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# Identifying excessive chronic alcohol use with phosphatidylethanol in patients with suspected severe injury-results from the IDART study

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## Abstract

**Introduction: Acute and chronic alcohol use are well-known risk factors for accidents and injuries, and concurrent psychoactive drug use can increase injury risk further. Phosphatidylethanol (PEth) 16:0/18:1 is a biomarker used to determine alcohol consumption the previous 3–4 weeks. The aim was to investigate the prevalence of chronic alcohol use in trauma patients, as determined by PEth 16:0/18:1 concentrations, and how excessive chronic alcohol use relate to demographic variables, injury mechanisms and drug use.**
**Setting: Patients received at Norwegian trauma hospitals from March 2019 to February 2020. The study is part of the Impairing Drugs and Alcohol as Risk factors for Traumatic Injuries study.**
**Methods: All patients aged ≥ 16 years received with trauma team were included in the study. Data on injury date and mechanism, gender and age was registered. Blood samples were analyzed for 22 psychoactive medicinal and illicit drugs, ethanol and phosphatidylethanol 16:0/18:1. Regression analyses were conducted to assess associations between alcohol use and gender, age, injury mechanism and drug use.**
**Results and Conclusion: Of the 4845 patients included in the study, 10% had PEth 16:0/18:1 concentration ≥ 600 nM (~430 ng/mL), indicative of excessive chronic alcohol use. Being male, between 44-61 years old, involved in violence, and testing positive for medicinal drugs was associated with excessive chronic alcohol use.**
**Excessive chronic alcohol use was common among males, middle-aged, patients with violence as injury mechanism and those with medicinal drug use. These findings emphasize the need to detect and treat excessive chronic alcohol use among trauma patients.**

**Keywords:** injury; alcohol use; PEth; delirium tremens; trauma

## Introduction

Alcohol use is a well-known risk factor for accidents and traumatic injuries (Dry *et al*. 2012), and around 7% of all deaths globally caused by injuries in 2019 were attributable to alcohol (Institute for Health Metrics and Evaluation 2019). A study across emergency departments (EDs) in 27 countries found that alcohol contributed to between 5% and 40% of all admissions due to injuries (Ye *et al*. 2019). In addition, patients with alcohol use disorders (AUD) have higher risk of morbidity and mortality after discharge (Colling *et al*. 2023).

Combining alcohol with certain types of psychoactive medicinal or illicit drugs can alter the blood concentration and the pharmacological effect of both drugs and alcohol. However, combining alcohol and medicinal drugs appears to be widespread. In a previously published article on the same trauma patient population we found that 38% of the patients that tested positive for alcohol also tested positive for one or more psychoactive substances (Bråthen *et al*. 2023).

Screening for harmful alcohol use can be done using questionnaires, such as the Alcohol Use Disorder Identification Test (AUDIT) (Babor *et al*. 2001). However, questionnaires can be difficult to administer in a clinical setting, especially during the initial phases of trauma care, and are often subject to recall bias and social desirability bias (Johnston 2021). In addition to questionnaires relying on self-report, there are several objective and indirect clinical biomarkers of excessive drinking, including mean corpuscular volume, aspartate aminotransferase, gamma-glutamyltransferase, and carbohydrate deficient transferrin (Harris *et al*. 2021). Direct biomarkers include ethanol itself, and alcohol derivatives

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such as ethyl glucuronide and ethyl sulfate. The drawbacks of the indirect biomarkers are that they can be affected by other health conditions and biological factors, and most direct biomarkers have a relatively short detection window (Harris *et al*. 2021).

Phosphatidylethanol (PEth) is a group of direct alcohol biomarker, where one of the most abundant and most commonly analyzed species is PEth 16:0/18:1. PEth is formed in cell membranes of red blood cells in the presence of alcohol, and PEth 16:0/18:1 production starts immediately after consumption of alcohol and peaks after about 8 h (Schröck *et al*. 2017). Degradation of PEth happens at a slower rate, with a half-life of 3–5 days (Viel *et al*. 2012). PEth is known to be detectable for up to 3–4 weeks (Wurst *et al*. 2010).

PEth 16:0/18:1-concentrations <30 nM (20 ng/ml) is generally considered to reflect abstinence or low alcohol consumption (≤2 alcoholic units/day) (Kechagias *et al*. 2015). Concentrations of PEth 16:0/18:1 between 30 and 285 nM (20–200 ng/ml) indicate moderate consumption (2–4 alcoholic units/day), while concentrations ≥285 nM (≥200 ng/ml) are defined as chronic high alcohol consumption (more than 4 alcoholic units/day) (Ulwelling and Smith 2018, Luginbühl *et al*. 2022). However, these cutoffs should be considered somewhat arbitrary, as there are individual differences in how much alcohol is needed to produce a specific amount of PEth. We have previously found that weekly consumption of 300–399 g of alcohol corresponded to a mean PEth 16:0/18:1-concentration of about 600 nM (Jørgenrud *et al*. 2021a). This amount of alcohol consumption is considered to confer medium risk (men) and high risk (women) for illness, injury, and death, according to the World Health Organization (WHO 2000), although no level of alcohol is considered safe for your health (Anderson *et al*. 2023). To differentiate between moderate and excessive alcohol consumption, several PEth thresholds have been proposed (Gnann 2011, Helander and Hansson 2013, Schröck *et al*. 2016).

Screening and identification of patients with harmful alcohol use is rarely performed in hospital settings, as the focus is often on treating the acute medical condition. Because alcohol and drug use are known risk factors for injuries and for morbidity and mortality after discharge, there is a strong need for an assessment of the prevalence chronic alcohol use and an identification of the factors associated with excessive alcohol use and concomitant drug use in this patient group. Hospitalization after trauma incidence may serve as a window of opportunity to intervene for these patients. The main aim of this study was to investigate the prevalence of excessive chronic alcohol use in Norwegian trauma patients, as determined by PEth 16:0/18:1 concentrations. A secondary aim was to examine how excessive chronic alcohol use among trauma patients relates to age, gender, injury mechanism, and concomitant drug use.

## Material and methods

### Study design

The Impairing Drugs and Alcohol as Risk Factors for Traumatic Injury (IDART) study is a national prospective study, where the aim is to assess the prevalence of psychoactive medicinal and illegal drugs and alcohol of all trauma patients admitted to trauma hospitals in Norway. All Norwegian trauma hospitals ($N = 38$) were invited to participate in the study, which took place between March 2019 and February 2020. All patients received with trauma team were included in the study. Trauma teams were activated by predefined activation criteria based on the principles described in the Centers for Disease Control and Prevention's guidelines for field triage (Sasser *et al*. 2012). Exclusion criteria were being under 16 years of age and foreign citizenship (without Norwegian social security number). Patients who were transferred between hospitals or were received with trauma teams on two or more separate occasions during the study period were only included with data from the initial admission. Ethical consent for this study was granted by the Regional Ethical Committee (2017/1363), and waived the need for informed consent. However, all included patients were sent written information after the inclusion and had the option to withdraw from the study. Included patients we could not reach by postal mail after discharge, with reasons being no available postal address or no postal address of the next of kin in case of death, were excluded. A data protection impact assessment was conducted in cooperation with Oslo University Hospital Data Protection officials. The study is registered at Clinical Trials (NCT03773614).

The IDART study included 4845 patients from 4878 trauma admissions, and 35 of the 38 Norwegian trauma hospitals contributed to the 12-month data collection (Bråthen *et al*. 2023).

### Blood sample collection and analysis

Left-over diagnostic blood samples from admission were used for analysis. Because of the large number of inclusion sites in this study, the pre-analytical handling and procedures at each hospital varied. In general, the samples were stored at ambient temperatures for 1–5 days at the laboratory at each study site, before they were sent by postal mail to the study laboratory at Section of Drug Abuse Research, Oslo University Hospital. There, the samples were stored at 4°C and generally analyzed within 1–4 days.

Analysis of ethanol was performed using an automated alcohol dehydrogenase method (Kristoffersen and Smith-Kielland 2005). For analysis of PEth 16:0/18:1 and psychoactive medicinal and illicit drugs, an ultra-high performance liquid chromatography tandem mass spectrometry method was used (Jørgenrud *et al*. 2021b). A total of 100-$\mu$l blood sample was prepared using 96-well supported liquid extraction. Chromatographic separation was performed on a biphenyl core shell column, with mobile phase A consisting of 10 mM ammonium formate (pH 3.1) and methanol as mobile phase B. In order to obtain good sensitivity for all compounds, each extract was injected twice; 2 $\mu$l was injected for analysis of PEth 16:0/18:1, buprenorphine, and THC; 0.4 $\mu$l was injected for the remaining compounds. Two different gradient profiles were used for the two injections.

### Variables

Trained trauma coordinators at each site registered data on each patient into the study database based on information concerning the injury incident from the emergency medical services system, including the ambulance service, the emergency department (ED), and log from the Emergency medical communication center. Information on injury mechanism (transport, work, violence, fall, and unknown/other), injury date, gender, age, and medicinal drugs given as part of trauma treatment was recorded for each patient. In addition, a left-over blood sample from routine diagnostics was collected and

analyzed for ethanol, PEth 16:0/18:1, illicit drugs, and the most commonly prescribed psychoactive medicinal drugs.

Age was divided into age categories according to quantiles (<27, 27–43, 44–61, and > 61 years). Gender was divided into male and female.

If a medicinal drug was given to a patient as part of trauma treatment, the blood concentration of that drug was set to 0. PEth 16:0/18:1 concentrations were categorized as: <30 nM (no or low long-term alcohol use), 30–299 nM (low to moderate long-term alcohol use), 300–599 nM (high long-term alcohol use) and ≥600 nM (excessive chronic alcohol use). No excessive chronic alcohol use vs excessive chronic alcohol use was defined as <600 and ≥600 nM, respectively.

Ethanol, psychoactive medicinal and illicit drug use was defined as concentrations equal to or higher than analytical cutoff, and is listed in a previous publication (Jørgenrud *et al.* 2021b).

## Data analysis

Statistics were performed using IBM SPSS statistics for Windows version 29.0.0 (Armonk, NY: IBM Corp). Demographic variables, injury mechanism and psychoactive drug use were reported as counts. Proportions of patients within different categories of PEth 16:0/18:1 concentration who also tested positive for ethanol, benzodiazepines/Z-hypnotics, opioids, stimulants, and THC were reported as percentages, and presented as histograms, made in MS Office Excel. Additionally, chi-square test of independence was performed, with an $\alpha < 0.05$ being significant. Violin-plots of ethanol-concentrations ($\ln(x+1)-$transformed) were generated using RStudio (version 1.4.1717) and package "ggplot2."

To investigate which variables on demographic, injury mechanism, and drug use were associated with excessive chronic alcohol use, logistic regression was performed, with chronic alcohol consumption (PEth 16:0/18:1 concentration under or over 600 nM) as dependent variable. Gender (women being reference), age group (<27 years being reference), injury mechanism (transport incidence being reference), psychoactive medicinal drug use (no use being reference), and illicit drug use (no use being reference) were used as independent variables.

To examine the relationship between gender (bivariate), age (categorical), injury mechanism (categorical) and psychoactive medicinal and illicit drug use (both bivariate) and PEth 16:0/18:1 concentration as a continuous outcome, linear regression with $\ln(y+1)$-transformed PEth 16:0/18:1 concentrations was used to estimate regression coefficients with 95% confidence intervals (CIs). Back-transformed estimates and geometric mean ratios (GMRs; the geometric mean relative to the reference group) with 95% CIs are presented.

# Results

In total, 4845 patients were included in the study after exclusion of patients ($n = 327$) (Supplementary Fig. 1). Around 2/3 (68%) of the patients were male, and a quarter of the patients were under 27 years old, a quarter was over 61 years old, and half of the patients were between 27 and 61 years old (Table 1). Almost half of the patients (48%) had been involved in a transport-related incident, 31% in a fall incident, 7% in violence incidents, and 4% in a work incident. For 11% of the patients, the injury circumstance was unknown.

**Table 1.** Prevalence of gender, age, injury mechanism, PEth 16:0/18:1 concentrations (categories), ethanol, and psychoactive substance use ($N = 4845$).

| Variable | Prevalence, *N* (%) |
|---|---|
| Gender | |
| Male | 3304 (68.2) |
| Female | 1541 (31.8) |
| Age group | |
| <27 years | 1256 (25.9) |
| 27–43 years | 1191 (24.6) |
| 44–61 years | 1202 (24.8) |
| >61 years | 1196 (24.7) |
| Injury mechanism | |
| Transport | 2311 (47.7) |
| Work | 171 (3.5) |
| Violence | 344 (7.1) |
| Fall | 1478 (30.5) |
| Other/unknown | 541 (11.2) |
| PEth 16:0/18:1 concentration | |
| No/low alcohol use (PEth 16:0/18:1 < 30 nM) | 2325 (48.0) |
| Low to moderate alcohol use (PEth 16:0/18:1 30–299 nM) | 1646 (34.0) |
| High alcohol use (PEth 16:0/18:1300–599 nM) | 380 (7.8) |
| Excessive chronic alcohol use (PEth 16:0/18:1 ≥ 600 nM) | 494 (10.2) |
| Ethanol concentration | |
| Ethanol ≥ 0.1 g/kg | 997 (20.6) |
| Psychoactive substance use | |
| Psychoactive medicinal/illicit drugs[a] | 1077 (22.2) |
| Psychoactive medicinal drugs[a] | 840 (17.3) |
| Benzodiazepines/Z-hypnotics[a] | 599 (12.4) |
| Opioids[a] | 459 (9.5) |
| Illicit drugs[a] | 557 (11.5) |
| Stimulants[a] | 365 (7.5) |
| THC[a] | 348 (7.2) |

[a]Prevalence of psychoactive or medicinal drugs equal to or above analytical cutoff. Cutoffs for medicinal and illicit drugs are described in Jørgenrud *et al.* (2021b).

A little less than half of the patients (48%) had PEth 16:0/18:1 concentrations indicating no or low long-term alcohol intake (<30 nM), around 34% had PEth 16:0/18:1 concentrations ranging from 30 to 299 nM (indicative of low to moderate long-term alcohol use). Around 8% of the patients had PEth 16:0/18:1 concentrations indicating high long-term alcohol use (300–599 nM), while 10% had concentrations indicating excessive chronic alcohol use ≥600 nM. Ethanol (≥0.1 g/kg) was detected in 21% of all the patients, and psychoactive medicinal and/or illicit drugs were detected in 22% of all the patients.

While only 0.8% of patients with PEth 16:0/18:1 <30 nM had detectable concentrations of ethanol, the proportion was 78% for those with PEth 16:0/18:1 ≥600 nM (Fig. 1a). Ethanol-concentration was also generally higher in patients categorized with high and excessive chronic alcohol use, as depicted by violin-plots (Fig. 1b). When dividing the four PEth 16:0/18:1 categories into ethanol-positive and ethanol-negative samples, median PEth 16:0/18:1 concentration within each category was generally lower in the ethanol-negative vs ethanol-positive, especially for those with PEth concentrations 30–300 nM [ethanol-positive: median PEth 16:0/18:1 = 182 nM ($n = 376$); ethanol-negative: median PEth 16:0/18:1 = 84 nM ($n = 1270$)] (Supplementary Table 1).

The results also demonstrated higher prevalence of psychoactive medicinal and illicit drug use among patients with excessive chronic alcohol use compared to those with lower

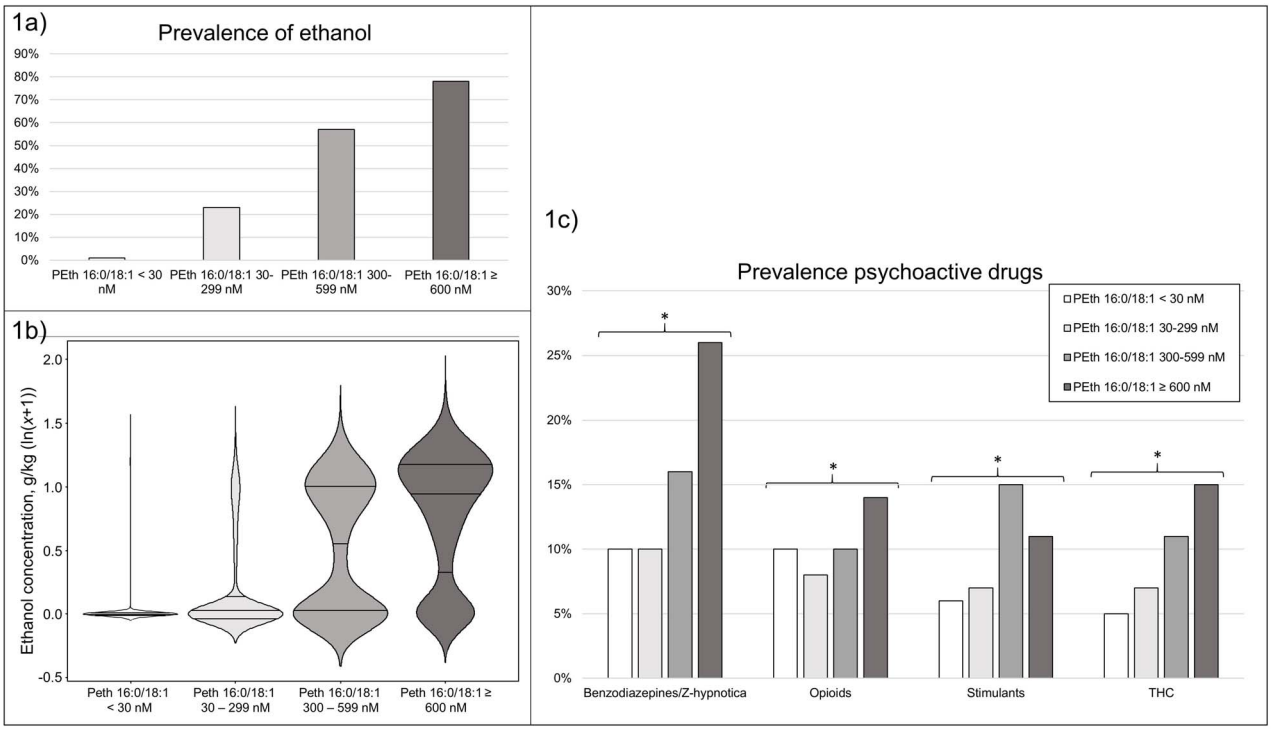


**Figure 1** Proportion (percentages) of patients categorized by PEth 16:0/18:1 categories that tested positive for ethanol and other psychoactive substances. (a) Proportion of patients ($N = 4845$) categorized by PEth 16:0/18:1 category that also tested positive for ethanol (≥0.1 g/kg). (b) Violin-plots of ethanol concentrations (g/kg, ln($x + 1$)-transformed) of all patients ($N = 4845$) categorized by PEth 16:0/18:1 category. 25th, 50th, and 75th percentiles marked within each violin-plot. (c) Proportion of patients (4845) categorized by PEth 16:0/18:1 category that also tested positive for benzodiazepines/Z-hypnotics, opioids, stimulants, and THC. *Chi-square test significance ≥0.001

alcohol use (Fig. 1c). Benzodiazepines/Z-hypnotics and opioids were found in the blood samples of 26% and 14% of patients with excessive chronic alcohol use. We found a higher proportion of stimulant use among those with high long-term alcohol use compared to those with excessive chronic alcohol use (15% vs 11%), and opposite for THC use with lower proportions among those with high alcohol use compared to excessive alcohol use (11% vs 15%).

A bivariate logistic regression with excessive chronic alcohol use (PEth 16:0/18:1 under or over 600 nM) as dependent variable, and injury mechanism, age group, gender, medicinal drug use, and illicit drug use as independent variables (both unadjusted and adjusted) was performed (Fig. 2). This showed that male patients (OR = 1.82; 95% CI: 1.43–2.30) and patients aged ≥26 years were associated with excessive chronic alcohol use, especially those aged 44–61 years old (OR = 3.21; 95% CI: 2.34–4.40). Also, being involved in violence (OR = 3.37; 95% CI: 2.41–4.71) or fall incidences (OR = 2.24; 95% CI: 1.76–2.84) was strongly associated with excessive chronic alcohol use compared to patients involved in traffic incidents. There was also an association between excessive alcohol use and medicinal drug use (OR = 2.02, 95% CI = 1.60–2.55), but no significant association between alcohol use and illicit drug use (OR = 1.30, 95% CI = 0.96–1.75).

We found that patients involved in violence and fall incidents had significantly higher PEth 16:0/18:1 concentrations compared to patients involved in transport incidents (GMR = 2.45; 95% CI = 1.85–3.25, and GMR = 1.81; 95% CI = 1.53–2.12, respectively) (Table 2). Males had significantly higher PEth 16:0/18:1 concentrations compared to females (GMR = 2.39; 95% CI = 2.06–2.76). Investigating the relationship between psychoactive substance use, we found that both patients with medicinal and illicit drug use had higher PEth 16:0/18:1 concentrations compared to those with no use (GMR = 1.32; 95% CI = 1.09–1.61, and GMR = 1.50; 95% CI = 1.18–1.91, respectively). Patients aged 44–61 years had higher PEth 16:0/18:1 concentrations compared to patients aged <27 years old (GMR = 1.41; 95% CI = 1.17–1.71).

## Discussion

In this study, we found a high proportion of trauma patients with high or excessive chronic alcohol use as determined by their blood PEth 16:0/18:1 concentrations. The majority of these patients also had an acute alcohol intake at the time of trauma admission. Factors associated with excessive alcohol use was being male, older than 26 years old, having injuries from violence or fall incidences, and medicinal drug use.

In a national perspective, the proportion of high and very high PEth 16:0/18:1 concentrations (≥300 nM) were higher among the trauma-patients (18%) compared to the general population (4.6%), as shown in the HUNT4 study, which took place in Trøndelag county in Mid-Norway (Skråstad *et al.* 2023). However, there were a larger proportion of women and a higher mean age in the HUNT4 population compared to the sample in this study. Furthermore, the proportion of patients with PEth 16:0/18:1 ≥ 300 nM in this study was higher compared to what we found among acute medically ill patients at a local hospital in Oslo (11.4%), although the medical patients were older compared to the trauma patients

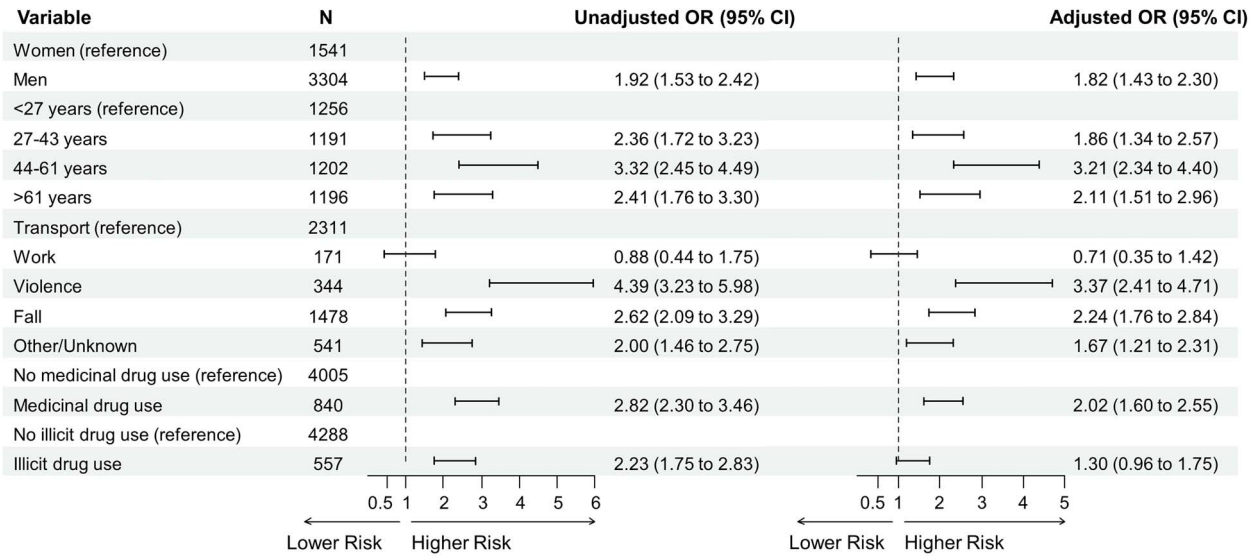


**Figure 2** Forestplot of bivariate logistic regression using PEth 16:0/18:1 ≥ 600 nM as dependent variable, and gender, age group, injury mechanism, medicinal drug use, and illicit drug use as independent variables. Cutoffs for medicinal and illicit drugs are described in Jørgenrud *et al.* (2021b)

**Table 2.** GMRs (exponential coefficients) and 95% CIs from linear regression of PEth 16:0/18:1 concentration (ln($y$ + 1)) on gender, age group, injury mechanism, medicinal and illicit drug use ($N$ = 4845).

| Variable | GMR (95% CI) |
|---|---|
| Gender | |
| Female | *1 (reference)* |
| Male | 2.39 (2.06–2.76) |
| Age (intervals) | |
| <27 years old | *1 (reference)* |
| 27–43 years old | 1.12 (0.93–1.36) |
| 44–61 years old | 1.41 (1.17–1.71) |
| >61 years old | 0.71 (0.59–0.87) |
| Injury mechanism | |
| Transport | *1 (reference)* |
| Work | 0.73 (0.50–1.06) |
| Violence | 2.49 (1.88–3.30) |
| Fall | 1.81 (1.54–2.13) |
| Other/unknown | 1.30 (1.04–1.63) |
| Medicinal drug use | |
| No | *1 (reference)* |
| Yes | 1.32 (1.09–1.61) |
| Illicit drug use | |
| No | *1 (reference)* |
| Yes | 1.50 (1.18–1.91) |

(Kabashi *et al.* 2019). These findings indicates that high and excessive chronic alcohol use was much more prevalent among Norwegian trauma patients compared to both the general population and patients acutely admitted to medical wards.

From logistic regression analysis, we found that PEth 16:0/18:1 concentrations ≥600 nM was associated with being male and older than 26 years old, especially 44–61 years old. Skråstad *et al.* (2023) similarly found higher mean PEth 16:0/18:1 concentrations among men and among persons aged 50–69 years old in the HUNT4 study, and Kabashi *et al.* (2019) found higher proportions of PEth 16:0/18:1 ≥ 300 nM among male patients and within age groups 41–70 years old. Paradoxically, from linear regression we found lower PEth 16:0/18:1 concentrations in age group >61 years compared to the youngest age group. This indicates a generalized lower alcohol consumption, but higher proportion of excessive drinkers in the oldest compared to the youngest age group. In a study on alcohol use and heavy drinking in Norway, Bye and Rossow (2021) found that heavy drinkers (AUDIT >9) were mostly in the youngest age groups (16–24 years old), whereas heavy drinkers (by volume) were mostly in the older age groups (45–79 years old). This might partly explain why we found a higher proportion of older patients with PEth 16:0/18:1 ≥ 600 nM in our study.

More than half of the patients in our study had PEth 16:0/18:1 concentrations equal to or higher than 30 nM. This is a higher proportion than what they found among 186 injury patients presenting to an ED in Brisbane, Australia (41.4%) (Cameron *et al.* 2023). However, the proportion of injury patients with PEth 16:0/18:1 ≥ 200 ng/ml (~285 nM) was 19.4%, similar to our study. A report from 2023 stated that alcohol-related injury accounted for 5.7% of all hospitalized injuries and 14% of injury deaths in Australia between 2019 and 2020 (Australian Institute of Health and Welfare 2023). These patients included those with both an injury condition and an alcohol-related condition (both alcohol-induced and alcohol-related), or an injury-related and an alcohol-related cause of death. Moreover, patients admitted to EDs with injuries have a higher frequency of harmful alcohol consumption compared to the general population (Cherpitel 2007, Gardner *et al.* 2017). These findings demonstrate that excessive alcohol use is common among injury patients and has implications on morbidity and mortality.

Consumption of alcohol resulting in PEth 16:0/18:1 concentrations ≥600 nM could be symptomatic of an AUD. Mean PEth 16:0/18:1 concentration in patients with alcohol use AUDs admitted for treatment of acute alcohol withdrawal was found to be 2038 nM (1475.32 ng/ml) (Novak *et al.* 2023). From 29 WHO World Mental Health surveys, the mean lifetime and 12-month prevalence of AUDs was estimated to be around 8.6% and 2.2%, respectively, but with large regional variations (Glantz *et al.* 2020). One explanation for these differences, which is discussed in the paper, is that heavy episodic drinking (or binge drinking) is more heavily

associated with AUDs than temperate drinking patterns. For persons with an AUD, abrupt decrease or discontinuation of alcohol use, such as during hospital admissions, can lead to the development of withdrawal symptoms. In 3%–5% of the cases, the persons may exhibit more severe withdrawal symptoms such as confusion, autonomic hyperactivity, and cardiovascular collapse, known as delirium tremens (Rahman and Paul 2023). The condition can occur as early as 48 h after alcohol cessation and can last up to 5 days. If undiagnosed and left untreated, delirium tremens can be fatal, with an anticipated mortality of 37% (Rahman and Paul 2023). However, chronic tolerance enables heavy drinkers to appear substantially less intoxicated even at blood alcohol concentrations that would be lethal to social drinkers (Brick and Erickson 2009). Intoxicated patients with a chronic excessive alcohol use can therefore be challenging to detect merely by visual assessment. It is important to note that patients who suffer traumatic brain injury may experience posttraumatic delirium, which is not alcohol-related (Roberson *et al*. 2021). For severely injured patients, especially respiratory patients, prolonged intensive care unit (ICU) stay is associated with ICU delirium, independently of alcohol use and traumatic brain injury (Kotfis *et al*. 2018). However, the conditions differ, emphasizing the need to diagnose and procure the correct treatment.

Our findings also show that patients with no or low long-term alcohol use (PEth 16:0/18:1 < 30 nM) mostly had low or no acute alcohol use (ethanol <0.1 g/kg). Patients with higher PEth 16:0/18:1 concentrations more often also tested positive for ethanol, and the proportion of ethanol-positive among those with the highest PEth 16:0/18:1 (≥600 nM) was 78%. This correlation between excessive acute and chronic alcohol intake suggests a persistent alcohol intake pattern over time, as PEth blood concentration reaches an equilibrium between production and degradation, reflecting the consumption of alcohol. However, it is also important to emphasize that PEth is produced *in vitro* in blood samples in the presence of ethanol (Beck *et al*. 2021). Our findings show that median PEth 16:0/18:1 concentrations generally were higher within each PEth 16:0/18:1 category for the ethanol-positive patients compared to the ethanol-negative patients. For patients who tested positive for ethanol it is therefore reasonable to believe that some of the PEth is formed post blood sampling, resulting in an overestimation of PEth concentrations.

Concomitant use of psychoactive medicinal drugs, especially benzodiazepines and Z-hypnotics, was found to be more prevalent among patients with very high PEth 16:0/18:1 (≥600 nM) compared to patients with low to high PEth 16:0/18:1 (<600 nM). Also illicit drug use was more prevalent among patients with high to very high PEth 16:0/18:1 compared to those with no or low to moderate PEth 16:0/18:1 concentrations. In addition, from logistic regression, testing positive for medicinal drugs was associated with having a very high PEth 16:0/18:1 concentration, while linear regression found 50% higher PEth 16:0/18:1 concentrations among patients with illicit drug use compared to those without illicit drug use. Association between alcohol and drug use among injury patients has been found in other studies (Bakke *et al*. 2016, Mundenga *et al*. 2019). Combining alcohol with psychoactive substances, especially benzodiazepines and Z-hypnotics, increases the risk of motor vehicle crash and fall injuries, beyond the risk of alcohol alone (Pariente *et al*. 2008, Chan and Anderson 2014, Díaz-Gutiérrez *et al*. 2017). Cherpitel *et al*. (2012) found that relative risk (RR) of injury was significantly related to alcohol use (RR = 3.3) and alcohol use combined with drug use (RR = 3.0), but not with drug use alone. In a Norwegian register-based study, a higher prevalence of psychoactive drug use was found among trauma patients in the Oslo University Hospital Trauma Registry compared to the general population (Torp *et al*. 2021). Data from the HUNT3 study also show that the use of medicinal drugs with addiction potential was frequent among older (≥65 years old) Norwegians who reported regular alcohol consumption (Tevik *et al*. 2017). Concomitant use of alcohol and psychoactive drugs may cause synergistic or additive effects, increasing the effects of the substance in a dose-dependent manner. Considering the intoxicating effects of high alcohol consumption alone, the effects of simultaneous use of drugs can be unpredictable and dangerous. The reasons for mixing alcohol with psychoactive drugs are varied, such as a desire to increase feelings of euphoria and sociability, or to alleviate anxiety or distress caused by stimulant use (Boileau-Falardeau *et al*. 2022). Regardless, hospital admissions offer a great opportunity to raise awareness of the potentially harmful effects of alcohol–drug interactions.

The strengths of this study are the large sample size ($N$ = 4845) and high completeness, with inclusion of patients from 35 of 38 Norwegian trauma hospitals, covering all geographical parts of Norway. Another strength is the use of leftover blood samples taken immediately after ED arrival, allowing blood substance concentrations to be similar to that at the time of the incident. However, there is a large varying degree of rurality in Norway. Higher degree of rurality will ultimately lead to a more considerable time period between incident and blood sampling, resulting in lower detected blood concentrations compared to the time of incident. Another limitation is the *in vitro* formation of PEth, as earlier mentioned (Beck *et al*. 2021). Our findings show that many of the PEth 16:0/18:1-positive patients also tested positive for ethanol, and it is reasonable to believe that for some of the patients PEth 16:0/18:1 has been formed *in vitro*, resulting in artificially higher concentrations and misclassification into PEth category. However, we find it plausible that such misclassification would be equally distributed across the covariates and therefore lead to similar interpretations of the results from the regression analysis. In future research, addition of a phospholipase D inhibitor, such as sodium metavanadate, to the blood sample is recommended to reduce post-sampling PEth formation (Beck *et al*. 2021). Other sources of bias can differential dropout, where excluded patients differ in various aspects from the included patients. Misclassification bias could have arisen when registering patient injury mechanism, although we believe this is minimized by using trained trauma coordinators.

After identifying patients with excessive chronic alcohol use, it is important to refer them to treatment, or motivate the patient to reduce their alcohol consumption. Brief interventions are short counseling sessions that can be provided by health personnel not specialized in addiction treatment. Interventions aimed at trauma patients with alcohol and/or illicit drug use have been estimated to halve the incidence of trauma recidivism (Cordovilla *et al*. 2017), and being cost-effective (Gentilello *et al*. 2005).

## Conclusion

In conclusion, our findings indicate a relatively high degree of very high acute and chronic alcohol use among trauma patients. Some of the patients with excessive chronic alcohol use might be at risk of developing withdrawal symptoms, even to the extent of delirium tremens. Delirium tremens risk assessment, observation, and treatment are effective in such cases. We found that being male, aged 44–61 years and having injuries from violence and falls was associated with excessive chronic alcohol use. Many of the patients with very high alcohol use were also using psychoactive medicinal and illicit drugs, which can inversely alter the effects of the substances. This emphasizes the need for a fast, inexpensive and objective method, such as PEth analysis, to identify harmful alcohol use among hospitalized patients to prevent morbidity and mortality after release from hospital.

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## Author contributions

Benedicte M. Jørgenrud (study design, data collection, blood sample analysis and data analysis, drafted the manuscript, and edited the full manuscript), Camilla C. Bråthen (study design, data collection, data analysis, drafting the manuscript, and editing the full manuscript), Jo Steinson Stenehjem (statistical analysis, drafting of the manuscript, and editing the full manuscript), Thomas Kristiansen (study design, data collection, data analysis, drafting the manuscript, and editing the full manuscript), Leiv Arne Rosseland (study design and drafting the manuscript), and Stig Tore Bogstrand (study design, data analysis, drafting the manuscript, and editing the full manuscript).

## Supplementary data

Supplementary data is available at *ALCALC Journal* online.

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## Data availability

We do not have permission to share the research data.

## References

Australian Institute of Health and Welfare. *Alcohol-Related Injury: Hospitalisations and Deaths, 2019–20*. AIHW, Canberra, 2023. Retrieved from https://www.aihw.gov.au/reports/injury/alcohol-related-injuries-2019-20.

Anderson BO, Berdzuli N, Ilbawi A. *et al.* Health and cancer risks associated with low levels of alcohol consumption. *Lancet Public Health* 2023;**8**:e6–7. https://doi.org/10.1016/S2468-2667(22)00317-6.

Babor TF, Higgins-Biddle JC, Saunders JB. *et al. AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care*, 2nd edn. Geneva, Switzerland: World Health Organization, 2001.

Bakke E, Bogstrand ST, Normann PT. *et al.* Influence of alcohol and other substances of abuse at the time of injury among patients in a Norwegian emergency department. *BMC Emerg Med* 2016;**16**:20. https://doi.org/10.1186/s12873-016-0085-2.

Beck O, Mellring M, Löwbeer C. *et al.* Measurement of the alcohol biomarker phosphatidylethanol (PEth) in dried blood spots and venous blood-importance of inhibition of post-sampling formation from ethanol. *Anal Bioanal Chem* 2021;**413**:5601–6. https://doi.org/10.1007/s00216-021-03211-z.

Boileau-Falardeau M, Contreras G, Gariépy G. *et al.* Patterns and motivations of polysubstance use: a rapid review of the qualitative evidence. *Health Promot Chronic Dis Prev Can* 2022;**42**:47–59. https://doi.org/10.24095/hpcdp.42.2.01.

Brick J, Erickson CK. Intoxication is not always visible: an unrecognized prevention challenge. *Alcohol Clin Exp Res* 2009;**33**:1489–507. https://doi.org/10.1111/j.1530-0277.2009.00979.x.

Bråthen CC, Jørgenrud BM, Bogstrand ST. *et al.* Prevalence of use and impairment from drugs and alcohol among trauma patients: a national prospective observational study. *Injury* 2023;**54**:111160. https://doi.org/10.1016/j.injury.2023.111160.

Bye EK, Rossow I. Heavy drinkers and the contexts of drinking among adults in Norway. *Drug Alcohol Depend* 2021;**229**:109127. https://doi.org/10.1016/j.drugalcdep.2021.109127.

Cameron CM, Vuong K, Mcwhinney B. *et al.* Prevalence of alcohol consumption in emergency presentations: novel approach using two biomarkers, ethanol and phosphatidylethanol. *Drug Alcohol Rev* 2023;**42**:146–56. https://doi.org/10.1111/dar.13534.

Chan LN, Anderson GD. Pharmacokinetic and pharmacodynamic drug interactions with ethanol (alcohol). *Clin Pharmacokinet* 2014;**53**:1115–36. https://doi.org/10.1007/s40262-014-0190-x.

Cherpitel CJ. Alcohol and injuries: a review of international emergency room studies since 1995. *Drug Alcohol Rev* 2007;**26**:201–14. https://doi.org/10.1080/09595230601146686.

Cherpitel CJ, Ye Y, Watters K. *et al.* Risk of injury from alcohol and drug use in the emergency department: a case-crossover study. *Drug Alcohol Rev* 2012;**31**:431–8. https://doi.org/10.1111/j.1465-3362.2011.00341.x.

Colling K, Kraft AK, Harry ML. Alcohol use disorder in the intensive care unit a highly morbid condition, but chemical dependency discussion improves outcomes. *Acute Crit Care* 2023;**38**:122–33. https://doi.org/10.4266/acc.2022.00584.

Cordovilla-Guardia S, Fernández-Mondéjar E, Vilar-López R. *et al.* Effect of a brief intervention for alcohol and illicit drug use on trauma recidivism in a cohort of trauma patients. *PloS One* 2017;**12**:e0182441. https://doi.org/10.1371/journal.pone.0182441.

Díaz-Gutiérrez MJ, Martínez-Cengotitabengoa M, Sáez De Adana E. *et al.* Relationship between the use of benzodiazepines and falls in older adults: a systematic review. *Maturitas* 2017;**101**:17–22. https://doi.org/10.1016/j.maturitas.2017.04.002.

Dry MJ, Burns NR, Nettelbeck T. *et al.* Dose-related effects of alcohol on cognitive functioning. *PloS One* 2012;**7**:e50977. https://doi.org/10.1371/journal.pone.0050977.

Gardner A, Forson PK, Oduro G. *et al.* Harmful alcohol use among injured adult patients presenting to a Ghanaian emergency department. *Inj Prev* 2017;**23**:190–4. https://doi.org/10.1136/injuryprev-2016-042104.

Gentilello LM, Ebel BE, Wickizer TM. *et al.* Alcohol interventions for trauma patients treated in emergency departments and hospitals: a cost benefit analysis. *Ann Surg* 2005;**241**:541–50. https://doi.org/10.1097/01.sla.0000157133.80396.1c.

Glantz MD, Bharat C, Degenhardt L. *et al.* The epidemiology of alcohol use disorders cross-nationally: findings from the world

mental health surveys. *Addict Behav* 2020;**102**:106128. https://doi.org/10.1016/j.addbeh.2019.106128.

Gnann H. *Phosphatidylethanol—Ein Alkoholkonsummarker Auf Dem Weg in Die Klinisch-Forensische Routinediagnostik [Phosphatidylethanol—An Alcohol Consumption Marker on its Way to Clinical and Forensic Routine Diagnostics]*. Germany: University of Freiburg, 2011, Dissertation. http://www.freidok.uni-freiburg.de/volltexte/8428/pdf/Diss_Heike_Gnann.pdf.

Harris JC, Leggio L, Farokhnia M. Blood biomarkers of alcohol use: a scoping review. *Curr Addict Rep* 2021;**8**:500–8. https://doi.org/10.1007/s40429-021-00402-7.

Helander A, Hansson T. National harmonization of the alcohol biomarker PEth. *Lakartidningen* 2013;**110**:1747–8.

Institute for Health Metrics and Evaluation. *Global Health Data Exchange*. University of Washington, Seattle, WA, USA, 2019. http://ghdx.healthdata.org/gbd-2019.

Johnston B. Identifying the assumptions and bias that affect screening and brief interventions for harmful alcohol use. *J Am Psychiatr Nurses Assoc* 2021;**28**:76–90. https://doi.org/10.1177/10783903211036494.

Jørgenrud BM, Kabashi S, Nadezhdin AV. *et al.* The association between the alcohol biomarker phosphatidylethanol (PEth) and self-reported alcohol consumption among Russian and Norwegian medical patients. *Alcohol Alcohol* 2021a;**56**:726–36. https://doi.org/10.1093/alcalc/agab013.

Jørgenrud BM, Skadberg E, De Carvalho PJ. *et al.* Determination of the alcohol biomarker phosphatidylethanol 16:0/18:1 and 33 compounds from eight different drug classes in whole blood by LC-MS/MS. *J Pharmacol Toxicol Methods* 2021b;**107**:106939. https://doi.org/10.1016/j.vascn.2020.106939.

Kabashi S, Vindenes V, Bryun EA. *et al.* Harmful alcohol use among acutely ill hospitalized medical patients in Oslo and Moscow: a cross-sectional study. *Drug Alcohol Depend* 2019;**204**:107588. https://doi.org/10.1016/j.drugalcdep.2019.107588.

Kechagias S, Dernroth DN, Blomgren A. *et al.* Phosphatidylethanol compared with other blood tests as a biomarker of moderate alcohol consumption in healthy volunteers: a prospective randomized study. *Alcohol Alcohol* 2015;**50**:399–406. https://doi.org/10.1093/alcalc/agv038.

Kotfis K, Marra A, Ely EW. ICU delirium - a diagnostic and therapeutic challenge in the intensive care unit. *Anaesthesiol Intensive Ther* 2018;**50**:160–7. https://doi.org/10.5603/AIT.a2018.0011.

Kristoffersen L, Smith-Kielland A. An automated alcohol dehydrogenase method for ethanol quantification in urine and whole blood. *J Anal Toxicol* 2005;**29**:387–9. https://doi.org/10.1093/jat/29.5.387.

Luginbühl M, Wurst FM, Stöth F. *et al.* Consensus for the use of the alcohol biomarker phosphatidylethanol (PEth) for the assessment of abstinence and alcohol consumption in clinical and forensic practice (2022 consensus of Basel). *Drug Test Anal* 2022;**14**:1800–2. https://doi.org/10.1002/dta.3340.

Mundenga MM, Sawe HR, Runyon MS. *et al.* The prevalence of alcohol and illicit drug use among injured patients presenting to the emergency department of a national hospital in Tanzania: a prospective cohort study. *BMC Emerg Med* 2019;**19**:15. https://doi.org/10.1186/s12873-019-0222-9.

Novak L, Soravia LM, Bünter A. *et al.* Alcohol biomarker phosphatidylethanol as a predictor of the severity of alcohol withdrawal syndrome. *Alcohol Alcohol* 2023;**58**:198–202. https://doi.org/10.1093/alcalc/agac071.

Pariente A, Dartigues JF, Benichou J. *et al.* Benzodiazepines and injurious falls in community dwelling elders. *Drugs Aging* 2008;**25**:61–70. https://doi.org/10.2165/00002512-200825010-00007.

Rahman A and Paul M. Delirium tremens. In: *STATPearls* [Internet]. Treasure Island (FL): StatPearls Publishing, 2023. http://www.ncbi.nlm.nih.gov/books/NBK482134/

Roberson SW, Patel MB, Dabrowski W. *et al.* Challenges of delirium management in patients with traumatic brain injury: from pathophysiology to clinical practice. *Curr Neuropharmacol* 2021;**19**:1519–44. https://doi.org/10.2174/1570159X19666210119153839.

Sasser SM, Hunt RC, Faul M. *et al.* Guidelines for field triage of injured patients: recommendations of the National Expert Panel on field triage, 2011. *Morb Mortal Wkly Rep Recomm Rep* 2012;**61**:1–20.

Schröck A, Hernández Redondo A, Martin Fabritius M. *et al.* Phosphatidylethanol (PEth) in blood samples from "driving under the influence" cases as indicator for prolonged excessive alcohol consumption. *Int J Leg Med* 2016;**130**:393–400. https://doi.org/10.1007/s00414-015-1300-5.

Schröck A, Thierauf-Emberger A, Schürch S. *et al.* Phosphatidylethanol (PEth) detected in blood for 3 to 12 days after single consumption of alcohol—a drinking study with 16 volunteers. *Int J Leg Med* 2017;**131**:153–60. https://doi.org/10.1007/s00414-016-1445-x.

Skråstad RB, Aamo TO, Andreassen TN. *et al.* Quantifying alcohol consumption in the general population by analysing phosphatidylethanol concentrations in whole blood: results from 24,574 subjects included in the HUNT4 study. *Alcohol Alcohol* 2023;**58**:258–65. https://doi.org/10.1093/alcalc/agad015.

Tevik K, Selbæk G, Engedal K. *et al.* Use of alcohol and drugs with addiction potential among older women and men in a population-based study. The Nord-Trøndelag health study 2006–2008 (HUNT3). *PloS One* 2017;**12**:e0184428.

Torp HA, Skurtveit S, Skaga NO. *et al.* Pre-injury dispensing of psychoactive prescription drugs in a ten years trauma population: a retrospective registry analysis. *Scand J Trauma Resusc Emerg Med* 2021;**29**:125. https://doi.org/10.1186/s13049-021-00939-6.

Ulwelling W, Smith K. The PEth blood test in the security environment: what it is; why it is important; and interpretative guidelines. *J Forensic Sci* 2018;**63**:1634–40. https://doi.org/10.1111/1556-4029.13874.

Viel G, Boscolo-Berto R, Cecchetto G. *et al.* Phosphatidylethanol in blood as a marker of chronic alcohol use: a systematic review and meta-analysis. *Int J Mol Sci* 2012;**13**:14788–812. https://doi.org/10.3390/ijms131114788.

WHO. *International Guide for Monitoring Alcohol Consumption and Related Harm*. Geneva, Switzerland: WHO, 2000.

Wurst FM, Thon N, Aradottir S. *et al.* CLINICAL STUDY/BIOMARKER: phosphatidylethanol: normalization during detoxification, gender aspects and correlation with other biomarkers and self-reports. *Addict Biol* 2010;**15**:88–95. https://doi.org/10.1111/j.1369-1600.2009.00185.x.

Ye Y, Shield K, Cherpitel CJ. *et al.* Estimating alcohol-attributable fractions for injuries based on data from emergency department and observational studies: a comparison of two methods. *Addiction* 2019;**114**:462–70. https://doi.org/10.1111/add.14477.