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Authors

Hahn, Judith A
Murnane, Pamela M
Vittinghoff, Eric
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11 **Authors:**

12 Judith A. Hahn, PhD. (corresponding author), Department of Medicine, and Department of Epidemiology
13 & Biostatistics, University of California, San Francisco, San Francisco CA, USA

14 Mailing address: 550 16th Street, 3rd Floor, San Francisco, 94143

15 E-mail: judy.hahn@ucsf.edu

16

17 Pamela M. Murnane, PhD, Department of Epidemiology & Biostatistics, University of California, San
18 Francisco, San Francisco CA, USA

19

20 Eric Vittinghoff, PhD, Department of Epidemiology & Biostatistics, University of California, San
21 Francisco, San Francisco CA, USA

22

23 Winnie R. Muyindike, MMED, Department of Internal Medicine, Mbarara University of Science and
24 Technology, Mbarara.

25

26 Nneka I. Emenyonu, DrPH, Department of Medicine, University of California, San Francisco, San
27 Francisco CA, USA

28

29 Robin Fatch, MPH, Department of Medicine, University of California, San Francisco, San Francisco CA,
30 USA.

31

32 Gabriel Chamie, MD, Department of Medicine, University of California, San Francisco, San Francisco
33 CA, USA

34

35 Jessica E. Haberer MD, Massachusetts General Hospital, Center for Global Health, Boston, MA, USA

36

37 Joel M. Francis, PhD, National Institute for Medical Research, Mwanza Centre, Mwanza, Tanzania, and
38 Department of Infectious Diseases Epidemiology, London School of Hygiene and Tropical Medicine,
39 and Department of Family Medicine and Primary Care, School of Clinical Medicine, University of the
40 Witwatersrand, Johannesburg, South Africa.

41

42 Saidi Kapiga, MD, London School of Hygiene & Tropical Medicine, London, UK
43
44 Karen Jacobson, MD, Boston University School of Medicine, Boston, MA, USA
45
46 Bronwyn Myers, PhD, Alcohol, Tobacco and Other Drug Research Unit, South African Medical Research
47 Council, Tygerberg, South Africa, and Department of Psychiatry and Mental Health, University of Cape
48 Town, Cape Town, South Africa
49
50 Marie Claude Couture, PhD, University of San Francisco, San Francisco, CA, USA
51
52 Ralph J. DiClemente, PhD, Department of Social and Behavioral Sciences, NYU School of Global Public
53 Health, New York, NY, USA
54
55 Jennifer L. Brown, PhD, Departments of Psychology and Psychiatry & Behavioral Neuroscience; Center
56 for Addiction Research, University of Cincinnati, Cincinnati, OH, USA
57
58 Kaku So-Armah, PhD, Department of Medicine, Boston University School of Medicine, Boston, MA,
59 USA
60
61 Mark Sulkowski, MD, Department of Medicine, Johns Hopkins School of Medicine, Baltimore MD, USA
62
63 Gregory M. Marcus, MD, Department of Medicine, University of California, San Francisco, CA, USA
64
65 Sarah Woolf-King, PhD, Syracuse University, Department of Psychology, Syracuse, NY, USA
66
67 Robert L. Cook, MD, Department of Epidemiology, University of Florida, Gainesville, FL
68
69 Veronica L. Richards, MPH, Department of Epidemiology, University of Florida, Gainesville, FL
70
71 Patricia Molina, MD, PhD, Comprehensive Alcohol-HIV/AIDS Research Center and Department of
72 Physiology & Comprehensive Alcohol Research Center, Louisiana State University Health Sciences
73 Center, New Orleans, LA, USA
74
75 Tekeda Ferguson, PhD, Comprehensive Alcohol-HIV/AIDS Research Center and Department of
76 Physiology & Comprehensive Alcohol Research Center, and School of Public Health, Louisiana State
77 University Health Sciences Center, New Orleans, LA, USA
78
79 David Welsh, MD, Comprehensive Alcohol-HIV/AIDS Research Center and Department of Physiology
80 & Comprehensive Alcohol Research Center and School of Medicine, Louisiana State University Health
81 Sciences Center, New Orleans, LA, USA
82
83 Mariann R. Piano, PhD, Center for Research Development and Scholarship, Vanderbilt University,
84 Nashville, TN. USA
85
86 Shane A. Phillips, PhD, University of Illinois at Chicago, Chicago, IL, USA
87
88 Scott Stewart, MD, Department of Family Medicine, Division of Addiction Medicine, University at
89 Buffalo, Buffalo, NY, USA
90

91 Majid Afshar, MD, Department of Medicine, School of Medicine and Public Health, University of
92 Wisconsin – Madison, Madison, WI, USA
93
94 Kimberly Page, PhD, Department of Internal Medicine, University of New Mexico; Albuquerque, NM,
95 USA
96
97
98 Kathleen McGinnis, West Haven VA Healthcare System, United States Department of Veterans Affairs,
99 West Haven, CT, USA
100
101 David A. Fiellin, MD, Yale School of Medicine and Yale School of Public Health, New Haven, CT, USA
102
103 Amy C. Justice, MD, Yale School of Medicine and Yale School of Public Health, New Haven, CT, and
104 West Haven VA Healthcare System, United States Department of Veterans Affairs, West Haven, CT,
105 USA
106
107 Kendall Bryant, PhD, National Institutes of Health, National Institute of Alcohol Abuse and Alcoholism,
108 Bethesda, MD, USA
109
110 Richard Saitz, MD, Department of Community Health Sciences, Boston University School of Public
111 Health, Section of General Internal Medicine, Boston University School of Medicine and Boston Medical
112 Center, and Grayken Center on Addiction, Boston Medical Center, Boston, MA, USA
113
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128 **Abstract**

129 **Background:** Objective measurement of alcohol consumption is important for clinical care and
130 research. Adjusting for self-reported alcohol use, we conducted an individual participant data
131 (IPD) meta-analysis to examine factors associated with the sensitivity of phosphatidylethanol
132 (PEth), an alcohol metabolite, among persons self-reporting unhealthy alcohol consumption.

133

134 **Methods:** We identified 21 eligible studies and obtained 4073 observations from 3085
135 participants with Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) positive
136 scores (≥ 3 for women and ≥ 4 for men) and PEth measurements. We conducted one-step IPD
137 meta-analysis using mixed-effects models with random intercepts for study site. We examined
138 the associations between demographic (sex, race/ethnicity, and age) and biologic (body mass
139 index -- BMI, hemoglobin, HIV status, liver fibrosis, and venous versus finger-prick blood
140 collection) variables with PEth sensitivity (PEth ≥ 8 ng/mL), adjusting for level of alcohol use
141 using the AUDIT-C score.

142

143 **Results:** One-third (31%) of participants were women, 32% were African, 28% African
144 American, 28% White, and 12% other race/ethnicity. PEth sensitivity (i.e. ≥ 8 ng/mL) was
145 81.8%. After adjusting for AUDIT-C, we found no associations of sex, age, race/ethnicity, or
146 method of blood collection with PEth sensitivity. In models that additionally included biologic
147 variables, those with higher hemoglobin and indeterminate and advanced liver fibrosis had
148 significantly higher odds of PEth sensitivity; those with higher BMI and those living with HIV

149 had significantly lower odds of PEth sensitivity. African Americans and Africans had higher
150 odds of PEth sensitivity compared to whites in models that included biologic variables.

151

152 **Conclusions:** Among people reporting unhealthy alcohol use, several biological factors
153 (hemoglobin, BMI, liver fibrosis, and HIV status) were associated with PEth sensitivity.

154 Race/ethnicity was associated with PEth sensitivity in some models; age, sex and method of
155 blood collection were not. Clinicians should be aware of these factors, and researchers should
156 consider adjusting analyses for these characteristics where possible.

157

158 **Introduction**

159

160 Alcohol use is responsible for at least 5.3% of worldwide mortality (2018); reducing this
161 modifiable harmful behavior is urgently needed. However, individual level interventions require
162 reliable detection and measurement of alcohol intake. Self-report of alcohol represents a
163 problematic gold-standard, in that it is low-cost and rapid, but reporting bias can impact
164 measurement, with social desirability bias causing under-reporting (Davis et al., 2010, Miller et
165 al., 2004, Miller et al., 2006). In contrast, direct alcohol metabolites, i.e. substances that are
166 formed in the body as alcohol is metabolized, can serve as objective measures of alcohol use to
167 replace or complement self-report.

168

169 Phosphatidylethanol (PEth) is a direct metabolite that is formed only in the presence of alcohol
170 (and is thus highly specific). PEth is detectable for 3-4 weeks after repeated heavy alcohol
171 consumption (defined as >60 g/day, on average), and has a half-life of 4-10 days (Hahn et al.,
172 2016a, Helander et al., 2019a). It is also detectable after a single drinking session for 3-12 days
173 (Schrock et al., 2016). PEth is measured from whole blood or dried blood spots (DBS) and is
174 most frequently analyzed using liquid chromatography with tandem mass spectrometry (LC-MS/
175 MS) (Jones et al., 2011). The most common homologue, PEth 16:0/18:1, has the longest half-life
176 and is frequently the only PEth homologue measured (Gnann et al., 2014). PEth has shown high
177 sensitivity (>88%) and specificity (>90%) for detecting prior month unhealthy drinking, defined
178 as drinking above recommended limits (Ghosh et al., 2019, Bajunirwe et al., 2014, Magidson et
179 al., 2019, Muyindike et al., 2017, Eyawo et al., 2018, Hahn et al., 2018, Walther et al., 2015,
180 Wang et al., 2017, Edelman et al., 2019, Ulwelling and Smith, 2018), and good correlations with

181 total self-reported volume of alcohol consumed ranging from 0.53 to 0.80 (Hahn et al., 2012,
182 Aradottir et al., 2006, Hartmann et al., 2007, Piano et al., 2015, Ferguson et al., 2020, Schröck et
183 al., 2017, Kechagias et al., 2015, Helander et al., 2019b, Walther et al., 2015, Cherrier et al.,
184 2020, Gerbase et al., 2020, Röhricht et al., 2020), although a few studies found correlations of
185 0.21-0.44 (Littlefield et al., 2017, Wang et al., 2017, Papas et al., 2016). These characteristics
186 make PEth a preferred biomarker of medium-term (several weeks) unhealthy alcohol use (the
187 spectrum from use of risky amounts through alcohol use disorder). However, a few studies have
188 observed low PEth sensitivity (approximately 50%) among persons reporting drinking heavy
189 amounts (Papas et al., 2016, Wang et al., 2017), raising concerns that PEth is not sufficiently
190 sensitive, or that it is less sensitive in certain subgroups of persons.

191

192 The level of PEth formation is directly proportional to the available concentration of ethanol in
193 the blood, which is dependent on short-term factors such as the amount and type of alcohol
194 consumed, stomach contents, and the rate of consumption, and factors that impact alcohol
195 metabolism, such as biological sex, lean body mass, genetically determined alcohol and
196 acetaldehyde dehydrogenases, and liver disease (Cederbaum, 2012). PEth formation may also be
197 influenced by the availability of phospholipase D and availability of phosphatidylcholine
198 (Schrock et al., 2018, Stenton et al., 2019). As such, PEth levels have been shown to vary
199 considerably between persons under controlled alcohol administration experiments (Javors et al.,
200 2016), and among persons entering treatment after periods of heavy drinking (Helander et al.,
201 2019a), thus research examining factors that might impact PEth sensitivity is needed.

202

203 A handful of small studies have examined factors that might influence PEth sensitivity, including
204 sex (Wurst et al., 2010, Hahn et al., 2012, Stewart et al., 2014), age (Hahn et al., 2012, Cherrier
205 et al., 2020, Hahn et al., 2016b), body mass index (BMI) (Wang et al., 2017), and hemoglobin
206 level (Beck et al., 2018, Nguyen and Seth, 2018) and liver disease (Cherrier et al., 2020); we are
207 aware of none that examined race/ethnicity, or HIV infection status. Lastly, examination of PEth
208 sensitivity in venous versus finger-prick blood collection is needed, due to the increased risk for
209 hemolysis and variability in blood volume and hematocrit from finger-prick blood collection
210 (Kummer et al., 2016b, De Kesel et al., 2013, Kummer et al., 2016a, Beck et al., 2018). Thus
211 study is needed to examine these factors.

212

213 Our primary aim was to examine factors that may be associated with PEth sensitivity in persons
214 self-reporting alcohol consumption at a level for which PEth is often detectable, i.e. unhealthy
215 alcohol use. These factors included demographic variables (sex, age, race/ethnicity), and biologic
216 variables (BMI, hemoglobin level, HIV status, liver fibrosis and method of sample collection).
217 To do so, we conducted an individual participant data meta-analysis to leverage the statistical
218 power of multiple studies with PEth testing and self-reported alcohol use. Since social
219 desirability bias suggests a tendency to under-report alcohol consumption (Adong et al., 2019),
220 we have chosen to evaluate the sensitivity of PEth among those volunteering substantial alcohol
221 consumption, i.e. unhealthy alcohol use.

222

223 **Methods**

224

225 *Search strategy*

226 We searched for studies that had collected self-reported alcohol use measures as well as PEth
227 testing that met the inclusion criteria described below to contribute de-identified data for these
228 analyses. We identified studies by contacting all the Principal Investigators in the National
229 Institutes of Health Consortiums for HIV/AIDS and Alcohol-Related Outcomes Research Trials
230 Consortium (CHAART), and other investigators known to be using PEth based on the first
231 author's (JAH) personal knowledge; and by searching PubMed using the combination of
232 "phosphatidylethanol" and "alcohol" for the record creation dates of January 1, 2000 (when the
233 first PEth paper was published (Varga et al., 2000)) through December 31, 2019. We (JAH)
234 determined which studies were eligible for inclusion by reading the titles, abstracts, and when
235 needed, the articles, and sent e-mails to the corresponding authors to confirm eligibility criteria.
236 Authors who agreed to contribute data completed a spreadsheet eliciting the requested variable
237 names and their definitions and sent these data electronically without identifiers. We conducted
238 range checks and calculated frequency tables for all variables and corresponded with data
239 managers as needed to resolve discrepancies; only minor issues were identified. We did not
240 evaluate bias within the studies because of the novelty of our study question; all the studies
241 included were designed to answer different study questions. The receipt of these data for this
242 analysis was approved by the University of California, San Francisco Institutional Review
243 Boards, and the data collection by the contributing studies were previously approved at each
244 institution.

245

246 *Study eligibility*

247 Studies were eligible for inclusion if they included: (1) PEth results for the 16:0/18:1 homologue,
248 tested with the limit of quantification ≥ 8 ng/mL; (2) self-reported current alcohol use, either by

249 the Alcohol Use Disorders Identification Test (AUDIT)(Babor et al., 2001) or the AUDIT –
250 Consumption (AUDIT-C)(Bradley et al., 2007, Bush et al., 1998), or by another method from
251 which the AUDIT-C could be calculated (e.g. Timeline Follow Back (Sobell and Sobell, 1992));
252 (3) the data set included at least 30 observations for which the AUDIT-C score was positive, i.e.
253 ≥ 3 for women, ≥ 4 for men. The latter eligibility criterion was to enable us to examine PEth
254 sensitivity among observations with “true positive” unhealthy drinking. To further minimize mis-
255 reporting, we excluded studies that focused on populations for whom there may be reasons to
256 mis-report alcohol use (prisoners, persons driving under the influence, persons entering alcohol
257 treatment, liver transplant patients, pregnant women) and clinical trials whose eligibility criteria
258 were based on self-reported alcohol use which may also cause mis-reporting (Devine et al., 2013,
259 Mccaull and Wand, 2018). We made exceptions for clinical trials that confirmed alcohol use at
260 entry via an objective measure such as transdermal alcohol monitoring or a positive alcohol
261 biomarker test. We excluded studies of infants and children.

262

263 *Variables*

264 The pre-specified outcome variable was PEth sensitivity, i.e., PEth ≥ 8 ng/mL versus <8 ng/mL.
265 PEth testing was previously conducted for each study at the Karolinska University Laboratory
266 (Stockholm) for one study (Francis et al., 2015), and at the United States Drug Testing
267 Laboratories (USDTL, Des Plaines) for the remainder of studies. We included the following
268 potential demographic predictors: age, sex, race/ethnicity. Sex was recorded as male or female
269 for all but four studies; for those studies we classified persons (n=12) with their assigned sex at
270 birth. To the extent that race/ethnicity data were available, and recognizing that these categories
271 are social constructs and not biological ancestry (Mersha and Abebe, 2015), we categorized race/

272 ethnicity as African-American, White, and other. Other included persons identified as
273 Latinx/Hispanic, Asian/Pacific Islander, Native American, mixed-race, or race/ethnicity not
274 specified. We created a category called African for those recruited from studies that occurred in
275 African countries (Hahn et al., 2016b, Magidson et al., 2019, Myers et al., 2018, Francis et al.,
276 2015). We examined the following biologic variables: BMI (kg/m^2), hemoglobin (g/dL) (or
277 hematocrit, where hemoglobin was not available), HIV status (positive vs. negative), and liver
278 fibrosis (measured by FIB-4, calculated using age, alanine aminotransferase, aspartate
279 aminotransferase, and platelets (Sterling et al., 2006)). We also examined the methods of blood
280 collection, which were either venous blood draws pipetted onto DBS cards, or finger-pricks
281 dropped onto DBS cards.

282

283 Self-reported alcohol use, measured by the AUDIT-C, was included as a control variable in all
284 analyses. The AUDIT-C was measured directly in most studies, albeit with varying associated
285 time frames, i.e. no time frame, prior one year, and prior three months (Table 1). For the studies
286 that did not collect the AUDIT-C, we calculated approximate scores from the 30-day timeline
287 follow back for two studies (Stewart et al., 2014) (and Miami study) and from a question
288 assessing the number of drinking days in a third study (Jain et al., 2014).

289

290 *Statistical analyses*

291 After confirming study eligibility and obtaining the individual level data for each study, we
292 included only observations within each study for which AUDIT-C was positive (≥ 3 for women
293 and ≥ 4 for men), to study PEth sensitivity among those drinking at a level that should be
294 enough for PEth to develop and be detected (Ghosh et al., 2019). We included multiple

295 observations per person, if available. To account for missing data on the biologic variables
296 within individual studies (all data were complete for AUDIT-C by design, gender, race/ethnicity,
297 and age), we first conducted multiple imputation by chained equations (MICE) within studies,
298 assuming data were missing at random (n=50 imputed datasets). Because the imputation was
299 conducted at the study level, it was not conducted for variables that were not collected within an
300 individual study (e.g. BMI was not collected in 8 of the 21 studies).

301

302 We calculated PEth sensitivity overall and within the levels of the variables of interest using the
303 imputed data. We created categories for the continuous variables as follows. We categorized
304 AUDIT-C, as in previous studies (Rubinsky et al., 2013), as medium alcohol use: AUDIT-C 3-5
305 for women and 4-5 for men; high alcohol use: AUDIT-C 6-7; and very high alcohol use:
306 AUDIT-C 8-12. We categorized age as 17-24, 25-34, 35-44, 45-54, and ≥ 55 years. We used
307 standard cutoffs for BMI with underweight: $<18.5 \text{ kg/m}^2$; normal/healthy weight: $18.5\text{-}24.9 \text{ kg/}$
308 m^2 ; overweight: $25\text{-}29.9 \text{ kg/m}^2$; and obese: $\geq 30 \text{ kg/m}^2$ (Weir and Jan, 2020). We categorized hemoglobin
309 using standard cutoffs as very anemic: $<11 \text{ g/dL}$; anemic: 11-11.9 for women, 11-12.9 for men;
310 no anemia: 12-15.5 for women, 13-17.5 for men); and high hemoglobin: >15.5 for women, >17.5
311 for men (Organization, 2011). Lastly, we categorized liver fibrosis as no fibrosis: $\text{FIB-4} < 1.45$;
312 inconclusive fibrosis: $\text{FIB-4} 1.45\text{-}3.25$; and fibrosis: $\text{FIB-4} > 3.25$ (Vallet-Pichard et al., 2007).

313

314 We used a one-step meta-analytic regression approach; we fit mixed effects models using a logit
315 link, a random intercept for each study to account for within study clustering, and robust
316 standard errors to account for clustering within individuals with multiple observations per
317 person. This one-step approach, in contrast to a two-step approach in which individual

318 regressions are conducted and then weighted averages are calculated, is less prone to bias and
319 preferred for individual participant level data when covariate adjustment is needed and when
320 there is heterogeneity between studies (Debray et al., 2013, Debray et al., 2015). This approach
321 also allowed us to include data from studies that did not include all levels of the variables of
322 interest, e.g., studies that included only one gender, a particular age group, or a single
323 racial/ethnic group.

324

325 To examine the form of the relationship of the continuous variables with PEth sensitivity for
326 regression modeling, we examined linear, quadratic, and categories (as defined above) variable
327 forms. We fit mixed effects models as described above for each, and chose the model with the
328 lowest Aikake's Information Criterion (AIC) score. We first determined the form for AUDIT-C,
329 the primary adjustment variable, and then chose the modeling form for age in models adjusted
330 for AUDIT-C, plus gender, and race/ethnicity. Lastly, we conducted similar analyses for BMI,
331 hemoglobin, and FIB-4 score, adjusting for AUDIT-C, gender, race/ethnicity and age. The AIC
332 was minimized for AUDIT-C and age when these variables were quadratic variables, when BMI
333 and hemoglobin were included as linear variables, and when FIB-4 was as a categorical variable
334 (data not shown). We used these forms in further modeling.

335

336 To examine the associations of each variable of interest with PEth sensitivity, we calculated
337 minimally adjusted odds ratios for the association with PEth positive results for each variable, by
338 fitting mixed effects models as described above, adjusted for AUDIT-C as a quadratic variable.
339 Finally, we used mixed effects models to examine the independent effects of the variables of
340 interest on PEth sensitivity, adjusting for AUDIT-C. We examined three models, because not all

341 datasets included the biologic variables of interest. In Model 1, we examined age, gender and
342 race/ethnicity, and method of sample collection in all 21 studies. In Model 2, we additionally
343 included BMI, hemoglobin, and HIV status as covariates, using the thirteen studies that included
344 these variables. In Model 3, we additionally included liver fibrosis, using the eight studies that
345 included the measures needed for the FIB-4 score. In all models, AUDIT-C and age were
346 modeled as quadratics. We calculated predicted probabilities for the levels of each variable, with
347 all the others held at their means. For variables that were included in the models as continuous
348 variables, we used the midpoints of previously define categories used in our initial analyses of
349 the form of the relationship of the continuous variables with PEth sensitivity, as described above.
350

351 We conducted the following sensitivity analyses to determine the robustness of our regression
352 results: (1) analyses including only the first observation per person, with repeat visits excluded,
353 (2) analyses excluding those who reported no drinking in the prior 30 days, or for whom recency
354 of alcohol use was not measured, (3) analyses including only those with high or very high self-
355 reported alcohol use (AUDIT-C \geq 6), (4) analyses excluding the largest study, which contributed
356 20.2% of the participants, and (5) analyses using complete case data, i.e. not using the multiple
357 imputation (Models 2 and 3).

358
359 Lastly, we explored interactions of the independent variables in Model 1 by race/ethnicity and by
360 gender; we considered p-values of less than 0.10 to be statistically significant. As a result of
361 interactions of race/ethnicity with more than one other variable, we conducted regression
362 analyses for the three models above, stratified by race/ethnicity. The analyses were performed
363 using Stata statistical software (2019).

364

365 **Results**

366 *Study inclusion*

367 We contacted 15 investigators of CHAART studies, yielding 12 studies that were eligible for
368 inclusion and willing to provide data. We identified additional 8 studies by the first author's
369 personal knowledge, yielding 7 studies for inclusion. The PubMed search produced 269 studies,
370 which yielded 2 more eligible studies not previously identified, for a total of 21 (Figure 1).

371 Seventeen of the studies were observational studies, and 2 were alcohol intervention studies
372 (with unhealthy alcohol use confirmed by a biomarker or biosensor), and two were studies of
373 interventions not targeted to alcohol use (Table 1). The number of included study participants
374 (i.e. those with positive AUDIT-C scores and concurrent PEth results) ranged from 36 to 622.

375

376 *Study participants*

377 The 21 included studies yielded 4073 observations meeting the inclusion criteria. These
378 represented 3085 individuals from Africa (32%), Asia (4%), Europe (13%), and North America
379 (50%) (Table 1). One third (30.9%) were women, the median age was 38 years (range: 17-89);
380 and 32% were African, 28% African American, 29% White, and 12% other race/ethnicity (Table
381 2). At the first available visit, the median AUDIT-C score was 6 (IQR: 4-8), 79% were PEth
382 positive, and the median PEth level was 70.0 ng/mL (IQR: 14.0-233.0). Among all study visits,
383 the proportion PEth positive was 82% (Table 3).

384

385 *Associations with PEth sensitivity*

386 Table 3 shows PEth sensitivity by each variable of interest among the 4073 observations.
387 Adjusting for level of alcohol use via the AUDIT-C, BMI, hemoglobin, and liver fibrosis were
388 associated with PEth sensitivity. In the Model 1 multivariable analysis that included all 21
389 studies, none of the variables of interest (gender, age, race/ethnicity, method of sample
390 collection), were associated with PEth sensitivity, although AUDIT-C, the adjustment variable,
391 was associated with PEth sensitivity (Table 4). In the Model 2 analysis that included the 13
392 studies in which BMI, hemoglobin, and HIV status data were collected, BMI (aOR=0.74; 95%
393 CI: 0.66-0.83 for +5 kg/m²), hemoglobin (aOR=2.12; 95% CI: 1.52-2.96 for +5 g/dL), and HIV
394 status (aOR=0.77; 95% CI: 0.66-0.89 positive versus negative) were associated with PEth
395 sensitivity; race/ethnicity, age, and AUDIT-C were also associated with PEth sensitivity in this
396 model. When we added FIB-4 to the model (Model 3, 9 studies included), we found the adjusted
397 odds of PEth sensitivity were increased for inconclusive and high FIB-4 scores compared to
398 normal scores (aOR=1.29; 95% CI: 1.02-1.63 and aOR=1.87; 95% CI: 1.28-2.75 for scores of
399 1.45 to 3.25 and >3.25 compared to <1.45, respectively), while BMI, hemoglobin, HIV status,
400 race/ethnicity, and AUDIT-C remained associated with PEth sensitivity. Predicted PEth
401 sensitivity for each level of categorical and categorized variables range from 0.75 to 0.93 (Table
402 5).

403

404 We conducted several sensitivity analyses and found no substantial differences in the results
405 (Tables 6-10). In exploratory analyses, we found significant interactions (p<0.10) between
406 race/ethnicity and the associations of age, method of sample collection, and AUDIT-C score with
407 PEth sensitivity in Model 1 (data not shown), thus we stratified by race/ethnicity (Table 11).
408 After stratification by race/ethnicity, we found reduced odds of PEth sensitivity for females

409 compared to males among African Americans (aOR = 0.41; 95% Confidence Interval [CI]: 0.29-
410 0.58). In addition, age was associated with PEth sensitivity among Africans in Models 1 and 2.

411

412 **Discussion**

413 We leveraged over 4000 observations from 21 studies, spanning 4 continents and including wide
414 representation of men and women, several racial/ethnic groups, and persons with and without
415 HIV, to conduct the largest analyses to date of the demographic and biological factors which
416 impact PEth sensitivity among persons reporting unhealthy alcohol use. These analyses are vital
417 to interpreting PEth results in clinical practice and research. Eighty-two percent (82%) of
418 observations in which unhealthy alcohol use was reported were PEth positive. In overall analyses
419 adjusted for self-reported level of alcohol use, we did not observe associations of gender, age,
420 race/ethnicity and method of blood collection with PEth sensitivity. When we examined
421 biological variables, we found that higher hemoglobin and indeterminate and advanced fibrosis
422 had significantly higher odds of PEth sensitivity, while higher BMI and living with HIV had
423 lower odds of PEth sensitivity. We also found increased odds of PEth sensitivity among Africans
424 and African Americans compared to whites in the analyses that included biologic variables. As
425 expected, PEth sensitivity increased with level of self-reported alcohol use. Our results were
426 robust in sensitivity analyses.

427

428 We expected that women might have higher PEth sensitivity compared to men because women
429 have higher peak blood alcohol levels, due to greater body fat and decreased water volume
430 compared to men of the same size (Cederbaum, 2012). However, we did not see a difference in
431 PEth levels by sex, which was consistent with other studies that found no sex differences in PEth

432 sensitivity (Wurst et al., 2010, Helander et al., 2019a, Hahn et al., 2012, Hill-Kapturczak et al.,
433 2018). We did not expected differences in PEth sensitivity by race/ethnicity, and did not find any
434 difference by race/ethnicity in Model 1, however the odds of PEth sensitivity were increased for
435 Africans and African Americans compared to whites in Model 2 and Model 3, which included
436 subsets of the data with biologic measures. These associations may have been caused by residual
437 confounding if the level of alcohol consumption was differentially under-reported by
438 race/ethnicity. We have observed high social desirability and under-report of alcohol use by
439 Ugandans living with HIV in prior studies (Adong et al., 2019, Bajunirwe et al., 2014,
440 Muyindike et al., 2017) and under-report has also been reported for racial and ethnic minorities
441 compared to whites in the United States (Johnson and Bowman, 2003, White et al., 2014).

442

443 We hypothesized that PEth might be increased for older persons, due to lower body water,
444 slower alcohol metabolism, and higher prevalence of liver disease than younger persons (Meier
445 and Seitz, 2008). However, we found no association between age and PEth sensitivity overall,
446 consistent with a recent examination of this issue (Cherrier et al., 2020). In our exploratory
447 stratified analyses, we observed higher odds of PEth sensitivity in the older compared to younger
448 ages among Africans, even after adjusting for BMI, thus this deserves more examination.

449

450 We examined several biologic variables that have been considered as possible factors in PEth
451 sensitivity. We examined BMI, because ethanol concentration in blood per standard drink is
452 inversely proportional to body weight (Cederbaum, 2012). We found that the odds of PEth
453 sensitivity were lower for those with higher BMI, consistent with two prior studies (Wang et al.,

454 2017, Hahn et al., 2012). In addition, since PEth is formed on the surface of red blood cells, it
455 has been suggested that red blood cell depletion may reduce PEth (Nguyen and Seth, 2018), thus
456 we examined hemoglobin levels. We found increased odds of PEth sensitivity with higher levels
457 of hemoglobin. We also found an association of HIV status and PEth sensitivity. While there
458 have been no published studies of this issue, there is a small and mixed literature on the impact
459 of HIV on alcohol metabolism. One study suggested slower alcohol elimination among persons
460 with HIV (McGinnis et al., 2016), while another reported lower blood alcohol levels among
461 persons with HIV compared to those without (Shuper et al., 2018). Our results of lower odds of
462 PEth sensitivity among persons with HIV compared to those without HIV are consistent with the
463 latter. Possible mechanisms to explain this might include decreased alcohol absorption in the
464 presence of antiretroviral medications. Further research is needed to explore this finding. Lastly,
465 liver damage slows alcohol elimination (Cederbaum, 2012), and we found that higher fibrosis
466 scores were associated with increased odds of PEth sensitivity, consistent with a recent study
467 (Blomdahl et al., 2020). However, fibrosis is frequently the result of high levels of alcohol
468 consumption, so this finding may instead or in part reflect residual confounding by under-
469 reported alcohol use. We had also hypothesized that PEth sensitivity may be impacted by sample
470 preparation, however we found no differences blood spots prepared from venous blood draws
471 compared to finger-pricks, consistent with prior literature (Kummer et al., 2016a, Beck et al.,
472 2018, Piano et al., 2015).

473

474 Our exploratory analyses of interactions showed reduced odds of PEth sensitivity among African
475 Americans for women compared to men. This finding is consistent with a study of women with
476 HIV, predominantly African American (83%), who reported high levels of alcohol use, among

477 whom only 47% tested PEth positive (Wang et al., 2017). This finding deserves further
478 examination, including whether differences in body fat distribution and hemoglobin among
479 African American women compared to African American men explain these results.

480

481 The overall clinical significance of these findings are that there are some biologic factors that
482 decrease PEth sensitivity. Thus for some groups, caution should be used in interpreting negative
483 PEth findings. However, the lowest predicted sensitivity was 75%, suggesting that PEth is very
484 sensitive overall, but that sensitivity is reduced for persons with some characteristics (e.g. anemia
485 or high BMI).

486

487 *Strengths and limitations*

488 The strength of this study is the large sample size, which allowed for analyses of variables not
489 previously systematically examined, including several biologic variables. Another strength is the
490 restriction to those reporting unhealthy alcohol consumption or more severe alcohol use, thereby
491 increasing the likelihood of valid self-report. A limitation is that some studies targeted
492 specialized populations, such as young persons who inject drugs, TB patients, entertainment
493 workers and their clients, and persons with HIV, limiting generalizability, and not all studies
494 collected data on all the variables of interest. However, our findings were consistent across
495 sensitivity analyses. We acknowledge that the race/ethnicity categories included represent social
496 constructs rather than genetic ancestry (Mersha and Abebe, 2015). It is also a limitation that we
497 did not have enough participants in Asian, Latinx/Hispanic, and Native American populations to
498 be able to examine these groups separately. In addition, while we grouped participants recruited
499 in Africa as Africans, immigrants participating in studies in the United States may have been

500 grouped with African Americans. We are also likely underpowered to detect important
501 differences by age. We could not examine the method of sample collection in models that
502 adjusted for the other biologic variables because as of the studies that measured these variables
503 had conducted the blood collection via venous blood draw.

504

505 There are limitations to our use of the AUDIT-C to control for the level of alcohol consumption.
506 Systematic reporting bias could lead to spurious conclusions due to residual confounding. We
507 attempted to limit mis-reporting by limiting the analyses to those with positive AUDIT-C scores,
508 and limiting the inclusion criteria to studies for which mis-report was unlikely; we found no
509 substantial differences in sensitivity analyses with even higher cutoffs (AUDIT-C ≥ 6).

510 However, differences in self-report by certain subgroups, such as those experiencing social
511 desirability bias, could have caused spurious associations. We were reassured that the strongest
512 and most consistent associations were observed with variables which had biologic plausibility to
513 be associated with PEth sensitivity (e.g. the associations of BMI and hemoglobin with PEth
514 sensitivity). Lastly, the self-reported alcohol use referred to time periods ranging from one month
515 to one year, or no time period was specified, while PEth detects alcohol use in the prior 2-4
516 weeks. Thus, we likely under-estimated PEth sensitivity for detecting recent unhealthy alcohol
517 use. To maximize the sample size, we decided to include all observations without regard to the
518 self-report period, and our sensitivity analyses that limited the data to those with known prior
519 month alcohol use showed results that were consistent with those obtained using the larger
520 sample.

521

522 A potential concern is that we did not include studies that used a higher cutoff, such as 20 ng/mL
523 for PEth detection. Among the PEth positive observations in this study, 9% were between 8 and
524 20 ng/mL, suggesting that detection of unhealthy but not severe drinking may be missed using a
525 cutoff of 20 ng/mL. The use of one laboratory for PEth testing for the majority of the studies may
526 limit the generalizability of our results. A recent study showed similar sensitivity rates and high
527 correlations between testing conducted at an academic laboratory compared to at USDTL, but
528 higher PEth values at the academic laboratory (Javors et al., 2019). We focused on the 16:0/18:1
529 PEth homologue, although others have differing formation and elimination patterns (Lopez-
530 Cruzan et al., 2018, Hill-Kapturczak et al., 2018).

531

532 *Conclusions*

533 These findings provide important information for clinicians and researchers using PEth. We
534 found associations of several biological characteristics with PEth sensitivity, with high overall
535 PEth sensitivity among those engaging in unhealthy alcohol use. Clinicians should be aware of
536 these factors, especially when considering negative PEth results, and researchers should consider
537 adjusting analyses for these characteristics where possible.

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831 Table 1. Characteristics of included studies.

Study code	Study name and reference	Study design	N persons included	N observations	Region	Location	Participants	AUDIT-C period	How blood collected for PEth
Total			3,085	4,073					
ADEPT	Alcohol Drinking Effects on Progression prior to Treatment (ADEPT) (Hahn et al., 2018)	Observational cohort study	162	315	Africa	Mbarara, Uganda	PLWH, ART-naïve, over sampling alcohol users, age ≥ 18	3 months	Venously
ADEPTT	Alcohol Drinkers' Exposure to Treatment for TB (ADEPTT)	Trial (no alcohol intervention)	80	162	Africa	Mbarara, Uganda	PLWH, latent tuberculosis infection, on ART ≥ 6 months, 2/3 prior 3 months alcohol use, age ≥ 18	3 months	Venously
BREATH	BREATH (Biomarker Research on Ethanol Among Those with HIV) (Hahn et al., 2016b)	Observational cohort study	162	301	Africa	Mbarara, Uganda	PLWH, new to HIV care, prior year alcohol use, age ≥ 18	3 months	Venously
DIPT	Drinkers Intervention to Prevent Tuberculosis (DIPT)	Randomized controlled trial (NCT#03492216)	254	461	Africa	Mbarara, Uganda	PLWH, latent tuberculosis infection, on ART for ≥ 6 months, unhealthy alcohol use, current alcohol use confirmed by ethyl glucuronide dipstick, age ≥ 18	3 months	Venously
META	Monitoring Early Treatment Adherence (Magidson et al., 2019)	Observational cohort study (baseline only)	79	79	Africa	Cape Town South Africa and south-western Uganda	PLWH, ART-naïve, age ≥ 18	3 months	Venously
TANZANIA	Validation of self-reported alcohol use among young people in northern Tanzania (Francis et al., 2015)	Observational cross-sectional study	172	172	Africa	Mwanza, Tanzania	Prior year alcohol use, age 15-24	1 year	Venously
TRUST	The Impact of Alcohol Consumption on TB Treatment Outcomes (TRUST)(Myers et al., 2018)	Observational cohort study (baseline only)	82	82	Africa	Cape Town, South Africa	Persons initiating TB treatment, age ≥ 15	Not specified	Venously
SIHANOUK	Sihanouk Risk Study(Couture et al., 2016)	Observational cross-sectional study	132	132	Asia	Preah Sihanouk, Cambodia	Female sex workers and male clients, age ≥ 18	3 months	Finger-prick
Russia Women	Reducing Alcohol Use Among HIV Positive Women in Care (Littlefield et al., 2017)	Observational cohort study	92	130	Europe	St. Petersburg Russia	PLWH, female, age 18-35	Not specified	Finger-prick
RUSSIA	Alcohol & Zinc Impact on Inflammatory Markers in HIV Disease (So-Armah et al., 2019)	Observational cohort study	323	603	Europe	St. Petersburg, Russia	PLWH, ART naïve, age 18-70	1 year	Venously
BOSTON	Addressing Alcohol/HIV in Substance Dependence (Saitz et al., 2018)	Observational cohort study (baseline only)	159	159	North America	Boston, MA	PLWH; substance dependence or ever injected drugs, age ≥ 18	3 months	Venously
CHAMPS	Chronic Hepatitis C Management to Improve Outcomes (Irvin et al., 2020)	Randomized controlled trial (no alcohol	38	38	North America	Baltimore, MD	PLWH, chronic hepatitis C virus, age ≥ 18	Not specified	Venously

		intervention) (NCT# 02402218)							
HOLIDAY	Holiday Heart	Observational cohort study	58	87	North America	San Francisco, CA	Persons diagnosed with atrial fibrillation and/or atrial flutter, alcohol use \geq 1x per month, age \geq 21	Not specified	Finger-prick
INVOICE	INVOICE Study	Observational cohort study	88	136	North America	San Francisco, CA and Syracuse, NY	PLWH, MSM/Transwomen	Not specified	Finger-prick
MIAMI	Effects of reductions in alcohol consumption on outcomes in older persons with HIV infection	Single arm trial (unhealthy alcohol use confirmed alcohol use with a biosensor) (NCT# 03353701)	24	36	North America	Miami, FL	Persons with unhealthy alcohol use, age 50-75	1 year	Venously
NOAH	New Orleans Alcohol Use in HIV Study (Ferguson et al., 2020)	Observational cohort study (baseline only)	204	204	North America	New Orleans, LA	PLWH, age \geq 18	1 year	Venously
Young Adults	Binge Drinking and Cardiovascular Risk in Young Adults (Piano et al., 2015)	Observational cohort study	97	97	North America	Chicago, IL	Persons without risk factors for cardiovascular disease, age 18-30	Not specified	Venously
Stewart	PEth in Liver Disease Patients (Stewart et al., 2014)	Observational cross-sectional study	66	66	North America	Charleston, SC	Persons with active liver disease, willing to discuss their alcohol use, ag \geq 18	AUDIT calculated from 90-day TLFB	Venously
TRAUMA	Phosphatidylethanol to Screen for Alcohol Misuse in Trauma Patients (Afshar et al., 2021)	Observational cohort study (baseline only)	108	108	North America	Maywood, IL	Trauma center patients, age \geq 18	Not specified	Venously
UFO	UFO Study (Jain et al., 2014)	Observational cohort study (baseline only)	83	83	North America	San Francisco, CA	Injected illicit drugs, prior 30 days, age 15-30	Calculated from prior 30 days questions	Venous and finger-prick
VACS	VACS Blood Study (Eyawo et al., 2018)	Observational cohort study (one visit only)	622	622	North America	Multiple US sites	US Veterans, including PLWH and persons without HIV	1 year	Venously

Abbreviations: PLWH: persons living with HIV; ART: antiretroviral therapy; MSM: men who have sex with men; TLFB: timeline followback

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Table 2. Distributions of the primary variables overall and by study (first observation per participant).

Study code	N	AUDIT-C score	PEth (ng/mL)	PEth ≥ 8 ng/mL	Sex =Female	Age	Race/ethnicity				BMI (kg/m ²)	Hemo-globin (g/dL)	FIB-4 score	HIV+
							African	African American	White	Other				
		Median (IQR)	Median (IQR)	n (%)	n (%)	Median (IQR)	n (%)	n (%)	n (%)	n (%)	Median (IQR)	Median (IQR)	Median (IQR)	n (%)
Total	3,085	6 (4-8)	70.0 (14.0-233.0)	2,445 (79.3%)	953 (30.9%)	38 (28-51)	991 (32.1%)	855 (27.7%)	879 (28.5%)	360 (11.7%)	23.6 (21.1-27.3)	14.1 (12.9-15.2)	1.2 (0.8-1.9)	2,074 (67.2%)
ADEPT	162	5 (4-7)	117.0 (29.0-414.0)	141 (87.0%)	90 (55.6%)	32 (27-38)	162 (100%)	---	---	---	22.8 (20.4-25.7)	15.0 (14.0-16.1)	---	162 (100%)
ADEPTT	80	5 (4-7)	124.5 (21.0-253.0)	65 (81%)	24 (30%)	38 (32.5-45)	80 (100%)	---	---	---	21.8 (19.5-25.2)	15.2 (14.1-15.9)	1.0 (0.7-1.4)	80 (100%)
BREATH	162	4 (4-6)	110.3 (45.2-310.0)	146 (90.1%)	71 (43.8%)	29 (24-35)	162 (100%)	---	---	---	21.8 (19.8-24.2)	14.2 (13.1-15.7)	---	162 (100%)
DIPT	254	7 (5-9)	266.0 (111.0-512.0)	251 (98.8%)	73 (28.7%)	39 (32-46)	254 (100%)	---	---	---	21.5 (19.3-23.9)	14.8 (13.7-16.0)	1.0 (0.7-1.4)	254 (100%)
META	79	5 (4-7)	137.0 (45.0-372.0)	74 (94%)	47 (59%)	31 (26-41)	79 (100%)	---	---	---	23.6 (20.7-26.4)	---	---	79 (100%)
TANZANIA	172	6 (4-8)	7.0 (0.0-63.3)	80 (46.5%)	31 (18.0%)	22 (21-24)	172 (100%)	---	---	---	---	---	---	---
TRUST	82	7.5 (6-9)	144.0 (14.0-378.0)	68 (83%)	29 (35%)	36 (28-48)	82 (100%)	---	---	---	18.5 (16.6-20.2)	12.4 (10.5-13.5)	0.6 (0.3-0.8)	26 (32%)
SIHANOUK	132	6 (5-8)	92.9 (24.6-232.6)	114 (86.4%)	85 (64.4%)	25 (22-29)	---	---	---	132 (100%)	---	---	---	5 (3.8%)
Russia women	92	4 (3-4)	29.5 (14.0-83.0)	75 (82%)	92 (100%)	30 (28.5-33)	---	---	92 (100%)	---	---	---	---	92 (100%)
RUSSIA	323	8 (6-10)	61.0 (12.0-208.0)	261 (80.8%)	98 (30.3%)	33 (30-37)	---	---	323 (100%)	---	22.5 (20.7-24.4)	15.0 (13.4-15.8)	1.4 (0.9-2.2)	323 (100%)
BOSTON	159	7 (5-10)	21.0 (1.0-83.3)	96 (60.4%)	61 (38.4%)	48 (41-53)	---	81 (50.9%)	29 (18.2%)	49 (30.8%)	25.9 (23.2-29.6)	13.4 (12.3-14.4)	1.2 (0.8-1.9)	159 (100%)
CHAMPS	38	5 (4-7)	199.5 (76.0-444.0)	34 (89%)	16 (42%)	53 (49-57)	---	36 (95%)	2 (5%)	---	24.1 (21.3-28.1)	13.7 (12.3-14.2)	2.3 (1.4-3.8)	38 (100%)
HOLIDAY	58	4 (4-5)	31.5 (14.0-68.0)	49 (84%)	12 (21%)	67 (60-74)	---	2 (3%)	48 (83%)	8 (14%)	---	---	---	---
INVOICE	88	7 (6-8)	24.5 (1.0-118.0)	51 (58%)	---	43.5 (31.5-50.5)	---	56 (64%)	12 (14%)	20 (23%)	---	---	---	88 (100%)
MIAMI	24	6 (5-9.5)	53.5 (11.5-114.0)	20 (83%)	10 (42%)	55 (54-59.5)	---	20 (83%)	3 (12%)	1 (4%)	24.4 (21.9-29.1)	13.2 (11.7-14.1)	1.3 (0.9-1.7)	12 (50%)
NOAH	204	6 (4-8)	90.0 (14.5-270.0)	159 (77.9%)	61 (29.9%)	51 (42-56)	---	170 (83.3%)	32 (15.7%)	2 (1.0%)	25.3 (22.6-29.8)	13.6 (12.5-14.5)	1.2 (0.8-1.7)	204 (100%)
Young adults	97	6 (4-9)	31.0 (15.1-66.2)	81 (84%)	64 (66%)	22 (20-24)	---	4 (4%)	73 (75%)	20 (21%)	22.7 (21.3-24.7)	13.3 (12.8-13.9)	---	---
Stewart	66	6 (4-9)	216.5 (47.0-475.0)	60 (91%)	25 (38%)	52 (42-57)	---	22 (33%)	42 (64%)	2 (3%)	---	---	---	2 (3%)

TRAUMA	108	6 (4-8)	148.0 (35.0-454.0)	98 (90.7%)	22 (20.4%)	46 (32.5-61)	---	20 (18.5%)	50 (46.3%)	38 (35.2%)	27.4 (23.4-31.1)	13.7 (12.5-14.8)	---	---
UFO	83	8 (5-10)	42.7 (0.0-154.0)	58 (70%)	19 (23%)	25 (22-27)	---	4 (5%)	63 (76%)	16 (19%)	---	---	---	3 (4%)
VACS	622	5 (4-7)	42.0 (7.0-147.0)	464 (74.6%)	23 (3.7%)	51 (47-56)	---	440 (70.7%)	110 (17.7%)	72 (11.6%)	25.8 (23.0-29.6)	14.0 (13.1-15.0)	1.3 (0.9-2.0)	385 (61.9%)

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Table 3. PEth sensitivity (≥ 8 ng/mL) overall and by demographic and biologic variables, all observations. Odds ratios and 95% confidence intervals are from separate mixed effects models, adjusted for AUDIT-C (N=4073).

Variable	n PEth positive (≥ 8 ng/mL)/N (%)	Odds Ratio (95% CI)	p-value
Overall	3,332/4,073 (81.8%)		
AUDIT-C score			
Medium (4-5men/3-5 women)	1,430/1,851 (77.3%)	1.00	
High (6-7)	801/963 (83.2%)	1.81 (1.37-2.39)	<0.001
Very high (8-12)	1,101/1,259 (87.5%)	2.89 (1.79-4.66)	<0.001
AUDIT-C, from quadratic model			
6 vs 4		1.86 (1.47-2.36)	<0.001
10 vs 4		3.59 (2.26-5.71)	<0.001
Gender			
Male	2,266/2,756 (82.2%)		
Female	1,066/1,317 (80.9%)	0.82 (0.58-1.17)	0.273
Race/ethnicity			
White	987/1,228 (80.4%)	1.00	
African	1,368/1,572 (87.0%)	2.20 (0.74-6.59)	0.157
African American	681/893 (76.3%)	1.37 (1.02-1.84)	0.036
Other	296/380 (77.9%)	1.18 (0.75-1.87)	0.481
Age			
15-24	391/546 (71.6%)		
25-34	1,013/1,198 (84.6%)	1.15 (0.72-1.83)	0.557
35-44	837/961 (87.1%)	1.44 (0.66-3.16)	0.358
45-54	643/810 (79.4%)	1.41 (0.67-2.99)	0.370
55+	448/558 (80.3%)	1.44 (0.67-3.05)	0.358
Age, from quadratic model			
30 vs 20		1.49 (0.97-2.29)	0.066
40 vs 20		1.90 (0.94-3.84)	0.072
50 vs 20		2.07 (0.90-4.74)	0.085
60 vs 20		1.93 (0.84-4.40)	0.120
Method of blood collection			
Finger-prick	436/568 (76.8%)		
Venous	2,896/3,505 (82.6%)	1.52 (0.60-3.83)	0.377
Body mass index			
Underweight (<18.5)	229/247 (92.7%)		
Normal (18.5-24.9)	1,655/1,895 (87.3%)	0.72 (0.44-1.17)	0.154
Overweight (25-29.9)	576/731 (78.8%)	0.50 (0.32-0.79)	0.003
Obese (≥ 30)	325/427 (76.1%)	0.44 (0.28-0.69)	<0.001
Body mass index, per 5 units		0.76 (0.68-0.84)	<0.001
Hemoglobin*			
Moderate/severe anemia	121/165 (73.3%)		
Mild anemia	316/400 (79.0%)	1.71 (1.05-2.79)	0.031
No anemia	2,058/2,412 (85.3%)	2.19 (1.34-3.59)	0.002
High hemoglobin	132/140 (94.3%)	3.54 (1.42-8.85)	0.009
Hemoglobin, per 5 units		1.94 (1.41-2.65)	<0.001
HIV status			
Negative	615/756 (81.3%)		
Positive	2,533/3,026 (83.7%)	0.97 (0.82-1.14)	0.691
FIB-4 score			
No/mild fibrosis: <1.45	923/1,169 (79.0%)		
1.45-3.25	471/574 (82.1%)	1.31 (1.05-1.63)	0.017
Advanced fibrosis: >3.25	161/183 (88.0%)	1.83 (1.24-2.71)	0.002

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*Hemoglobin (HGB) cutoffs: Moderate/severe anemia: <11 g/dL HGB; Mild anemia =<12 g/dL HGB for women, <13 g/dL HGB for men; No anemia: 12-15.5 g/dL HGB for women, 13-17.5 HGB for men; High hemoglobin: >15.5 g/dL for women, >17.5 g/dL for men.

Table 4. Adjusted odds ratios 95% confidence intervals, and p-values for the associations of demographic and biologic variables with PEth sensitivity (PEth ≥ 8 ng/mL) among observations with unhealthy drinking reported. Statistically significant comparisons are bolded.

Predictors	Model 1	Model 2	Model 3
N Studies	21	13	9
N	4073	3188	2367
AUDIT-C score*			
6 vs 4	1.78 (1.40-2.27, p<0.001)	1.64 (1.28-2.10, p<0.001)	1.38 (1.11-1.72, p<0.001)
10 vs 4	3.37 (2.05-5.53, p<0.001)	2.62 (1.79-3.83, p<0.001)	2.10 (1.55-2.87, p<0.001)
Sex: Female vs Male	0.86 (0.61-1.22, p=0.396)	1.08 (0.82-1.42, p=0.589)	1.12 (0.81-1.54, p=0.500)
Race/Ethnicity			
African vs White	2.41 (0.81-7.21, p=0.115)	3.05 (1.07-8.72, p=0.037)	3.57 (0.73-17.42, p=0.116)
African American vs White	1.30 (0.96-1.76, p=0.090)	1.54 (1.00-2.37, p=0.047)	1.70 (1.06-2.72, p=0.027)
Other vs White	1.16 (0.72-1.86, p=0.540)	1.10 (0.85-1.43, p=0.471)	1.22 (0.90-1.64, p=0.202)
Age*			
30 vs 20	1.44 (0.93-2.23, p=0.098)	1.68 (1.02-2.76, p=0.041)	1.10 (0.62-1.95, p=0.737)
40 vs 20	1.81 (0.89-3.69, p=0.101)	2.27 (1.01-5.12, p=0.048)	1.14 (0.45-2.94, p=0.786)
50 vs 20	1.98 (0.86-4.58, p=0.110)	2.47 (0.95-6.40, p=0.062)	1.12 (0.36-3.42, p=0.847)
60 vs 20	1.88 (0.82-4.32, p=0.135)	2.17 (0.86-5.45, p=0.099)	1.03 (0.34-3.11, p=0.965)
Method of blood collection: Venous vs finger-prick	0.92 (0.29-2.93, p=0.885)	---	---
BMI (per 5 kg/m ²)		0.74 (0.66-0.83, p<0.001)	0.73 (0.65-0.81, p<0.001)
Hemoglobin (per 5 g/dl)		2.12 (1.52-2.96, p<0.001)	2.28 (1.57-3.30, p<0.001)
HIV+ (vs HIV-)		0.77 (0.66-0.89, p<0.001)	0.78 (0.64-0.95, p=0.013)
FIB-4 score			
1.45-3.25 vs <1.45			1.29 (1.02-1.63, p=0.032)
>3.25 vs <1.45			1.87 (1.28-2.75, p=0.001)

*Fitted values from quadratic variable

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Table 5. Predicted PEth sensitivity for each variable calculated from the regression models, holding all others at their means. Categories for continuous variables are the midpoints of categories defined in Table 3.

Predictors	Model 1	Model 2	Model 3
AUDIT-C score			
Medium: 4	77.1% (68.5-85.6)	82.5% (76.4-88.6)	78.9% (70.9-86.9)
High: 6	84.8% (78.1-91.5)	88.2% (83.0-93.4)	83.5% (77.4-89.5)
Very high: 10	90.9% (86.2-95.5)	92.1% (88.2-96.1)	88.2% (84.0-92.3)
Sex			
Male	86.3% (79.8-92.8)	88.8% (83.8-93.9)	84.4% (78.8-89.9)
Female	84.6% (77.5-91.8)	89.5% (84.1-94.9)	85.7% (79.3-92.0)
Race/ethnicity			
African	90.2% (81.9-98.6)	93.2% (87.9-98.4)	91.5% (82.2-100.8)
African American	84.1% (77.1-91.1)	87.7% (81.3-94.0)	84.3% (78.2-90.5)
White	80.7% (72.1-89.4)	82.6% (73.4-91.8)	76.8% (66.9-86.8)
Other	82.7% (73.7-91.7)	83.9% (74.8-93.0)	79.8% (66.9-92.7)
Age			
20	78.4% (68.5-88.2)	79.0% (67.6-90.5)	83.0% (67.7-98.3)
30	83.3% (76.9-89.8)	85.9% (80.1-91.7)	84.2% (75.7-92.8)
40	86.0% (79.5-92.5)	89.0% (83.9-94.0)	84.7% (78.9-90.5)
50	86.9% (80.0-93.8)	89.7% (84.5-95.0)	84.4% (78.9-89.9)
60	86.4% (79.2-93.5)	88.6% (83.2-93.9)	83.3% (77.6-89.1)
Method of blood collection			
Finger-prick	86.6% (73.7-99.4)		
Venous blood collection	85.7% (79.2-92.2)		
Body mass index (kg/m²)			
Underweight: 17.5		92.3% (88.4-96.1)	89.3% (84.2-94.3)
Normal: 22		90.3% (85.8-94.9)	86.5% (81.2-91.9)
Overweight: 27.5		87.1% (81.1-93.0)	82.1% (76.2-87.9)
Obese: 33		83.2% (75.2-91.2)	76.8% (70.1-83.6)
Hemoglobin (g/dL)			
Moderate/severe: 10		82.0% (74.1-89.8)	74.9% (66.4-83.4)
Mild anemia: 11.5		84.8% (78.2-91.5)	78.9% (71.8-86.0)
No anemia: 14		88.8% (83.7-94.0)	84.5% (78.9-90.1)
High hemoglobin: 17.5		92.9% (89.0-96.8)	90.3% (85.6-95.0)
HIV status			
Negative		90.9% (86.4-95.5)	87.1% (81.5-92.7)
Positive		88.6% (83.4-93.8)	84.3% (78.7-89.9)
FIB-4 score			
No/mild fibrosis: <1.45			83.1% (77.3-88.8)
1.45-3.25			86.1% (80.2-92.1)
Advanced fibrosis: >3.25			89.8% (84.8-94.8)

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Table 6. Adjusted odds ratios, 95% confidence intervals, and p-values for the associations of demographic and biologic variables with PEth sensitivity (PEth \geq 8 ng/mL) among persons reporting unhealthy drinking, first observation per person included only (sensitivity analyses). Statistically significant comparisons are bolded.

Predictors	Model 1	Model 2	Model 3
N Studies	21	13	9
N	3085	2315	1786
AUDIT-C score*			
6 vs 4	1.89 (1.46-2.45, p<0.001)	1.72 (1.34-2.21, p<0.001)	1.46 (1.20-1.77, p<0.001)
10 vs 4	3.39 (1.88-6.11, p<0.001)	2.53 (1.64-3.91, p<0.001)	2.05 (1.45-2.88, p<0.001)
Sex: Female vs Male	0.86 (0.58-1.26, p=0.443)	1.02 (0.75-1.40, p=0.885)	1.03 (0.73-1.45, p=0.859)
Race/Ethnicity			
African vs White	2.26 (0.78-6.60, p=0.135)	2.76 (1.01-7.57, p=0.049)	3.36 (0.70-16.09, p=0.129)
African American vs White	1.32 (0.98-1.78, p=0.071)	1.57 (1.03-2.39, p=0.036)	1.69 (1.07-2.68, p=0.024)
Other vs White	1.05 (0.79-1.41, p=0.733)	1.10 (0.85-1.44, p=0.457)	1.22 (0.91-1.63, p=0.179)
Age*			
30 vs 20	1.34 (0.89-2.00, p=0.159)	1.50 (0.95-2.37, p=0.079)	1.17 (0.60-2.28, p=0.648)
40 vs 20	1.61 (0.84-3.09, p=0.154)	1.91 (0.91-4.02, p=0.088)	1.26 (0.42-3.80, p=0.679)
50 vs 20	1.75 (0.81-3.75, p=0.152)	2.05 (0.86-4.89, p=0.105)	1.26 (0.34-4.65, p=0.727)
60 vs 20	1.71 (0.81-3.63, p=0.161)	1.86 (0.80-4.32, p=0.147)	1.16 (0.32-4.19, p=0.815)
Method of blood collection: Venous vs finger-prick	0.94 (0.29-3.02, p=0.922)		
BMI (per 5 kg/m ²)		0.71 (0.64-0.79, p<0.001)	0.71 (0.64-0.79, p<0.001)
Hemoglobin (per 5 g/dl)		2.29 (1.56-3.36, p<0.001)	2.43 (1.58-3.75, p<0.001)
HIV+ (vs HIV-)		0.73 (0.63-0.85, p<0.001)	0.76 (0.63-0.91, p=0.003)
FIB-4 score			1.00
1.45-3.25 vs <1.45			1.26 (0.99-1.61, p=0.061)
>3.25 vs <1.45			1.77 (1.18-2.65, p=0.006)

*Fitted values from quadratic variable

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Table 7. Adjusted odds ratios, 95% confidence intervals, and p-values for the associations of demographic and biologic variables with PEth sensitivity (PEth \geq 8 ng/mL) among persons reporting unhealthy drinking, data limited to observations with prior 30-day alcohol use assessed/reported (sensitivity analyses). Statistically significant comparisons are bolded.

Predictors	Model 1	Model 2	Model 3
N Studies	14	10	7
N	2552	2173	1538
AUDIT-C score*			
6 vs 4	1.50 (1.13-1.97, p<0.001)	1.41 (1.01-1.96, p=0.043)	1.13 (0.81-1.57, p=0.471)
10 vs 4	3.38 (2.26-5.05, p<0.001)	2.81 (1.96-4.01, p<0.001)	2.25 (1.39-3.65, p=0.001)
Sex: Female vs Male	0.82 (0.57-1.17, p=0.269)	1.05 (0.80-1.38, p=0.743)	1.14 (0.83-1.55, p=0.412)
Race/Ethnicity			
African vs White	2.70 (0.94-7.76, p=0.065)	3.21 (1.30-7.95, p=0.012)	3.57 (0.80-15.96, p=0.095)
African American vs White	1.53 (1.01-2.30, p=0.042)	1.70 (1.07-2.67, p=0.023)	1.96 (1.11-3.49, p=0.021)
Other vs White	0.76 (0.58-1.00, p=0.048)	0.78 (0.58-1.07, p=0.123)	0.79 (0.50-1.26, p=0.322)
Age*			
30 vs 20	1.63 (0.90-2.95, p=0.109)	1.64 (0.83-3.24, p=0.154)	0.91 (0.47-1.77, p=0.790)
40 vs 20	2.20 (0.86-5.65, p=0.102)	2.07 (0.71-6.04, p=0.182)	0.81 (0.28-2.31, p=0.689)
50 vs 20	2.47 (0.84-7.23, p=0.100)	2.01 (0.62-6.56, p=0.246)	0.69 (0.21-2.23, p=0.532)
60 vs 20	2.30 (0.79-6.68, p=0.125)	1.50 (0.53-4.27, p=0.443)	0.56 (0.19-1.64, p=0.294)
Method of blood collection: Venous vs finger-prick	0.73 (0.19-2.72, p=0.634)		
BMI (per 5 kg/m ²)		0.73 (0.62-0.86, p<0.001)	0.73 (0.62-0.86, p<0.001)
Hemoglobin (per 5 g/dl)		2.13 (1.46-3.12, p<0.001)	2.32 (1.43-3.77, p<0.001)
HIV+ (vs HIV-)		0.78 (0.39-1.57, p=0.487)	0.98 (0.48-2.02, p=0.959)
FIB-4 score			1.00
1.45-3.25 vs <1.45			1.43 (0.97-2.11, p=0.074)
>3.25 vs <1.45			2.30 (1.49-3.54, p<0.001)

*Fitted values from quadratic variable

Table 8. Adjusted odds ratios, 95% confidence intervals, and p-values for the associations of demographic and biologic variables with PEth sensitivity (PEth \geq 8 ng/mL) among persons reporting unhealthy drinking, limited to observations with high/very high drinking (AUDIT-C \geq 6) only (sensitivity analyses). Statistically significant comparisons are bolded.

Predictors	Model 1	Model 2	Model 3
N Studies	21	13	9
N	2222	1799	1436
AUDIT-C score*			
6 vs 4	1.66 (0.84-3.29, p=0.143)	1.59 (0.79-3.20, p=0.192)	1.41 (0.71-2.80, p=0.327)
10 vs 4	3.22 (1.19-8.72, p=0.021)	2.65 (1.10-6.40, p=0.030)	2.18 (0.92-5.16, p=0.077)
Sex: Female vs Male	0.93 (0.58-1.51, p=0.783)	0.98 (0.63-1.54, p=0.946)	1.07 (0.65-1.77, p=0.745)
Race/Ethnicity			
African vs White	1.54 (0.43-5.49, p=0.508)	2.45 (0.67-8.93, p=0.175)	3.36 (0.86-13.19, p=0.083)
African American vs White	0.69 (0.32-1.52, p=0.361)	0.77 (0.26-2.31, p=0.640)	0.78 (0.26-2.35, p=0.655)
Other vs White	0.72 (0.37-1.42, p=0.344)	0.67 (0.34-1.32, p=0.246)	0.54 (0.36-0.82, p=0.004)
Age*			
30 vs 20	1.02 (0.69-1.51, p=0.921)	1.05 (0.76-1.45, p=0.750)	1.00 (0.62-1.60, p=0.993)
40 vs 20	1.08 (0.57-2.04, p=0.814)	1.15 (0.66-2.01, p=0.612)	1.03 (0.46-2.29, p=0.940)
50 vs 20	1.19 (0.56-2.49, p=0.654)	1.31 (0.65-2.65, p=0.447)	1.10 (0.41-2.97, p=0.844)
60 vs 20	1.35 (0.65-2.82, p=0.425)	1.55 (0.71-3.38, p=0.267)	1.22 (0.43-3.51, p=0.706)
Method of blood collection: Venous vs finger-prick	1.00 (0.22-4.59, p=0.997)		
BMI (per 5 kg/m ²)		0.72 (0.61-0.85, p<0.001)	0.72 (0.62-0.85, p<0.001)
Hemoglobin (per 5 g/dl)		2.08 (1.24-3.50, p=0.006)	2.27 (1.33-3.88, p=0.003)
HIV+ (vs HIV-)		0.67 (0.49-0.93, p=0.016)	0.76 (0.65-0.88, p<0.001)
FIB-4 score			1.00
1.45-3.25 vs <1.45			1.32 (0.96-1.81, p=0.091)
>3.25 vs <1.45			2.49 (1.67-3.73, p<0.001)

*Fitted values from quadratic variable

Table 9. Adjusted odds ratios, 95% confidence intervals, and p-values for the associations of demographic and biologic variables with PEth sensitivity (PEth \geq 8 ng/mL) among persons reporting unhealthy drinking, excluding the largest single study (sensitivity analyses). Statistically significant comparisons are bolded.

Predictors	Model 1	Model 2	Model 3
N Studies	20	12	8
N	3451	2566	1745
AUDIT-C*			
AUDIT-C: 6 vs 4	1.92 (1.47-2.51, p<0.001)	1.75 (1.27-2.40, p<0.001)	1.41 (1.02-1.94, p=0.039)
AUDIT-C: 10 vs 4	4.26 (2.68-6.78, p<0.001)	3.25 (2.25-4.69, p<0.001)	2.46 (1.70-3.58, p<0.001)
Sex: Female vs Male	0.91 (0.62-1.32, p=0.614)	1.14 (0.84-1.55, p=0.041)	1.19 (0.81-1.75, p=0.381)
Race/Ethnicity			
African vs White	2.37 (0.74-7.62, p=0.148)	3.29 (1.05-10.26, p=0.041)	4.46 (0.87-22.82, p=0.073)
African American vs White	1.46 (0.82-2.57, p=0.195)	2.26 (1.25-4.08, p=0.007)	2.60 (1.21-5.58, p=0.019)
Other vs White	1.20 (0.60-2.41, p=0.611)	0.94 (0.70-1.25, p=0.662)	1.03 (0.68-1.57, p=0.883)
Age*			
Age: 30 vs 20	1.42 (0.88-2.27, p=0.149)	1.76 (0.99-3.12, p=0.055)	1.00 (0.48-2.07, p=0.993)
Age: 40 vs 20	1.76 (0.82-3.77, p=0.147)	2.38 (0.94-6.02, p=0.066)	0.97 (0.30-3.09, p=0.856)
Age: 50 vs 20	1.92 (0.79-4.66, p=0.149)	2.50 (0.86-7.21, p=0.091)	0.92 (0.25-3.36, p=0.896)
Age: 60 vs 20	1.84 (0.77-4.42, p=0.173)	2.02 (0.74-5.50, p=0.169)	0.85 (0.26-2.78, p=0.785)
Method of blood collection: Venous vs finger-prick	0.97 (0.26-3.59, p=0.967)		
BMI (per 5 kg/m ²)		0.77 (0.65-0.90, p<0.001)	0.74 (0.64-0.86, p<0.001)
Hemoglobin (per 5 g/dl)		2.20 (1.42-3.39, p<0.001)	2.34 (1.36-4.01, p=0.002)
HIV+ (vs HIV-)		0.70 (0.34-1.44, p=0.335)	1.16 (0.81-1.65, p=0.413)
FIB-4 score			1.00
FIB-4 1.45-3.25 vs <1.45			1.33 (0.94-1.89, p=0.113)
FIB-4 >3.25 vs <1.45			2.35 (1.44-3.84, p<0.001)

*Fitted values from quadratic variable

Table 10: Adjusted odds ratios, 95% confidence intervals, and p-values for the associations of demographic and biologic variables with PEth sensitivity (PEth \geq 8 ng/mL) among observations with unhealthy drinking reported and complete case data (sensitivity analyses). Statistically significant comparisons are bolded.			
Predictors	Model 1	Model 2	Model 3
N Studies	21	13	9
N	4073	3019	1773
AUDIT-C score*			
6 vs 4	1.78 (1.40-2.27, p<0.001)	1.62 (1.29-2.02, p<0.001)	1.45 (1.21-1.73, p<0.001)
10 vs 4	3.37 (2.05-5.53, p<0.001)	2.62 (1.78-3.87, p<0.001)	2.12 (1.57-2.85, p<0.001)
Sex: Female vs Male	0.86 (0.61-1.22, p=0.396)	1.08 (0.80-1.47, p=0.610)	1.15 (0.76-1.76, p=0.511)
Race/Ethnicity			
African vs White	2.41 (0.81-7.21, p=0.115)	2.96 (1.05-8.36, p=0.040)	3.59 (0.82-15.72, p=0.089)
African American vs White	1.30 (0.96-1.76, p=0.090)	1.48 (0.99-2.22, p=0.055)	1.71 (1.08-2.68, p=0.021)
Other vs White	1.16 (0.72-1.86, p=0.540)	1.06 (0.79-1.44, p=0.687)	1.21 (0.90-1.64, p=0.214)
Age*			
30 vs 20	1.44 (0.93-2.23, p=0.098)	1.61 (0.95-2.73, p=0.076)	1.24 (0.44-3.47, p=0.655)
40 vs 20	1.81 (0.89-3.69, p=0.101)	2.17 (0.92-5.13, p=0.077)	1.23 (0.37-4.15, p=0.685)
50 vs 20	1.98 (0.86-4.58, p=0.110)	2.45 (0.90-6.66, p=0.078)	1.14 (0.35-3.72, p=0.734)
60 vs 20	1.88 (0.82-4.32, p=0.135)	2.31 (0.89-6.02, p=0.085)	1.24 (0.44-3.47, p=0.824)
Method of blood collection: Venous vs finger-prick	0.92 (0.29-2.93, p=0.885)		
BMI (per 5 kg/m ²)		0.74 (0.66-0.83, p<0.001)	0.72 (0.65-0.80, p<0.001)
Hemoglobin (per 5 g/dl)		2.19 (1.69-2.84, p<0.001)	2.63 (1.84-3.74, p<0.001)
HIV+ (vs HIV-)		0.78 (0.68-0.89, p<0.001)	0.76 (0.61-0.94, p=0.010)
FIB-4 score			
1.45-3.25 vs <1.45			1.27 (1.02-1.58, p=0.035)
>3.25 vs <1.45			1.81 (1.27-2.59, p=0.001)

*Fitted values from quadratic variable

Table 11. Adjusted odds ratios, (95% confidence intervals, and p-values for the associations of demographic and biologic variables with PEth sensitivity (PEth \geq 8 ng/mL) among observations with unhealthy drinking reported; stratified by race/ethnicity. Statistically significant comparisons are bolded.

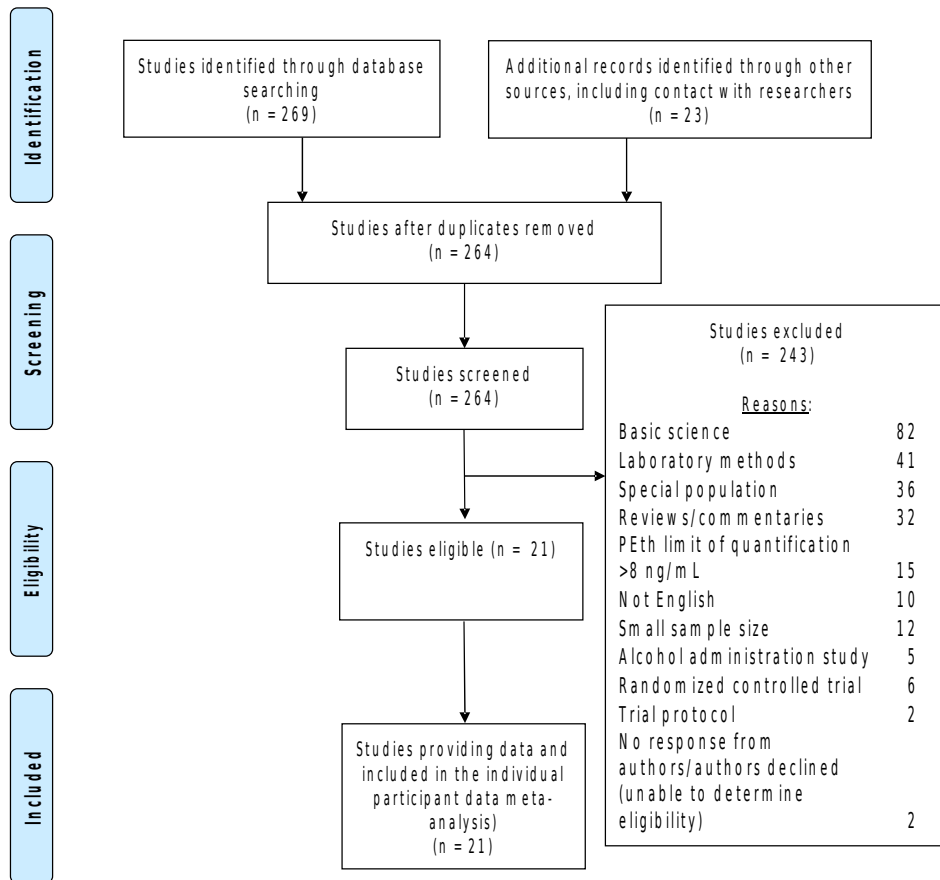
Model 1				
	African	African American	White	Other
N Studies	7	11	13	11
N	1572	893	1228	380
AUDIT-C score*				
6 vs 4	2.09 (1.51-2.88, p<0.001)	1.22 (0.80-1.84, p=0.320)	2.05 (1.06-3.98, p=0.034)	1.85 (0.98-3.49, p=0.059)
10 vs 4	8.29 (3.95-17.39, p<0.001)	1.42 (0.68-2.94, p=0.591)	5.17 (1.87-14.30, p=0.002)	2.91 (1.23-6.89, p=0.015)
Sex: Female vs Male	1.01 (0.59-1.74, p=0.970)	0.41 (0.29-0.58, p<0.001)	1.17 (0.81-1.71, p=0.402)	1.37 (0.48-3.90, p=0.556)
Age*				
30 vs 20	3.45 (2.24-5.32, p<0.001)	0.70 (0.33-1.46, p=0.340)	1.05 (0.73-1.51, p=0.782)	0.73 (0.39-1.38, p=0.336)
40 vs 20	6.77 (3.43-13.37, p<0.001)	0.57 (0.19-1.74, p=0.323)	1.05 (0.56-1.97, p=0.872)	0.68 (0.26-1.74, p=0.417)
50 vs 20	7.54 (3.39-16.75, p<0.001)	0.55 (0.18-1.69, p=0.394)	1.00 (0.44-2.27, p=0.997)	0.78 (0.29-2.09, p=0.624)
60 vs 20	4.76 (1.91-11.85, p<0.001)	0.61 (0.27-1.37, p=0.231)	0.91 (0.35-2.36, p=0.840)	1.14 (0.47-2.77, p=0.777)
Method of blood collection: Venous vs finger-prick	NA	3.18 (0.49-20.71, p=0.226)	0.77 (0.18-3.31, p=0.724)	1.01 (0.35-2.85, p=0.992)
Model 2				
	African	African American	White	Other
N Studies	5	7	8	6
N	1321	782	903	182
AUDIT-C score*				
6 vs 4	2.07 (1.49-2.89, p<0.001)	1.28 (0.81-2.03, p=0.285)	1.77 (0.78-4.00, p=0.169)	2.01 (1.02-3.95, p=0.044)
10 vs 4	5.53 (2.43-12.60, p<0.0001)	1.18 (0.68-2.05, p=0.551)	4.16 (1.26-13.72, p=0.019)	2.61 (0.99-6.88, p=0.052)
Sex: Female vs Male	1.13 (0.64-1.97, p=0.679)	0.63 (0.43-0.92, p=0.018)	1.44 (0.90-2.30, p=0.122)	1.17 (0.43-3.21, p=0.754)
Age*				
30 vs 20	3.11 (1.98-4.91, p<0.001)	0.72 (0.26-2.00, p=0.525)	1.18 (0.80-1.76, p=0.404)	1.29 (0.50-3.37, p=0.597)
40 vs 20	5.85 (2.88-11.88, p<0.001)	0.58 (0.11-3.02, p=0.518)	1.22 (0.61-2.46, p=0.570)	1.70 (0.39-7.41, p=0.476)
50 vs 20	6.64 (2.89-15.26, p<0.001)	0.53 (0.08-3.42, p=0.502)	1.11 (0.44-2.79, p=0.830)	2.28 (0.47-11.19, p=0.308)
60 vs 20	4.54 (1.68-12.29, p<0.001)	0.53 (0.10-2.93, p=0.431)	0.87 (0.29-2.63, p=0.830)	3.11 (0.70-13.76, p=0.015)

	p=0.003)	p=0.472)	p=0.810)	p=0.134)
BMI (per 5 kg/m ²)	1.03 (0.74-1.45, p=0.847)	0.69 (0.63-0.76, p<0.001)	0.73 (0.63-0.83, p<0.001)	0.68 (0.48-0.95, p=0.025)
Hemoglobin (per 5 g/dl)	2.72 (1.33-5.57, p=0.006)	2.25 (1.43-3.52, p<0.001)	1.84 (1.28-2.65, p=0.001)	2.13 (0.61-7.38, p=0.234)
HIV+ (vs HIV-)	0.67 (0.47-0.96, p=0.029)	0.81 (0.63-1.04, p=0.093)	0.54 (0.28-1.03, p=0.063)	0.18 (0.07-0.45, p<0.001)
Model 3				
	African	African American	White	Other
N Studies	3	5	6	4
N	7045	758	780	124
AUDIT-C score*				
6 vs 4	1.83 (0.91-3.65, p=0.089)	1.23 (0.77-1.98, p=0.285)	1.54 (0.65-3.63, p=0.324)	1.38 (0.62-3.05, p=0.426)
10 vs 4	9.36 (4.48-19.52, p<0.001)	1.12 (0.64-1.94, p=0.701)	3.40 (0.92-12.61, p=0.065)	1.42 (0.47-4.33, p=0.535)
Sex: Female vs Male	1.68 (0.53-5.28, p=0.374)	0.68 (0.46-0.99, p=0.045)	1.49 (0.82-2.71, p=0.181)	1.02 (0.30-3.47, p=0.980)
Age*				
30 vs 20	1.66 (0.75-3.66, p=0.211)	0.60 (0.18-1.97, p=0.396)	1.02 (0.60-1.74, p=0.924)	2.09 (0.44-9.97, p=0.387)
40 vs 20	2.19 (0.49-9.75, p=0.304)	0.41 (0.06-2.84, p=0.369)	0.98 (0.37-2.65, p=0.979)	3.99 (0.32-49.15, p=0.280)
50 vs 20	2.30 (0.28-18.96, p=0.438)	0.34 (0.04-2.98, p=0.328)	0.89 (0.22-3.53, p=0.867)	7.01 (0.39-125.67, p=0.186)
60 vs 20	1.93 (0.14-27.03, p=0.627)	0.32 (0.04-2.29, p=0.256)	0.75 (0.13-4.19, p=0.744)	11.30 (0.67-189.36, p=0.092)
BMI (per 5 kg/m ²)	0.99 (0.54-1.82, p=0.987)	0.70 (0.64-0.77, p<0.001)	0.73 (0.63-0.85, p<0.001)	0.56 (0.37-0.86, p=0.009)
Hemoglobin (per 5 g/dl)	3.26 (0.58-18.25, p=0.178)	2.31 (1.41-3.78, p=0.001)	2.27 (1.49-3.47, p<0.001)	2.24 (0.54-9.36, p=0.267)
HIV+ (vs HIV-)	---	0.77 (0.57-1.03, p=0.074)	0.75 (0.37-1.50, p=0.414)	0.21 (0.05-0.85, p=0.028)
FIB-4 score	1.00	1.00	1.00	1.00
1.45-3.25 vs <1.45	1.67 (0.69-4.06, p=0.246)	1.65 (1.34-2.03, p<0.001)	1.19 (0.81-1.75, p=0.382)	0.26 (0.09-0.81, p=0.020)
>3.25 vs <1.45	(merged groups)	2.01 (1.14-3.54, p=0.014)	2.13 (1.34-3.37, p<0.001)	0.59 (0.15-2.39, p=0.458)

*Fitted values from quadratic variable



PRISMA A Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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