Letters

RESEARCH LETTER

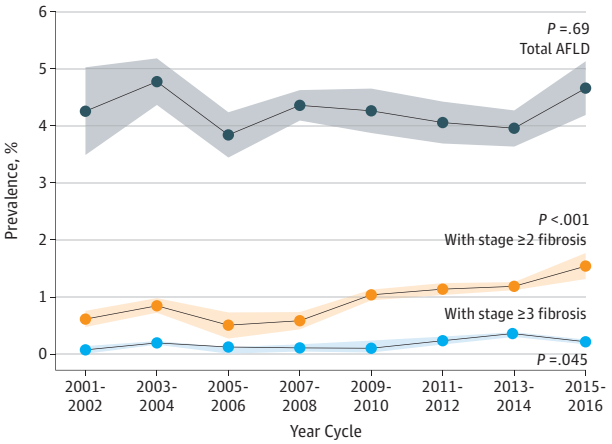
Prevalence of Alcoholic Fatty Liver Disease Among Adults in the United States, 2001-2016

Alcoholic liver disease (ALD), comprising a spectrum of diseases ranging from alcoholic fatty liver disease (AFLD) to advanced ALD (including alcoholic hepatitis, cirrhosis, and cirrhosis complications),[1] is a leading cause of mortality in the United States, with nearly 250 000 deaths attributed to ALD in 2010.[2,3] Overall US clinical burden of ALD remains unclear, perhaps because of lack of a definitive standard for identifying ALD. This study focused on the specific, more well-defined subset of AFLD to estimate national prevalence among US adults.

Methods | We used the 2001-2016 National Health and Nutrition Examination Survey (NHANES) data set, a series of cross-sectional, nationally representative surveys of the noninstitutionalized US population, including in-person interviews and health examinations in mobile examination centers. The NHANES 2001-2016 overall response rate was 70.3% (range, 60.7%-78.3%) for interviews and 67.2% (range, 58.1%-72.7%) for examinations. AFLD was identified based on alcohol use (>28 g/d in women and >42 g/d for men in the past 12 months) and elevated liver enzyme levels (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >25 U/L [0.42 μkat/L] in women and >35 U/L [0.58 μkat/L] in men), in the absence of elevated total bilirubin level (<3 mg/dL [51.3 μmol/L]) and after excluding hepatitis C and hepatitis B infections.[1] Individuals with metabolic syndrome (National Cholesterol Education Program Adult Treatment Panel III[4] criteria) were excluded given associated increased risks of nonalcoholic fatty liver disease. Hepatic fibrosis was assessed using an AST-to-platelet ratio index ([AST/upper limit of normal for AST]/platelet count) greater than 0.7 (stage ≥2 fibrosis) and Fibrosis-4 score ([age × AST]/[platelet count × $ALT^{½}$]) greater than 2.67 (stage ≥3 fibrosis), which represent standard definition cutoffs of well-validated tools for assessing hepatic fibrosis.

Multivariable logistic regression with appropriate sample weights was used to derive AFLD prevalence. Linear trends in prevalence were analyzed using orthogonal polynomial contrasts. Interaction terms were included in logistic regression models to assess whether prevalence changes differed by sex, age, and race/ethnicity. Missing data, ranging from less than 1% to 15%, were addressed using multivariable imputation by chained equations, which included relevant demographic and clinical covariates. Two-tailed $P < .05$ indicated statistical significance (Stata version 14.0 [StataCorp]). The Alameda Health System institutional review board granted exempt status and waiver of informed consent.

Figure. Trends in Prevalence of Total Alcoholic Fatty Liver Disease (AFLD), AFLD With Stage 2 or Greater Fibrosis, and AFLD With Stage 3 or Greater Fibrosis Among US Adults From 2001-2002 to 2015-2016



Shaded areas adjacent to curves indicate 95% CIs. Data are based on 34 423 individuals in NHANES surveys.

Results | Among 34 423 respondents included, 4.3% were identified with AFLD (60.6% men; 63.0% non-Hispanic white; mean age, 40.2 years). From 2001-2002 to 2015-2016, AFLD prevalence remained stable from 4.3% (95% CI, 3.5%-5.0%) to 4.7% (95% CI, 4.2%-5.1%) ($P = .69$), AFLD with stage 2 or greater fibrosis increased from 0.6% (95% CI, 0.5%-0.8%) to 1.5% (95% CI, 1.3%-1.8%) ($P < .001$), and AFLD with stage 3 or greater fibrosis increased from 0.1% (95% CI, 0.02%-0.10%) to 0.2% (95% CI, 0.2%-0.4%) ($P = .045$) (**Figure**). Changes in prevalence over time did not differ by sex, age, or race/ethnicity, and no significant interactions were observed across all variables (**Table**).

Discussion | The prevalence of AFLD among US adults remained stable from 2001 to 2016, affecting 4.7% of adults in 2015-2016. However, the prevalence of AFLD with stage 2 or greater fibrosis and AFLD with stage 3 or greater fibrosis increased significantly, affecting 1.5% and 0.2% of adults, respectively, in 2015-2016. This is a particularly concerning observation given that developing fibrosis is the strongest predictor of progression to cirrhosis, liver cancer, and death.[5] While studies evaluating national ALD prevalence are lacking, existing studies have demonstrated increasing burden of ALD in population subsets. For example, among patients with end-stage liver disease, ALD became the leading indication for US liver transplants in 2016,[6] and a 2018 US population-based study demonstrated increasing cirrhosis death rates largely driven by alcoholic cirrhosis, particularly among individuals aged 25 to 34 years.[3]

Table. Prevalence and Number of Adults Aged 20 Years or Older With Alcoholic Fatty Liver Disease (AFLD) and Fibrosis in the United States by Sex, Age, and Race

	2001-2002		2015-2016		*P* Value for Interaction[c]
	No.[a]	Prevalence, % (95% CI)[b]	No.[a]	Prevalence, % (95% CI)[b]	
AFLD Among Total Population					
Sex					
Men	108	5.2 (4.2-6.2)	116	5.8 (3.5-6.3)	.45
Women	56	3.4 (2.8-4.0)	64	3.7 (2.6-4.2)	Reference
Age, y					
20-44	117	5.6 (4.6-6.6)	108	6.5 (5.9-7.1)	Reference
45-64	40	3.6 (2.9-4.4)	61	4.3 (3.7-7.1)	.86
≥65	7	1.0 (0.7-1.3)	11	4.2 (3.7-4.9)	.88
Race/ethnicity[d]					
White	71	3.8 (2.9-5.2)	61	4.1 (3.2-5.8)	Reference
Black/African American	21	3.1 (1.6-4.8)	22	3.4 (1.7-4.0)	.36
Hispanic	69	8.3 (4.9-10.0)	87	9.3 (8.7-10.0)	.91
Other	3	2.5 (1.6-3.8)	10	2.7 (1.0-3.4)	.97
Total	164	4.3 (3.5-5.0)	180	4.7 (4.2-5.1)	
AFLD With Stage ≥2 Fibrosis Among Total Population					
Sex					
Men	17	0.7 (0.6-0.9)	38	1.8 (1.5-3.0)	.34
Women	9	0.5 (0.4-0.6)	19	1.3 (1.1-1.6)	Reference
Age, y					
20-44	15	0.6 (0.5-0.8)	24	1.6 (1.3-2.2)	Reference
45-64	10	0.8 (0.6-0.9)	26	2.0 (1.6-2.3)	.42
≥65	1	0.3 (0.1-0.6)	7	0.6 (0.5-0.8)	.94
Race/ethnicity[d]					
White	12	0.6 (0.1-1.0)	23	1.4 (1.1-1.8)	Reference
Black/African American	5	0.5 (0.3-0.7)	7	1.2 (0.4-2.0)	.09
Hispanic	8	1.1 (0.8-1.4)	23	2.8 (2.5-3.2)	.53
Other	1	0.3 (0.1-0.4)	4	0.7 (0.5-0.9)	.73
Total	26	0.6 (0.5-0.8)	57	1.5 (1.3-1.8)	
AFLD With Stage ≥3 Fibrosis Among Total Population					
Sex					
Men	5	0.1 (0.02-0.2)	12	0.4 (0.2-0.7)	.81
Women	1	0.05 (0.02-0.1)	3	0.1 (0.1-0.2)	Reference
Age, y					
20-44	0	NA	2	0.1 (0.03-0.2)	Reference
45-64	5	0.2 (0.04-0.3)	7	0.4 (0.1-0.5)	.25
≥65	1	0.1 (0.03-0.2)	6	0.3 (0.1-0.8)	NA
Race/ethnicity[d]					
White	1	0.07 (0.05-0.2)	4	0.2 (0.1-0.4)	Reference
Black/African American	2	0.08 (0.03-0.1)	3	0.3 (0.1-0.7)	.70
Hispanic	2	0.1 (0.04-0.2)	8	0.4 (0.1-0.8)	.31
Other	1	0.03 (0.01-0.05)	0	NA[e]	NA
Total	6	0.1 (0.02-0.1)	15	0.2 (0.2-0.4)	

Abbreviation: NA, not analyzable.

[a] Unweighted number of respondents from National Health and Nutrition Examination Survey study sample.

[b] Derived from multivariable logistic regression with sample weights.

[c] Derived from the interaction term between the time variable (reference = 2001-2002 cycle) and covariate for prevalence.

[d] Self-reported by survey participants in response to interview questions and included the following options: Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, other race. In this study we categorized non-Hispanic white as "white," non-Hispanic black as "black/African American," and other race as "other." Mexican American and other Hispanic individuals were combined into a single category, "Hispanic." Race/ethnicity were analyzed because existing data demonstrate racial differences in epidemiology of other chronic liver diseases, alcohol use disorders, and alcoholic-related diseases.

[e] Not analyzable because of insufficient number of respondents.

Limitations include the challenges in accurately identifying AFLD using observational data, which may have been affected by misclassification. Noninvasive serologic markers of fibrosis used in this study are well validated, but not specifically for AFLD. The increasing prevalence of US adults with AFLD with stage 2 or greater fibrosis and AFLD with stage 3 or greater fibrosis is concerning and emphasizes the need for greater awareness of unhealthy alcohol use and need for early prevention and intervention efforts.

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COMMENT & RESPONSE

Prophylactic Hypothermia for Severe Traumatic Brain Injury

To the Editor In a multicenter randomized clinical trial, Dr Cooper and colleagues reported that early prophylactic hypothermia (33-35°C) compared with active normothermia did not improve neurologic outcome at 6 months after severe traumatic brain injury (TBI).[1] However, we believe that the study had some limitations that preclude definite conclusions.

The objective of brain resuscitation is intracranial pressure control, but cerebral blood flow or cerebral oxygenation (eg, by transcranial Doppler or brain tissue oxygen partial pressure monitoring) were not reported in the study. Hence, patients may have experienced silent decreased brain oxygenation.

In addition, $Paco_2$ values were similar in both groups, and there was no effect of hypothermia on intracranial pressure. Therefore, $Paco_2$ was managed according to the pH-stat principle, which means that relative hypocapnia induced by hypothermia was balanced by changing the respirator settings (ie, decreasing minute volume). However, to make therapeutic hypothermia effective in the management of intracranial pressure, relative hypocapnia must be tolerated (alpha-stat principle).[2] Under these conditions, the decline in cerebral blood flow is compensated by the concomitant decrease in brain metabolism, which is measured by the stability of the cerebral oxygenation indexes.[2] In contrast, permissive hypercapnia (pH-stat management) is acceptable only in the case of low intracranial pressure, as is often observed after resuscitated cardiac arrest.

We believe that management of $Paco_2$ is decisive for hypothermia after severe TBI and needs to be adapted to the primary study objective. If the aim is control of intracranial pressure, alpha-stat management should be prioritized while monitoring cerebral oxygenation to avoid low cerebral blood flow. If the aim is neuroprotection, pH-stat management is preferable but requires intracranial pressure monitoring because there is a risk of relative hypercapnia.

Three other randomized trials assessed effect of hypothermia after severe TBI. The NABIS:HII study failed to show a neuroprotective effect of hypothermia[3] with management of $Paco_2$ according to the alpha-stat principle. The Eurotherm3235 study did not demonstrate a positive effect of hypothermia on the control of intracranial hypertension during which the management of $Paco_2$ followed the pH-stat principle.[4] None of these studies thus fully corresponded to the above criteria. Only in the B-HYPO study was $Paco_2$ managed correctly for assessing neuroprotective effect (pH-stat principle), with negative results that need confirmation.[5]

In summary, management of $Paco_2$ and adapted monitoring are key issues for the success or failure of studies of hypothermia after severe TBI.

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