	27
Ferritin (μg/L)	170.9 (161.5)	1662	286.4 (344.6)	1700	<0.001	68
Hb (g/dl)	14.5 (1.59)	1651	14.6 (1.54)	1699	0.011	0.7

Notes: Mean (SD) are reported for all clinical chemical analyses. A *P*-value for a difference in the levels of the clinical chemical analyses, and % difference from the normal to the high PEth groups is also reported.

reference range in the groups where moderately elevated PEth was seen. A high ferritin level should also be accompanied by anamnestic information of alcohol consumption and by interpretation of alcohol biomarkers. Previous literature has reported an association between ferritin levels and atrial fibrillation[13] and other cardiovascular causes of deaths,[12] and this relation could have been confounded by alcohol consumption.

The association between alcohol consumption and HDL-C is more thoroughly documented from previous literature,[7,31–33] and the present study added knowledge about the quantitative relation. It was previously experimentally shown by Rimm et al. that each additional 1 g of ethanol per day gave an increase in HDL-C in men of about 0.0035 mmol/L. Other studies showed comparable numbers.[8,34,35] In the present study, the HDL-C levels in men differed with 0.37 mmol/L in those showing normal PEth levels, compared to those showing high PEth levels. This could indicate that those showing high PEth levels drink on average presumably 100 g of pure ethanol (about 8 units) a day more than those showing normal PEth levels. Studying the group of men with the highest PEth values (>2.5 μmol/L), the mean HDL-C concentration ($n = 64$) indicated on average about 20 units of ethanol consumption a day more than those showing normal PEth levels. It should be noted that the relation between total cholesterol and PEth probably is due to the increased HDL-C concentrations.

The present study showed that AST had a closer relation to alcohol consumption than ALT, in accordance with previous studies.[1] AST is present in cardiac muscle and skeletal muscle, in addition to liver tissue. One contributing factor to the increase in AST levels could therefore be the relation to alcoholic cardiomyopathy.[36] Also, as skeletal muscle may be affected by alcohol intake, this could lead to possible leakage of AST and a subsequent increase in serum values.[37] It should especially be noted that the sensitivity of both AST and ALT to detect harmful alcohol consumption is low, as the present study showed that only about 20%–30% of those showing high PEth levels showed AST and ALT levels above the reference range. However, patients with PEth values above 2.00 μmol/L have AST values above the reference range in 60%–80% of the cases. This indicated that relatively high alcohol consumption is necessary before the liver tests become abnormal. The low sensitivity is also seen from the relatively high percentage of subjects in the low AST and ALT group showing high PEth values. If considering PEth a gold standard, the present study showed that the sensitivity to detect harmful alcohol consumption was actually lower for AST and ALT than for ferritin.

The relation between the different clinical chemical analyses and CDT was generally weaker than what was the case for PEth. This could be explained by the fact that PEth is a direct and a more sensitive biomarker for

alcohol consumption, thereby detecting closer to the true number of high consumers compared to CDT.[3] Interesting, however, is the closer association of age and sex to CDT compared to PEth (data not shown). This is in accordance with previous studies, indicating lack of age and sex effects on PEth levels.[17,38] CDT showed an inverse relation to LDL-C which was not seen for PEth.

The dataset included complete PEth and CDT values. However, the other tests were examined as requested. Therefore, the statistics used in the present article could not include all clinical chemical variables in one statistical model, and one model for each clinical chemical test was investigated. Due to a large dataset, it is assumed that comparison of the coefficients gave an impression of the strength of the relation to PEth/CDT. The fact that PEth levels in all groups are quite similar, as seen in Table 1, strengthens the assumption that data are missing at random.

The main weakness of the present study is the lack of a standardized questionnaire about alcohol consumption, and most of all, the lack of information about diseases. PEth is considered a reliable marker of alcohol consumption, but it should be noted that it does not provide information about pattern of use, and elevated levels could be caused by both moderate regular drinking and episodic heavy drinking. The fact that samples are analysed according to what was requisitioned from the doctors will affect the prevalence, for instance, of high PEth levels, but it will not affect the quantitative relation between PEth or CDT and the clinical chemical analytes, which was the aim of the present study. Also, causality cannot be concluded from the present study since the clinical chemistry tests may be affected in many conditions. It could therefore not be concluded that all patients showing high levels of AST, GGT, ferritin and HDL-C would show elevated levels of PEth and the lack of longitudinal design makes it difficult to conclude on which analytes that will increase first. The main strength of the study is the large material and the use of fully validated analytical methods. We also studied the materials in different ways: firstly, the relation between PEth or CDT and the clinical chemical analytes, secondly the PEth levels within those with low and high levels of the clinical chemical analytes and thirdly the levels of clinical chemical analytes within those with normal and high PEth. All these different approaches showed relatively similar results, and this strengthened the findings.

In conclusion, the present study showed that not only AST and GGT but also ferritin and HDL-C are associated with alcohol consumption. Although many factors influence analytes like ferritin and HDL-C, excessive alcohol intake should be kept in mind when elevated levels are observed.

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CONFLICT OF INTEREST

None of the authors have any conflicts of interests.

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