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REVIEW

ADDICTION SSA

Validating transdermal alcohol biosensors: a meta-analysis of associations between blood/breath-based measures and transdermal alcohol sensor output

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Abstract

Background and aims: Transdermal alcohol sensors carry immense promise for the continuous assessment of drinking but are inconsistent in detecting more fine-grained indicators of alcohol consumption. Prior studies examining associations between transdermal alcohol concentration (TAC) and blood/breath alcohol concentration (BAC) have yielded highly variable correlations and lag times. The current review aimed to synthesize transdermal validation studies, aggregating results from more than three decades of research to characterize the validity of transdermal sensors for assessing alcohol consumption.

Methods: Databases were searched for studies listed prior to 1 March 2022 that examined associations between transdermal alcohol sensor output and blood and breath-based alcohol measures, resulting in 31 primarily laboratory-derived participant samples (27 precise effect sizes) including both healthy and clinical populations. Correlation coefficients and lag times were pooled using three-level random-effects meta-regression. Independent raters coded study characteristics, including the body position of transdermal sensors (ankle- versus arm/hand/wrist-worn device) and methodological bias (e.g. missing data).

Results: Analyses revealed that, in this primarily laboratory-derived sample of studies, the average correlation between TAC and BAC was large in magnitude [$r = 0.87$, 95% confidence interval (CI) = 0.80, 0.93], and TAC lagged behind BAC by an average of 95.90 minutes (95% CI = 55.50, 136.29). Device body position significantly moderated both TAC–BAC correlation ($b = 0.11$, $P = 0.009$) and lag time ($b = -69.41$, $P < 0.001$). Lag times for ankle-worn devices were approximately double those for arm/hand/wrist-worn devices, and TAC–BAC correlations also tended to be stronger for arm/hand/wrist-worn sensors.

Conclusions: This meta-analysis indicates that transdermal alcohol sensors perform strongly in assessing blood/breath alcohol concentration under controlled conditions, with particular promise for the newer generation of wrist-worn devices.

KEYWORDS
Alcohol biosensors, blood alcohol concentration, body location, meta-analysis, temporal sensitivity, transdermal, validation

FIGURE 1 (a) Secure Continuous Remote Alcohol Monitoring (SCRAM) ankle monitor ([35]; left); (b) BACtrack Skyn ([36]; right)

INTRODUCTION

Transdermal alcohol sensors have the potential to substantially bolster our toolkit of measures within addiction science. Although existing measures of alcohol consumption have contributed valuable knowledge to our understanding of drinking behaviors, all are associated with limitations. Blood-based alcohol measures are highly accurate, but invasive and impractical for use in the field [1, 2]. Breathalyzer readings demand motivated action on the part of the user and, when used improperly, can be impacted by residual mouth alcohol [1–4]. Self-reports of drinking, although cost-effective and widely employed in alcohol research, are nonetheless subjective and vulnerable to bias [5–9]. Leveraging the fact that approximately 1% of ingested alcohol is expelled from the skin in the form of water vapor, transdermal sensors complement extant tools by assessing drinking via a device that rests on the skin's surface [2, 10, 11]. Thus, transdermal sensors have the potential to assess drinking continuously, passively and unobtrusively by measuring the concentration of alcohol in sweat and insensible perspiration. In addition to their existing application as abstinence monitors in the criminal justice system [12, 13], a range of additional uses have been proposed for transdermal sensors, including as relapse-detecting monitors capable of prompting 'just-in-time' addiction intervention [14, 15], as drinking risk-level indicators to inform the advisability of driving [14, 16, 17] and as continuous trackers capable of unobtrusively assessing drinking during the course of months and even years for implementation in research studies [5, 18–20].

The current moment represents an exciting time for transdermal alcohol sensing technology. The use of transdermal abstinence monitors has burgeoned in recent years to encompass hundreds of thousands of individuals globally [13]. Further, a new generation of sleek, smartphone-integrated transdermal sensor has recently emerged that promises to exponentially expand the range of applications for alcohol biosensors [14, 16, 21–23]. At the same time, the current moment represents a perplexing time for researchers seeking to understand the potential of transdermal sensors, as the relationship between transdermal alcohol concentration (TAC) and blood/breath alcohol concentration (BAC[1]) is complex, and the performance of transdermal technology in detecting more fine-grained indicators of alcohol consumption has emerged as inconsistent. Indeed, reflecting this complexity, extant studies in the literature have produced TAC–BAC correlations ranging from moderate [27, 28] to extremely strong [29, 30], and lag times between peak TAC and peak BAC varying from 30 minutes [31–33] to several hours in duration [34]. Further complicating the task of understanding the potential of transdermal technology, the extent to which limitations and complexities observed with respect to data produced by older sensors might apply equally to the newer generation of transdermal technology is currently unclear [12]. Of note, despite more than three decades of empirical research devoted to validating transdermal sensor output, there has not previously been a quantitative synthesis of the literature exploring the TAC–BAC association. The current meta-analysis is aimed at filling this gap.

[1]Note that the amount of alcohol measured in blood is not the same as the amount of alcohol measured in breath. However, these two are highly correlated and breath alcohol measures are often used as a proxy for blood alcohol concentration [24–26]. Thus, within this manuscript we use the abbreviation 'BAC' to refer to both blood and breath alcohol concentration.

Transdermal sensor types and factors impacting transdermal alcohol detection

Since their first conception several decades ago [11], transdermal alcohol sensors have undergone considerable evolution. Among the first transdermal sensors made widely available to researchers was the Secure Continuous Remote Alcohol Monitor (SCRAM) (AMS, Denver, CO; see Fig. 1a [13]). SCRAM is a relatively bulky ankle bracelet intended primarily for use with criminal justice-involved populations [18, 37, 38]. SCRAM devices have demonstrated discriminative validity in detecting drinking episodes [12], albeit with limited ability to detect low level drinking [39–42], and thus appear well suited to their primary intended purpose as abstinence monitors in forensic settings [12, 43]. However, SCRAM ankle monitors have properties that may make them less well suited to tasks requiring fine-grained and/or time sensitive estimation. The relationship between TAC and BAC can vary depending on where on the body TAC is assessed [32, 44]. A range of factors that vary across body locations can impact transdermal sensor performance, including sensor–skin distance variability, skin thickness, sweat gland density and blood vessel distribution, and some have theorized that the ankle positioning of SCRAM may be suboptimal for sensitive transdermal assessment of BAC [12, 21, 32, 44, 45]. Further, SCRAM devices rely on a pump to actively generate airflow across the transdermal sensor, restricting the transdermal sampling interval to a relatively sparse 30 minutes. Probably due in part to this sparse

sampling schedule, SCRAM-measured TAC has been found to lag behind BAC by extended periods, with studies indicating that the delay between BAC and SCRAM-measured TAC can extend up to 5 hours [34]. Such protracted lag times have sometimes been presumed to be also physiologically based, thus potentially extending beyond only SCRAM to encompass all transdermal sensors [46, 47]. As some of the more critical applications of transdermal alcohol sensing technology require detection of drinking episodes in near real-time (e.g. just-in-time intervention/relapse prevention, applications for determining driving advisability), these extended lag times have been cited as a key factor limiting the utility of transdermal alcohol sensors more broadly [21, 23, 46].

Although the SCRAM ankle monitor is currently the most widely researched transdermal sensor, researchers have also examined a range of monitors that employ alternative designs, with the availability of these alternative sensors burgeoning in recent years. While the majority of alternative devices examined in research have been wrist-worn, some earlier iterations of these devices were affixed to the palm or worn as an arm band [27, 30]. Wrist-worn devices have ranged from early sensors such as Giner WriSTAS (Giner Inc., Newton, MA, USA; resembling a wrist watch, now discontinued [33, 34, 48]) to new-generation devices such as the BACtrack Skyn (from BACtrack/KHN Solutions Inc., San Francisco, CA, USA; see Fig. 1b [16, 21, 23, 49]), featuring smartphone connectivity and sleek, fitbit-like designs [14, 16, 23, 46]. Wrist- and arm-worn devices have traditionally employed sensors that rely on passive (rather than active pump-generated) airflow across the sensor, which has diminished demands on battery life and so permitted faster sampling speeds. TAC sampling intervals for wrist-worn transdermal sensors are relatively brief when compared with ankle-worn devices, ranging from 5 minutes (WrisTAS [31]) to 20 sec (BACtrack Skyn [16, 23]). Early research with wrist-worn devices indicated high failure rates, although newer devices demonstrate substantial improvement [21, 34]. Little research has permitted direct comparison between ankle- and arm-worn devices, and the research that does exist has had low power for such comparisons [21, 34, 49]. However, some early research points to the possibility of improved temporal sensitivity for new-generation wrist-worn devices over old-generation ankle monitors indicating that, when combined with machine-learning models capable of forecasting readings into the future, such devices might permit drinking episode detection in near real-time [21].

Besides the body position of the transdermal devices themselves, a range of contextual and individual characteristics have been theorized to impact the TAC–BAC relationship. Transdermal sensors are sensitive to a variety of contextual factors, including temperature, motion and interfering gases [32]. These factors are considerably less variable in laboratory (versus real-world) contexts, where the majority of transdermal sensor validation research has thus far taken place [27, 29, 50–52]. Further, studies assessing the validity of transdermal sensors via objective means have relied upon a range of approaches for assessing alcohol consumption, including both blood- and breath-based measures of intoxication. Although blood- and breath-based alcohol measures are highly correlated [24–26], breath measures assess alcohol levels via indirect means and thus it remains possible that measured TAC–BAC associations could vary across these assessment techniques [2]. Finally, characteristics of the research participants themselves, including biological sex and also drinking history (e.g. heavy drinkers versus social drinkers), can impact the metabolism of alcohol and so cause variability in the TAC–BAC relationship, thereby affecting the performance of transdermal alcohol sensors [51, 53]. However, in a literature characterized by extremely small sample sizes (average $n < 20$), individual studies have generally had insufficient power to explore moderators of the TAC–BAC link.

The current study

The current review aims to organize and synthesize the literature examining the validity of transdermal alcohol sensors for the assessment of BAC. Interest in transdermal alcohol measurement has surged in recent years, with seven reviews of transdermal sensor research published in the past 2 years alone [5, 14, 16, 17, 22, 46, 54]; for a registered report, see also Kiarnersi *et al*. [55]. Although numerous narrative reviews exist, no meta-analysis has quantified the association between TAC and BAC. In the current review, by examining studies employing objective assessment of alcohol intoxication we aim to explore associations between ingested alcohol and alcohol that can be detected at the skin's surface via transdermal means. More specifically, the aims of the current review are to: (1) quantify the magnitude of the TAC–BAC correlation across samples and studies; (2) quantify the magnitude of the TAC–BAC lag time across samples and studies; and (3) explore the extent to which device body position (ankle, arm, etc.), study type (laboratory versus ambulatory), alcohol measures (BAC versus BrAC; alcohol dose) and sample characteristics (gender composition; healthy versus clinical/heavy drinking) moderate these TAC–BAC correlations and lag times.

METHODS

Systematic review and meta-analytical procedures employed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [56]. The databases PubMed and PsycInfo were searched for articles published prior to 1 March 2022. The following search terms were used: 'alcohol' AND 'transdermal'. Bibliographies of studies meeting inclusion were scanned for additional eligible studies, as were the reference sections of three review articles [21, 22, 37]. A protocol for meta-analytical procedures can be accessed at https://osf.io/nq6fc/. The meta-analysis was not pre-registered.[2] In total, 1804 records were screened for inclusion (see Fig. 2).

Studies were required to meet the following eligibility criteria: (1) examine data collected from human participants; (2) include measurement of TAC via a wearable device assessing alcohol

[2]Work on this review was initiated before pre-registration of meta-analyses was standard practice. Note that we test aims here, not directional hypotheses.

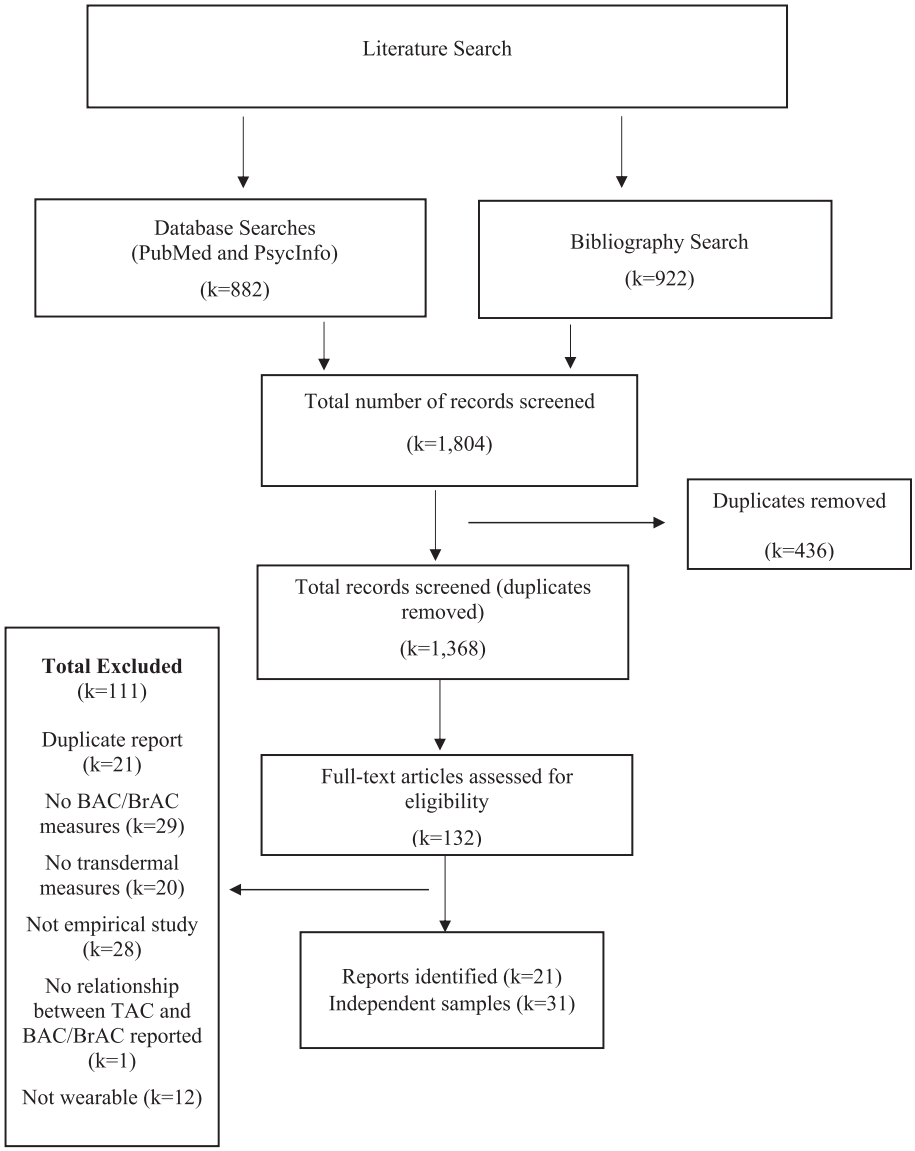

FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrating the process of identifying eligible studies

concentration within sensible/insensible perspiration; (3) include measurement of alcohol intoxication via objective means—e.g. via breathalyzer or direct blood/plasma measure; (4) examine the relationship between TAC and BAC; and (5) report available in English language. Studies featuring transdermal devices that were not clearly 'wearable' (e.g. [57]) and also studies featuring sweat patches or tattoos (e.g. [58]) were excluded. Studies that did not measure BAC directly but rather estimated BAC from self-reports or quantity of ingested alcohol (e.g. [59]) were also excluded. If multiple reports were published based on the same exact participant sample, the first publication was included.

All eligible studies were coded by two independent raters for the following characteristics: (1) sample size; (2) sex composition: % female participants in final sample; (3) study type: laboratory versus ambulatory; (4) target population: healthy versus clinical/heavy-drinker sample; (5) body position: ankle- versus arm/hand/wrist-worn transdermal sensor; (6) alcohol measure: breathalyzer (breath), direct measure of alcohol content in blood or plasma (blood), or a combination of these methods; (7) peak BAC: for laboratory studies featuring fixed dosing, average peak BAC across all alcohol conditions; (8) publication year; (9) average lag (in minutes) between peak BAC and peak TAC; and (10) correlation between BAC and TAC.[3] We also assessed methodological quality/bias of included studies through three items, based loosely on tools employed in the literature (e.g. Cochrane risk-of-bias tools; [60]) including: (1) random assignment: whether or not doses were randomly assigned and/or counterbalanced across subjects (laboratory studies); (2) missing data: proportion of initial participant sample represented in final sample analyzed; and (3) number of drinking sessions: average number of drinking sessions/events per participant. The average inter-rater agreement was 84% (range = 71–100%). Disagreements were resolved by a third rater.

[3]In most cases authors reported the association between raw TAC and BAC, but in other cases they also reported associations between BAC and a transformed version of TAC intended to more closely approximate BAC. We took an inclusive view to coding effect sizes, so effects reported in this review encompass associations with both raw and transformed versions of TAC.

Statistical analysis

We employed three-level random-effects meta-regression models accounting for non-independence of effect sizes within samples [61–63]. Studies included in this meta-analysis sometimes produced several effect sizes, reporting data derived from more than one transdermal device type or alcohol measurement method within the same participant sample, and this three-level meta-analytical framework enabled us to assess moderators that varied at not only the between-sample but also the within-sample level. Moderators were first explored in single-predictor regression models, and effects that reached significance ($P < 0.05$; two-tailed tests) were then entered into multivariable regression models to account for possible covariation across predictors. The significance of level 2 ($\sigma^2_{L2;}$ within-sample) and level 3 (σ^2_{L3}; between-sample) variance parameters were assessed using log-likelihood tests comparing models with and without these variance components. As the significance of such tests is impacted by the number of samples/observations, we also calculated I^2 values representing the proportion of total variance captured at each level. To test for publication bias, Egger's test of the intercept [64] and the trim-and-fill method [65] were conducted at the level of the sample. Cook's distance was examined to detect influential datapoints [66].

RESULTS

Descriptives

The search process yielded a total of 31 independent participant samples derived from 21 reports. The final group of studies for which effect size estimation was possible included a total of 16 correlation coefficients derived from 14 independent samples and 11 lag times derived from nine independent samples. Of this final group of studies, 16 samples assessed intoxication using only breathalyzer measures, three samples using only blood/plasma measures and one using a combination of breath and blood measures. Eight samples employed only the SCRAM (ankle-worn) device, nine studies employed only arm/hand/wrist-worn devices, and three studies employed both wrist- and ankle-worn devices within the same participant sample. Most studies included in this review employed laboratory study designs: all samples yielding lag time effect sizes ($k = 9$) utilized a laboratory methodology, whereas within studies yielding a correlation coefficient effect size ($k = 14$), one employed an ambulatory design. Three samples yielding lag time effect sizes and five samples yielding a correlation coefficient effect size examined clinical/heavy-drinker samples. The average number of drinking sessions per participant within reviewed studies was three. See Table 1 for sample descriptives. All data and codes needed to replicate the results presented here are provided at https://osf.io/nq6fc/.

Aggregated effect size and moderator analyses

Analyses revealed that the average correlation between TAC and BAC was large in magnitude ($r = 0.87$, 95% CI = 0.80, 0.93). The majority of variability in correlation coefficients was observed at the within-sample level ($\sigma^2_{L2} = 0.004$, $P = 0.037$; $\sigma^2_{L3} = 0.002$, $P = 0.378$). Inspection of I^2 values indicated that 48.3% of variance was within-samples and 20.9% was between-samples (the remaining 30.8% of variance was attributable to sampling error). Moderator analyses indicated significant effects of body position in predicting the strength of TAC–BAC correlations ($b = 0.11$, $P = 0.009$). Specifically, TAC–BAC correlations tended to be larger when TAC was measured using a device positioned on the arm, hand or wrist ($r = 0.93$, 95% CI = 0.87, 0.99) versus the ankle ($r = 0.82$, 95% CI = 0.75, 0.89). In analyses focused on variability within the arm/hand/wrist subgroup, we found no significant differences in the strength of correlations for devices worn on the hand versus arm versus wrist ($F_{(2,\ 4)} = 4.05$, $P = 0.109$). In addition to body position, three other variables emerged as significant in single-predictor moderator analyses: missing data ($b = 0.36$, $P = 0.040$), publication year ($b = -0.004$, $P = 0.017$) and alcohol measure ($b = -0.12$, $P = 0.040$). However, when all significant predictors were included in the same model, only body position and missing data remained significant, indicating that the effects of alcohol measure and publication year were probably non-independent. No other moderators reached significance in predicting the strength of TAC–BAC correlations (see Table 2). See Fig. 3 for aggregated effects according to device body position and Supporting information, Fig. S1 for a forest plot of sample-level effects.

Analyses of lag times indicated that TAC lagged behind BAC by an average of 95.90 minutes ($M_{diff} = 95.90$, 95% CI = 55.50, 136.29).[§] There was variability in the size of this effect ($\sigma^2_{L2} = 2043.73$, $P < 0.001$; $\sigma^2_{L3} = 996.95$, $P = 0.264$). Inspection of I^2 values indicated that 65.3% of variance in effect sizes was within-samples, whereas 31.9% of variance was between-samples (the remaining 2.9% of variance was attributable to sampling error). Moderator analyses revealed that the amount of time by which TAC lagged behind BAC was significantly impacted by the body position of the transdermal sensor (ankle versus arm/hand/wrist; $b = -69.41$, $P < 0.001$) (Table 2). TAC lagged behind BAC by an average of 135.84 minutes when TAC was assessed using an ankle-worn sensor ($M_{diff} = 135.84$, 95% CI = 105.69, 165.99), whereas TAC lagged behind BAC by a comparatively brief 66.43 minutes when measured using a device positioned on the hand, arm, or wrist ($M_{diff} = 66.43$, 95% CI = 39.97, 92.89). In analyses focused on the arm/hand/wrist subgroup, we found no significant differences in lag times for devices worn on the hand versus arm versus wrist, ($F_{(1,\ 5)} = 0.018$, $P = 0.899$). No other moderators reached significance. See Fig. 3 for aggregated effects according to device body position and Supporting information, Fig. S1 for a forest plot of sample-level effects.

TABLE 1 Studies comparing transdermal alcohol biosensor output to objective indices of alcohol consumption

Study	*n*	%Fem	Type	BevC	Hlth	Sess	Locat	AlcM	Lag (SE)	*r* (SE)
Davidson *et al.* 1997 [27]	15 (12)	58.33%	Lab	0.04%, 0.02%, 0.01%, ctrl	Y	3	Arm	Comb	NR	0.59 (*0.22*)
Dougherty *et al.* 2012 [29]	11 (10)	0.00%	Lab	0.08%, 0.064%, 0.048%, 0.032%, 0.016%	Y	5	Ankle	Breath	NR	0.86 (*0.10*)
	11 (11)	100.00%	Lab	0.08%, 0.06%, 0.04%, 0.02%	Y	4	Ankle	Breath	NR	0.91 (*0.06*)
Dumett *et al.* 2008 [48]	2 (2)	NR	Lab	0.08%	Y	1	Wrist	Breath	NR	NR
		NR	Amb	NA	Y	NR	Wrist	Breath	NR	NR
Fairbairn & Kang 2019 [21]	50 (30)	50.00%	Lab	0.08%, ctrl	N	0.5	Ankle	Breath	119.92 (*10.00*)	0.56 (*0.14*)
		50.00%	Lab	0.08%, ctrl	N	0.5	Wrist	Breath	54.24 (*4.58*)	0.72 (*0.09*)
Fairbairn *et al.* 2019 [67]	48 (40)	50.00%	Lab[a]	0.074%, ctrl	N	1	Ankle	Breath	124.78 (*10.30*)	NR
Fairbairn *et al.* 2020 [49]	110 (73)	55.00%	Lab	0.084%, ctrl	N	0.5	Ankle	Breath	NR	0.76 (*0.05*)
		55.00%	Lab	0.084%, ctrl	N	0.5	Wrist	Breath	NR	0.91 (*0.02*)
Giles *et al.* 1987 [30]	4 (4)	75.00%	Lab	0.08%	Y	1	Palm	Blood	NR	0.99 (*0.02*)
	5 (5)	NR	Lab	NR	N	NR	Palm	Blood	NR	0.96 (*0.06*)
	10 (10)	NR	Lab	NR	N	NR	Palm	Breath	NR	0.94 (*0.04*)
Hawekotte *et al.* 2021 [68]	40 (40)	NR	Lab	NR	Y	3.65	Arm	Breath	NR	NR
Hill-Kapturczak *et al.* 2014 [52]	13 (11)	0.00%	Lab	NR (5, 4, 3, 2, 1 beers)	Y	5	Ankle	Breath	NR	0.86 (*0.09*)
	9 (8)	100.00%	Lab	NR (5, 4, 3, 2, 1 beers)	Y	5	Ankle	Breath	NR	0.87 (*0.11*)
Hill-Kapturczak *et al.* 2015 [51]	21 (21)	47.62%	Lab	0.082%, 0.066%, 0.055%, 0.042%, 0.026%	Y	5	Ankle	Breath	128.60 (*5.40*)	0.87 (*0.06*)
Lawson *et al.* 2019 [69]	6 (2)	50.00%	Lab	0.08%, 0.05%	Y	1	Wrist	Comb	52.50 (*27.50*)	NR
Li *et al.* 2020 [32]	2 (1)	0.00%	Lab	0.053%, 0.037%	Y	6	Arm	Breath	27.3[b]	NR
		0.00%	Lab	NR (2 standard drinks)	Y	1	Ankle	Breath	NR	NR
Luczak & Rosen, 2014 [33]	1 (1)	100.00%	Lab	0.05%	Y	1	Wrist	Breath	27.60, 0.00[b,c]	NR
		100.00%	Amb	NA	Y	10	Wrist	Breath	74.64, 15.60[b,c]	NR
Marques & McKnight 2009 [34]	22 (22)	31.82%	Lab	0.083%	Y	1	Ankle	Breath	270.00 (*37.10*)	NR
		31.82%	Lab	0.083%	Y	1	Wrist	Breath	136.80 (*19.19*)	NR
		31.82%	Amb	NA	Y	NR	Ankle	Breath	NR	NR
		31.82%	Amb	NA	Y	NR	Wrist	Breath	NR	NR
Rash *et al.* 2019 [28]	22 (21)	31.82%	Amb	NA	N	8.6	Ankle	Breath	NR	0.58 (*0.21*)
Sakai *et al.* 2006 [12]	24 (24)	50.00%	Lab	0.088%, 0.056%, ctrl	Y	0.67	Ankle	Breath	NR (120–180)	0.67 (*0.16*)
	10 (10)	70.00%	Amb	NA	Y	NR	Ankle	Breath	NR	NR
	10 (10)	60.00%	Amb	NA	N	NR	Ankle	Breath	NR	NR
Saldich *et al.* 2021 [70]	2 (2)	50.00%	Lab	0.072%, 0.066%, 0.043%, 0.039%	Y	4	Arm	Breath	104.38 (*23.97*)[c]	NR
Sirlanci *et al.* 2019 [71]	32 (15)	46.88%	Lab	0.05%	Y	1	Wrist	Breath	42.60 (*11.09*)[c]	NR
Swift *et al.* 1992 [31]	10 (10)	20.00%	Lab	NR (0.75 mL/kg)	Y	1	Arm	Breath	36.00 (*8.28*)	0.76 (*0.17*)

(Continues)

TABLE 1 (Continued)

Study	*n*	%Fem	Type	BevC	Hlth	Sess	Locat	AlcM	Lag (SE)	*r* (SE)
	5 (5)	40.00%	Lab	NR	N	1	Arm	Breath	NR (up to 120)	NR
	10 (10)	NR	Amb	NA	Y/N	NR	Arm	Breath	NR	NR
Wang *et al.* 2019 [16]	2 (2)	50.00%	Lab	0.09%, 0.07%	N	1	Wrist	Breath	65.00 (10.00)	NR
Wang *et al.* 2021 [23]	3 (3)	33.33%	Lab	0.04%	Y	1	Ankle	Breath	NR	NR
	3 (3)	33.33%	Lab	0.04%	Y	1	Wrist	Breath	NR	NR
	10 (10)	60.00%	Amb	NA	Y	1	Wrist	Breath	NR	NR

Studies included in this table/research synthesis were required to be published on-line before the date of our initial search (25 May 2021). *n* = Initial sample size (final sample size after accounting for exclusion/data loss); %Fem = percentage of female participants in the final sample; Type = study type; Lab = laboratory study; Amb = ambulatory study; BevC = beverage condition [achieved or target blood/breath alcohol concentration (BAC) in laboratory studies]; ctrl = control condition; NA = not applicable; Hlth = healthy; Y = yes (healthy sample); N = no (clinical/heavy-drinking sample); Sess = average number of drinking sessions per participant; Locat = body position of the transdermal device; AlcM = how BAC was measured in the study; blood = direct measure of BAC via blood or plasma; Breath = breathalyzer; Comb = combined blood and breath measures; Lag = average time (in minutes) transdermal alcohol concentration (TAC) lagged behind BAC; NR = not reported or insufficient information provided for the calculation of the effect; *r* = correlation coefficients between TAC and BAC; SE = standard error associated with effect size.

[a]Although the study employed a combination of laboratory and ambulatory methods, calculation of lag time between BAC and TAC was possible based only on information collected in the laboratory, as this information was unavailable in the ambulatory study arm.

[b]Effect sizes (lag time) for Luczak & Rosen, 2014 and Li *et al.*, 2020 were omitted from statistical analysis because they only included a sample size of one.

[c]Luczak & Rosen, 2014, Saldich *et al.* 2021 and Sirlanci *et al.* 2019 applied an estimation model to predict peak TAC time. Lag times of both raw peak TAC and estimated TAC were reported in Luczak & Rosen, 2014.

Influence diagnostics and publication bias

In light of variable sample sizes across studies reviewed here, we conducted additional influence diagnostics to explore the extent to which individual effect sizes might exert an outsized influence on effects. Investigation of Cook's distance plots (see Supporting information, Fig. S2) indicated several datapoints potentially exerting a large influence within aggregated analyses of correlation coefficients, as well as within our moderator analyses of body position. Leave-one-out analyses indicated that the moderating effect of body position in predicting correlation coefficients remained largely consistent across model iterations, but effects were no longer significant when either effect size from a single large sample [49] were removed. However, these same analyses indicated that overall correlation coefficients (*r*s ranging from 0.85 to 0.88), overall lag times (lags ranging from 86.30 to 103.22), and also results of moderator analyses on lag time (*b*s ranging from 64.40 to 88.60) remained consistently significant even after each of the large influence datapoints was omitted.

Egger's test of the intercept did not provide evidence of significant publication bias in either analysis of correlation coefficients (b = 0.62, 95% CI = −0.87, 2.10) or for lag times (b = −1.36, 95% CI = −9.21, 6.48). The trim-and-fill method produced an imputed point estimate of r = 0.81 (95% CI = 0.73, 0.87) for correlation coefficients and an estimate of M_{diff} = 92.93 (95% CI = 61.61, 120.58) for lag times. Funnel plots for both correlation coefficients and lag times are provided in Supporting information, Fig. S3. Taken as a whole, analyses indicated publication bias was unlikely to have had a major impact on findings.

DISCUSSION

The current review synthesizes more than three decades of research to yield initial validity estimates for transdermal alcohol biosensors. Results indicated that, within the sample of studies reviewed here, which focused mainly upon laboratory-based methodologies, the average cross-sample correlation between TAC and BAC emerged as extremely strong (r = 0.87). The average interval by which peak TAC lagged behind peak BAC was 96 minutes in duration. Moderator analyses indicated that correlations were significantly higher and lag times significantly shorter within studies employing arm/hand/wrist-worn versus ankle-worn devices.

Of note, the time interval by which TAC lagged behind BAC increased by a factor of nearly twofold when studies estimated TAC via an ankle- versus arm-worn sensor. The lag time derived specifically from arm-worn sensors was measured as lasting only 66 minutes, whereas the average lag time for ankle-worn devices was estimated at a comparatively long 136 minutes. Note that, as a variety of factors aside from body position vary across extant ankle- versus arm-worn transdermal devices—e.g. the sampling interval of TAC, mechanical properties of the sensor, the recency of sensor development—this review is incapable of pinpointing the exact mechanism driving these differential lag times. Nonetheless, in light of individual reports suggesting the TAC–BAC lag can average as long as 5 hours [34],

TABLE 2 Results of moderator analysis

	B	*t*-value	*P*-value	95% CI
Correlation coefficients (*rs*)				
Study type ($n_{effects}$ = 16)	−0.291	−1.294	0.217	(−0.774, 0.191)
Alcohol measure ($n_{effects}$ = 16)	−0.116*	−2.268	0.040	(−0.226, −0.006)
Body position ($n_{effects}$ = 16)	0.111**	3.011	0.009	(0.032, 0.191)
Publication year ($n_{effects}$ = 16)	−0.004*	−2.710	0.017	(−0.007, −0.001)
Sex composition ($n_{effects}$ = 14)	0.001	1.059	0.311	(−0.001, 0.004)
Random assignment ($n_{effects}$ = 13)	0.089	1.269	0.231	(−0.065, 0.244)
Target population ($n_{effects}$ = 16)	−0.032	−0.528	0.606	(−0.161, 0.097)
Missing data ($n_{effects}$ = 16)	0.355*	2.266	0.040	(0.019, 0.690)
Peak BAC ($n_{effects}$ = 10)	0.452	0.162	0.875	(−5.977, 6.882)
Number of drinking sessions ($n_{effects}$ = 14)	0.002	0.129	0.899	(−0.034, 0.038)
Lag time (minutes)				
Alcohol measure ($n_{effects}$ = 11)	47.865	0.722	0.489	(−102.153, 197.883)
Body position ($n_{effects}$ = 11)	−69.407***	−7.001	<0.001	(−91.833, −46.981)
Publication year ($n_{effects}$ = 11)	0.371	0.163	0.874	(−4.787, 5.528)
Sex composition ($n_{effects}$ = 11)	−0.433	−0.225	0.827	(−4.775, 3.909)
Random assignment ($n_{effects}$ = 11)	10.386	0.255	0.805	(−81.913, 102.685)
Target population ($n_{effects}$ = 11)	−7.492	−0.185	0.857	(−99.014, 84.030)
Missing data ($n_{effects}$ = 11)	97.299	1.351	0.210	(−65.642, 260.240)
Peak BAC ($n_{effects}$ = 10)	1456.034	0.960	0.365	(−2041.555, 4953.624)
Number of drinking sessions ($n_{effects}$ = 11)	7.865	0.615	0.554	(−21.053, 36.784)

Study type was excluded in the analysis of lag time due to no variability across studies. $n_{effects}$ = number of effect sizes. BAC = blood/breath alcohol concentration; CI = confidence interval.
*$P < 0.05$;
**$P < 0.01$;
***$P < 0.001$.

these aggregate cross-study lag estimates offer a relatively auspicious view of the temporal sensitivity of transdermal alcohol biosensors. When considered together with prior research indicating promise for modern computational approaches such as machine learning in yielding real-time transdermal BAC estimates from new-generation sensors [33, 49, 71], these findings suggest that transdermal sensors might potentially be employed in applications requiring alcohol-use information in near real-time.

In addition to these lag-time effects, results of this review suggest TAC–BAC correlations may be stronger in magnitude for arm/hand/wrist- versus ankle-worn devices. Of note, however, only two studies contributed a within-sample comparison of ankle- versus arm-worn devices to these correlation analyses (i.e. arm- and ankle-worn devices worn by the same sample in the same study), and the influence of diagnostics further indicated that individual larger samples within our review may have played a sizeable role in driving these aggregate body position correlation effects. More research is needed to directly compare TAC–BAC correlations yielded by arm- versus ankle-worn sensors within the context of the same study/sample.

To date, the majority of studies exploring the validity of transdermal sensors have been conducted in a laboratory context, and thus studies included in this review focus on laboratory methodologies. Laboratory methods allow researchers to collect highly precise estimates of BAC, including via direct blood/plasma samples, making these methods well suited to this first-stage of research exploring the validity of transdermal alcohol biosensors. However, given contextual effects on TAC–BAC associations, correlations between TAC and BAC are almost certain to be lower when assessed in real-world contexts versus when assessed in the laboratory. Of note, the TAC–BAC associations yielded in this initial quantitative synthesis were remarkably high. Transdermal sensors demonstrating substantially lower sensitivity to BAC—e.g. sensors capable of simply detecting drinking versus non-drinking in near real-time or those capable of retroactively tracking broad, day-level risk level—might still have a range of key applications (e.g. as relapse trackers in just-in-time intervention, as long-term health trackers in prevention initiatives [14]). Thus, in light of the wide range of applications for transdermal sensors, including sensors demonstrating lower levels of accuracy and temporal sensitivity, this review indicates strong potential for these devices. Nonetheless, transdermal validation research is needed featuring large participant samples and objective BAC tracking in real-world contexts.

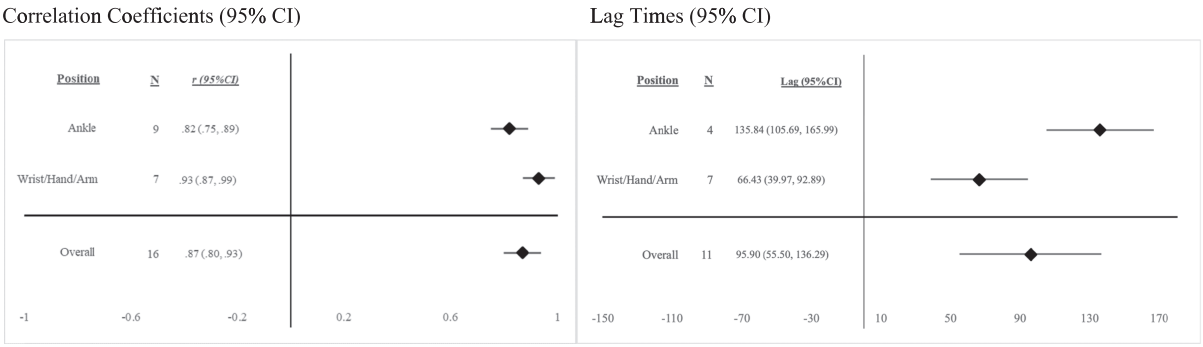

FIGURE 3 Forest plot of aggregated effects by body position. *Note*: Average transdermal alcohol concentration (TAC) and blood/breath alcohol concentration (BAC) correlation coefficients (left panel) and lag times (right panel; minutes TAC lags behind BAC) together with 95% confidence intervals for these effects. Within the sample of studies for which effect size calculation was possible, all but one employed laboratory methods and thus results reported above are most representative of the relationship between BAC and TAC in a controlled context. *N* refers to the number of effect sizes contributing to each estimate. Moderator analyses indicated that TAC–BAC correlations were significantly impacted by sensor body position, with a trend for correlations to be lower for ankle-worn sensors, $b = -0.11$, $P = 0.009$. Lag times were significantly longer for ankle-worn versus wrist/arm/hand-worn sensors, $b = -69.41$, $P < 0.001$. Note that, as transdermal devices employing different body positions also tend to systematically vary in their sampling interval (i.e. ankle-worn devices tend to sample TAC less frequently), the mechanism underlying these differential lags is yet to be determined

Limitations of the current review should be noted. Similar to most meta-analytical reviews, we did not have access to participant-level data and thus were limited to examining many of our individual-level moderators (e.g. biological sex) aggregated at the level of the sample. Such sample-level comparisons can obscure effects and, in some cases, may be especially likely to lead to confounds. Future participant-level analyses might usefully re-examine some of the moderators identified here, especially factors such as biological sex that have emerged in prior studies as probable moderators of the TAC–BAC link [51]. Further, young, healthy, social drinkers were disproportionately represented in samples included in our review. Although approximately 35% of samples featured populations of heavy drinkers and/or those hospitalized for disordered drinking, the majority were healthy individuals. Future empirical research should explore the validity of transdermal alcohol sensors in older and clinical populations. Relatedly, although our sample of studies was sufficiently large to examine many of the effects of interest here, in the case of some moderator analyses, subsamples of studies became quite small (e.g. comparison of wrist- versus arm-versus hand-worn devices). More research will need to accrue before some of these moderators can be productively examined in meta-analysis. Additionally, some studies included in this review involved disproportionately large samples [49] and effect sizes [34] with the potential to influence findings. Beyond the influence of single effect sizes, several studies included in our analysis were from the same research group (e.g. [21, 49, 68] and [51, 52]). In this nascent field, it remains possible that results of specific research groups might be exhibiting an outsize influence on effects.

In summary, results of the current meta-analysis indicate the strong performance of transdermal alcohol sensors in assessing BAC under controlled conditions. When considered together with the wide range of applications for unobtrusive alcohol biosensors, including those requiring lower accuracy and temporal-specificity levels, results of this review present a relatively positive initial view of the potential of transdermal alcohol sensing technology. Future research is needed to assess the validity of these sensors in real-world contexts.

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DECLARATION OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Jiachen Yu: Data curation; formal analysis; visualization. **Catharine Fairbairn:** Conceptualization; formal analysis; funding acquisition; methodology; project administration; supervision; visualization. **Laura Gurrieri:** Data curation. **Eddie Caumiant:** Data curation.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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