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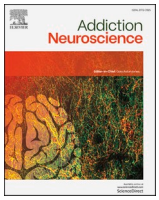

HPA axis function in alcohol use disorder: A systematic review and meta-analysis

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A B S T R A C T

Alcohol use disorder (AUD) is a culturally pervasive and often treatment resistant disorder. Stress is a major trigger for relapse in AUD. Allostasis in response to stress is governed by the hypothalamic-pituitary-adrenal axis (HPA axis). Investigation into HPA axis functioning in response to stress in AUD may provide a novel drug target for AUD treatment. This systematic review found 46 studies concerning ongoing AUD, withdrawal from alcohol, early-abstinence (<6 months), and late-abstinence (>6 months). Cortisol responses were mixed in ongoing AUD and higher in withdrawal. In early abstinence, significantly lower responses to stress compared to healthy controls were found for ACTH (SMD = -1.47, $p = < .001$, I^2: 35.68%) and cortisol (SMD = −1.32, $p = < .001$, I^2: 38.97%). Baseline values did not significantly differ compared to healthy controls for ACTH (SMD = −0.39, $p = < .001$, I^2: 81.11%) and cortisol (SMD = 0.74, $p = .015$, I^2: 88.66%). HPA axis functionality may normalise following 6 months of abstinence, though this may be confounded by selection bias. HPA axis hypoactivity was associated with a higher risk of relapse. Future research should aim to investigate all sexes and races, increase methodological consistency and participant follow up, and use HPA-sensitising drugs during early abstinence to assess their effects on relapse rates. Overall, the HPA axis presents strong potential as a novel treatment target in AUD.

1. Introduction

Alcohol use disorder (AUD) is a culturally pervasive disorder wherein an addiction to alcohol can cause significant dysfunction in an individual's physical, occupational, and social life. The prevalence of AUD has only increased during the COVID-19 pandemic [1,2]. AUD is a major public health concern in Ireland, causing 4% of all deaths from 2008-2017 [3]. Within Ireland, AUD costs the taxpayer 3.7 billion euro annually [4], making research into effective treatment options an attractive policy endeavour. Current pharmacological treatments for AUD focus on withdrawal symptom alleviation and abstinence maintenance [5]. Previous research places the lifetime relapse rate between 28-68% [6,7]. These figures highlight the need for a novel treatment target that can reduce the high relapse rate in AUD. Stress has been well established as a major trigger for relapse in AUD [8–10]. The physiological response to stress is governed by the hypothalamic-pituitary-adrenal axis (HPA axis) [11]. Therefore, investigating its functioning in AUD may provide this novel target that can improve treatment outcomes.

The HPA axis is a term describing the interactions between those respective brain areas responsible for the allostatic adaption to a stressor. When faced with a stressor, the hypothalamus produces corticotropin-releasing hormone, which causes the anterior pituitary gland to release adrenocorticotropin releasing hormone (ACTH), which induces glucocorticoid secretion from the adrenal gland, enabling the 'fight or flight' response. Cortisol then initiates a negative feedback loop that returns the body to homeostasis [11] (Fig. 1).

Allostasis refers to the process of metabolic adaption to external or internal stressors in a bid to return to homeostasis i.e., regular functioning [12,13]. When faced with these stressors, the body significantly alters its metabolic processes through the HPA axis to adapt to their effects and attempt to return the body to regular functioning levels [12,13]. When faced with a chronic stressor, such as a dysfunctional home life or repeated substance misuse, the body faces an increased allostatic load. Like overclocking a computer, where more power is given to the computers CPU to allow it to temporarily work at a higher capacity at the cost of the hardware's longevity, allostasis allows the body to work "overtime" to overcome stressors, but repeated allostasis due to chronic stress leads to damage, called allostatic load [12,13]. The biochemicals released during allostatic adaption, such as ACTH and cortisol, are useful in a homeostatic capacity, but when found at consistently higher levels like during allostatic adaption, they can exert pathological effects like increased anxiety or neurotoxicity [12,13]. In the case of substance misuse, the drug can be considered both a reward and a stressor, as it inputs its hedonic effects while chronic use forces persistent allostatic adaption to a new baseline- called an allostatic state [12,13]. Altered HPA axis functioning is important to investigate as it may reveal novel pharmaco- or psychotherapeutic targets when treating alcohol

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dependence.

HPA axis functioning can be investigated using multiple stress inductions. Psychological stressors can include public speaking, mental arithmetic, or cue exposure tasks [14]. Physical stressors used are exercise or exposure to hot or cold temperatures for long periods of time [15–17]. Pharmacological stressors include administration of CRH, which kickstarts the HPA axis stress response [15–17]. Despite experimental separation of stressors into physical or pharmacological, there is overlap between these. Such as temperature changes, noted above as a physical stressor, may also induce psychological stress in such forms of anxiety [15]. Prior to, immediately following, and typically up to 60 or 120 min following these stressors, plasma, urinary, or salivary cortisol and ACTH are measured to assess the HPA axis response. Using these biomarkers, the functioning of the HPA axis can be compared to both the participant's baseline and healthy controls to investigate differences in said functioning and where these differences occur, so that a novel drug target can be identified.

The AUD population is studied in different stages. Firstly, ongoing AUD, which consists of individuals with diagnosed AUD who are still drinking. Secondly, withdrawal- estimated to last up to 2 weeks, characterised by difficult physical and psychological symptoms [18]. Thirdly, early abstinence is defined as following withdrawal which may last up to 6 months. Long term withdrawal can be defined as abstinence lasting greater than 6 months [18].

Examining HPA axis functioning in AUD, and compiling all the research to date on it, will provide a guide to inform clinicians and future researchers of the current knowledge and methodologies, as well as exposing gaps of the current work. This review will hopefully benefit AUD patients by further informing their pathology throughout all stages of disorder and guiding their treatment.

2. Method

The Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRSIMA) and its 27-item checklist were used a guide to perform and present the present study [19].

2.1. Databases used

PubMed, Embase, Cochrane Library, and Psychinfo were the databases used. Pubmed was chosen as the primary database due to the ease of its search function and string building. Embase was chosen as a secondary database as it is estimated to have an 85% overlap with PubMed [20]. Cochrane Library was used as it contains many non-indexed journals, but is limited to reviews, trials, and clinical notes [20]. Google Scholar was not used as a database due to discovery of the "bubble effect" [21].

2.2. Search terms

Search terms were decided through inserting "alcohol", "alcohol use disorder" and "HPA axis" into the NCBI MeSH Database and the term-tagging of articles concerning alcohol use disorder, the HPA axis, and its associated biomarkers on PubMed. From these sources the following search string was generated:

(Alcohol-related disorders[MeSH Terms] OR ethanol [MesH Terms]) AND (Allostasis [MeSH Terms] OR Hypothalamo-Hypophyseal System [MeSH Terms]) AND (alcohol [tiab]) AND (allostatic load [tiab] OR cortisol [tiab]) NOT (Review [Publication Type]) NOT (case reports [publication type])

The filters "humans", "English", and "adults" were applied. This search string was used for PubMed and adapted for other databases.

2.3. Eligibility criteria

The present study aimed to assess the relationship between AUD and allostasis. Using this as a context, the eligibility criteria were developed using the population, intervention, control, and outcome process (P.I.C.O.) as a guide [22]. Where population included individuals diagnosed with AUD. The interventions included an induction of stress (psychological or chemical) for the meta-analysis, whilst observational studies were included in the narrative review. Studies using healthy controls were included to examine recovery in abstinent patients and compare the differences in HPA axis functioning in AUD and non-AUD respectively. Outcome measures were biomarkers predictive of HPA axis functioning including plasma or salivary cortisol and ACTH levels.

Papers were excluded if the participants had a significant co-morbidity that would affect HPA axis activity such as depression and if the participants were taking drugs that would affect HPA axis activity such as psychotropic medications.

Duplicate removal was performed using EndNote. Following duplicate removal, the titles and abstracts of records were assessed to determine if they matched the eligibility criteria outlined above. Following this screening, the remaining records full texts were reviewed, and eligibility was confirmed or retracted. The reference lists of these articles were investigated to find any missing studies. Eligibility criteria screening was performed by 2 authors independently and then results were compared and inclusion finalised.

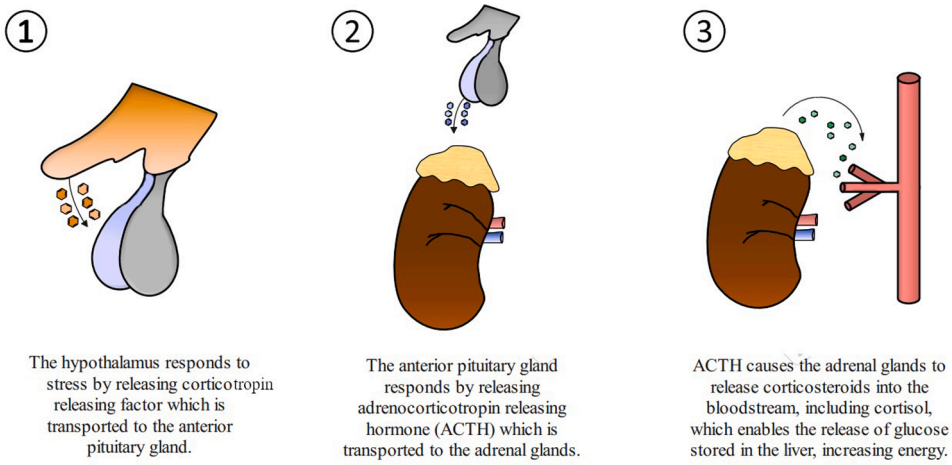

Fig. 1. HPA-axis's action in response to stress.
This graphic details the processes involved in the HPA-axis' biochemical response to an environmental stressor. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

A third reviewer with no involvement in the manuscript reviewed a random sample (n = 6/75) of the excluded papers and cross-validation. No discrepancy between excluded papers was reported.

2.4. Study quality assessment

The risk of bias in studies selected was assessed using the Cochrane Collaboration tool modified by Cochrane EPOC and Arditi et al. [23] to expand its scope to non-randomised studies. Studies were assigned a low, high, or unclear risk of bias in 12 categories- random sequence generation, allocation concealment, baseline characteristics, level of confoundment, appropriate analysis, sample representation of source populations, intervention independence of other changes, integrity of the intervention, blinding of outcome assessments, addressing of incomplete outcome data, and levels of other bias.

2.5. Data extraction

Data extraction was performed using Microsoft Excel. The following information was extracted from each article during the title/abstract review and full text review- The reference, the n of the treatment group, the n of the control group, the mean age of the population (+/- standard

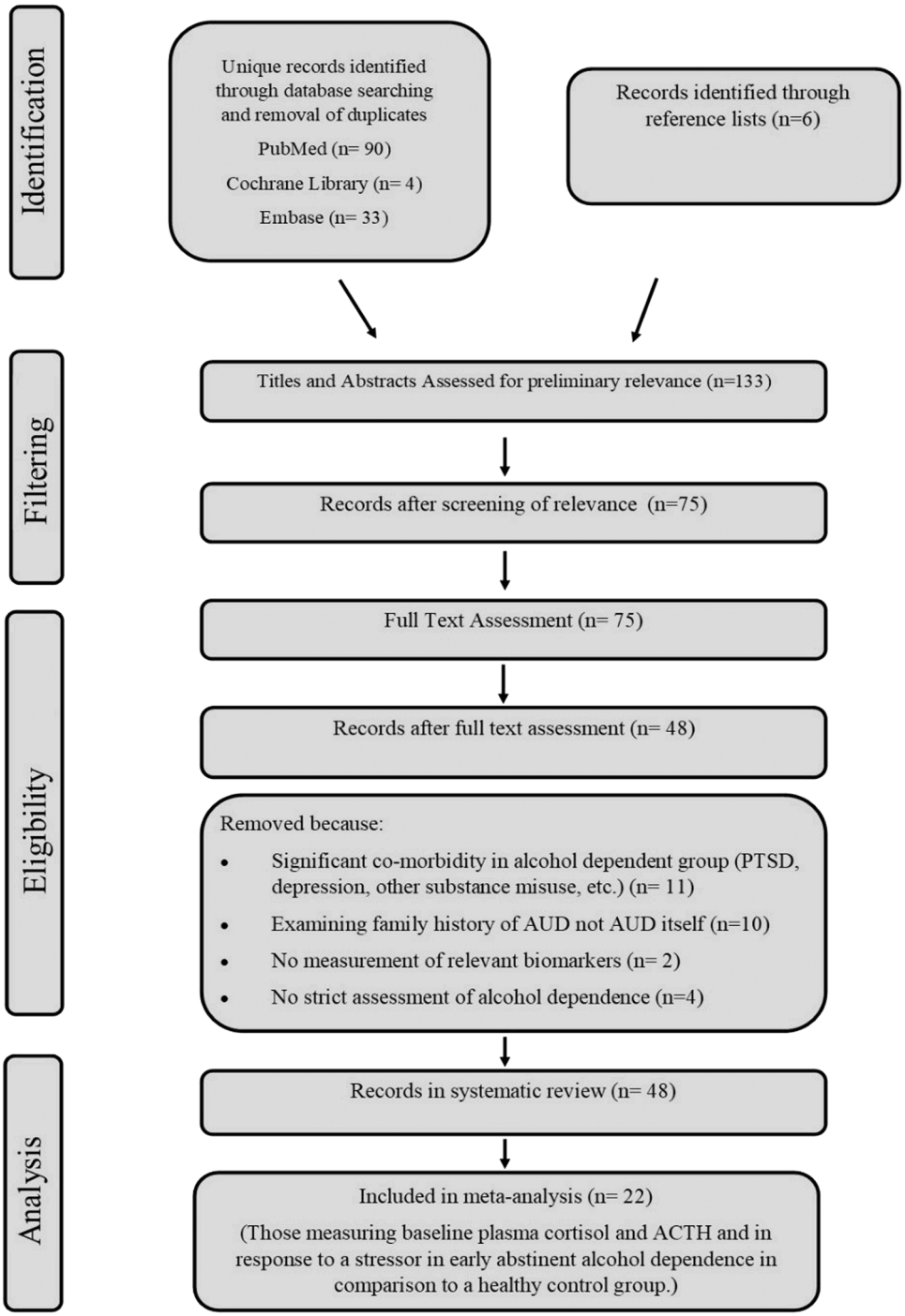

Fig. 2. PRISMA Flow-chart
This graphic outlines the screening process and results of such according to the PRISMA guidelines.

deviation, the gender ratio of the population in %, the racial breakdown of the population, the length of the populations abstinence from alcohol (where relevant), the study's method of control, the study's method of intervention, the biomarkers used to measure HPA axis functioning, and a summary of the study's results. Where results were separated upon ethnic or gender lines, data were combined proportional to the demographics of the sample.

2.6. Data analysis

Quantitative analysis was performed using meta-analysis. Records that focused on recently abstinent participants (2-6 weeks of abstinence), used a stress inducing intervention, measured plasma cortisol or ACTH 60 min following stress induction, where participants were not under significant pharmacological treatment (psychotropics, acamprosate, naloxone, naltrexone, other substance misuse etc.), and used a healthy control, were included in the meta-analysis. For meta-analyses of resting cortisol and ACTH levels, the same criteria as above applied minus the stress induction. Data were extracted from records using Get Data Digitizer [24]. Meta-analysis was performed using Jamovi [25]. Further analysis was performed in SPSS. A random effects model was chosen as studies varied in methodologies such as different stress inductions, levels of abstinence, and cortisol assays [26]. Heterogeneity was the measurement of variability between studies in a meta-analysis. It was represented using the I2 statistic, which provides a percentage quantification of heterogeneity. Here 25% indicated low heterogeneity, and 75% as high. In the case of significant heterogeneity, 'leave-out' analysis was used. Rosenthal's fail-safe n was used to measure publication bias.

Articles outside of early abstinence were not analysed using meta-analysis, instead a narrative summary of their data were given. This was due to a lower number of papers in these sections and methodological inconsistencies.

3. Results

3.1. Search results

Screening results at each stage of the PRISMA process can be seen in Fig. 2. 48 records were included in the final review.

3.2. Ongoing AUD

Results for ongoing AUD were mixed. Six eligible studies were found to focus on HPA axis functioning in AUD patients who were currently drinking (Table 1). One study found that ongoing AUD patients had a blunted cortisol response to stress induction [27] while 2 studies found a higher cortisol response to stress in ongoing AUD [28,29]. One study found a blunted ACTH response to stress [28] while another found there was no difference in biomarker response to stress between AUD and control [30]. Three studies used both male and female participants (Table 1). Caucasian participants were the majority in every study where recorded (Table 1). Two studies used pharmacological stressors and 2 used psychological (Table 1). Overall, evidence suggests that further research is needed to discern whether currently drinking AUD patients have alterations in the HPA axis and may vary from individual to individual.

3.2.1. Risk of bias in ongoing AUD studies

The risk of bias in studies selected was assessed using the Cochrane Collaboration tool modified by Cochrane EPOC and Arditi et al. (2016) [23] to expand its scope to non-randomised studies (Fig. 3). Bias may have come from baseline characteristic differences like large wealth disparities between participants [32]. Confoundment chance was increased due to the use of only a public speaking task for stress induction, which would vary between individual participants and was not validated with another stress task [29]. Most studies did not describe an outcome assessment blinding procedure (Fig. 5).

Table 1
Summary table of articles included in the "Ongoing AUD" section.

Reference	n T	n C	Age M + SD	Gender %M:F	Race	State of current drinking	Method of Control	Intervention Method	HPA axis measurements	Summary
Berman et al., 1989 [28]	7	8	30	Male	Not recorded	Ongoing AUD	Healthy Individuals	Insulin	ACTH Cortisol	Higher cortisol, lower ACTH, researchers note this may be due to overnight abstinence
Bibbey et al., 2015 [30]	15	18	19.2 (0.67)	46:54 M:F	96% white	Ongoing AUD	Healthy	Arithmetic and Public speaking Task	Salivary Cortisol	No significant differences between Alcohol Dependent group and Controls
Gianolakis et al., 2003 [31]	151	152	38 (3.3)	50:50	Majority White	Ongoing AUD/ withdrawal	Non-drinking matched participants	n/a	ACTH, Cortisol, Beta endorphin	Plasma ACTH and beta-END levels were significantly lower in females than males of all age and drinking category groups.
Ransome et al., 2017 [32]	1129	n/a	53.2 (11.4)	46:54	White and Black	Ongoing AUD	Healthy	None-Observational	Cortisol, Norepinephrine, DHEA-S	Examined the interaction between race and AUD on HPA axis. Blacks had lower mean cortisol, DHEA-S, epinephrine and norepinephrine than whites
Starcke et al., 2013 [29]	23	20	42.13 (13.17)	male	n/a	0 weeks-24 months abstinent, and currently drinking	healthy	TSST	Salivary cortisol, heart rate, and skin conductance levels	Abstinent AUD had comparable cortisol response to controls, actively drinking AUD had a higher cortisol response. Duration of abstinence was positively correlated with cortisol response in abstinent AUD
Wand & dobs, 1991 [27]	14	13	34 (2)	Male	Not recorded	Ongoing AUD	Healthy Individuals	Metyrapone	ACTH, Cortisol, 11 deoxycortisol	AUD group had a blunted response compared to controls

Summary of studies included in the ongoing AUD section. nT = n of AUD group. nC = n of control group. OCRH = Ovine Corticotropin Releasing Hormone. TSST = Trier Social Stress Task.

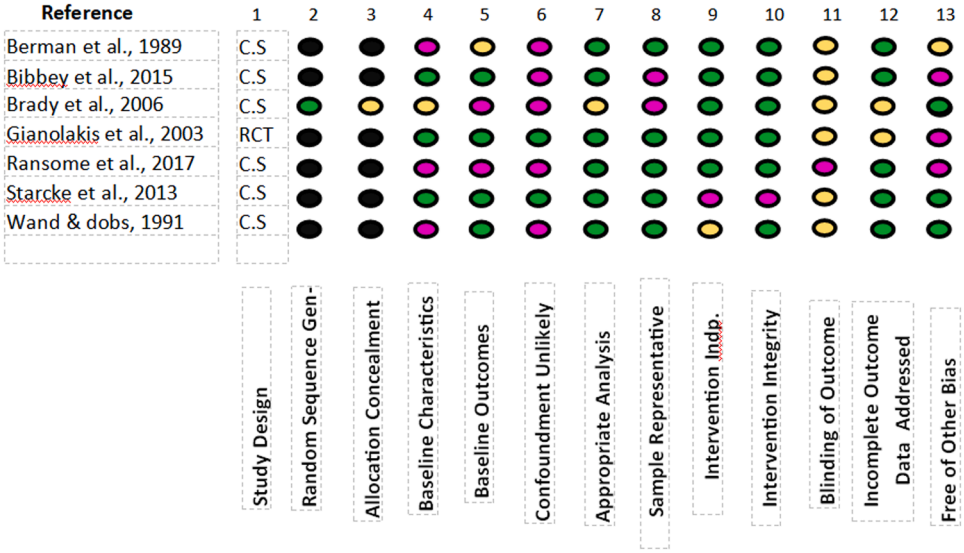

Fig. 3. Risk of Bias in Ongoing AUD Studies
This infographic shows the risk of bias found in each study for this analysis. Categories of bias are detailed horizontally below. Risk was analysed using Cochrane Collaboration tool modified by Cochrane EPOC and Arditi et al. (2016) [23] to expand its scope to non-randomised studies (Fig. 3). Green denotes low risk of bias, red- high risk, and yellow- unclear risk. Where C.S = Comparative Study. R.C.T. = Randomised Control Trial. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.3. Withdrawal in AUD

A review of studies focusing on AUD patients going through withdrawal from alcohol suggest that cortisol rise as the patient goes through detox. Higher baseline cortisol during withdrawal was found in all 7 studies (Table 2). Five studies induced stress in participants and found that ACTH and cortisol was increased in AUD patients compared to healthy controls [33–37].Withdrawal was estimated to last from 5 days to 2 weeks. Three studies used a mix of male and female participants, while the rest used males only (Table 2). All studies used majority white participants (where recorded) (Table 2). Two studies used psychological stressors, 1 used physical stressors, and 3 used pharmacological stressors (Table 2). Overall, the current research points towards an increase in HPA axis activity throughout the withdrawal process.

3.3.1. Risk of bias in withdrawal in AUD studies

The risk of bias in studies selected was assessed using the Cochrane Collaboration tool modified by Cochrane EPOC and Arditi et al. (2016) [23] to expand its scope to non-randomised studies (Fig. 4). High risk of bias was found in baseline characteristics due to differences in the years spent drinking [33,38], differences in withdrawal system intensity [39], or other substance misuse [37]. Confoundment chance was increased due to the use of only a public speaking task for stress induction, which would vary between individual participants and was not validated with another stress task [35,36]. Most studies did not describe an outcome assessment blinding procedure (Fig. 4).

Table 2
Summary table of articles included in the "Withdrawal" section.

Reference	n T	n C	Age M + SD	Gender %	Race	Length of Withdrawal	Method of Control	Intervention Method	HPA axis measurements	Summary
Costa et al., 1996 [33]	12	10	53.4 (5.9)	male	n/a	7-14 days	Healthy	OCRH and insulin	ACTH cortisol	AUD group had a reduced response to OCRH test
Heinz et al., 1995 [38]	12	14	42.9 (9.5)	male	n/a	withdrawal then 3 weeks	Healthy	n/a	cortisol, prolactic, lut hormone, follicle stim hormone, testosterone, androstenedione, estradiol, sex hormone binding globulin	cortisol fell during abstinence, significantly higher during withdrawal but no significant differences after 3 weeks abstinence
Hundt et al., 2001 [34]	19	19	42.7 (8.4)	48:52	n/a	1 day	Healthy	dexmeathsone and OCRH	cortisol ACTH	AUD had higher cortisol at start, cortisol normal and ACTH lower than control after withdrawal
Iranamesh et al., 1989 [39]	10	7	41 (11)	male	n/a	3-16 days	Healthy	n/a	cortisol	Alterations in the circadian rhythm of cortisol persist after 6 weeks of abstinence
McRae et al., 2006 [35]	10	6	30.7 (8.6)	55:45	80.6% white	5 days	Healthy	cold pressor and TSST	ACTH cortisol	Cortisol higher in AUD group
Muelhan et al., 2020 [36]	33	38	44.4 (10.07)	68:32	n/a	10 to 11 days	Healthy	TSST	ACTH cortisol	Higher cortisol in AUD than controls
Ozsoy et al., 2008 [37]	30	20	40.3 (9)	males	n/a	1 day	Healthy	dexmethasone suppression test	Dh-eas and cortisol	Lower dh-eas in late and early withdrawal than control, higher cortisol in late withdrawal

Summary of studies included in the withdrawal section. nT = n of AUD group. nC = n of control group. OCRH = Ovine Corticotropin Releasing Hormone. TSST = Trier Social Stress Task.

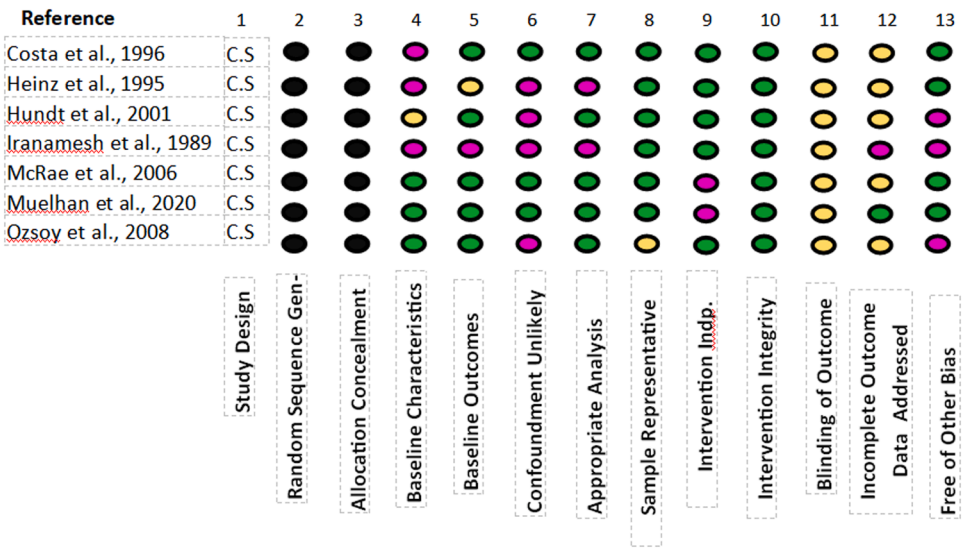

Fig. 4. Risk of bias in withdrawal in AUD studies
This infographic shows the risk of bias found in each study for this analysis. Categories of bias are detailed horizontally below. Risk was analysed using Cochrane Collaboration tool modified by Cochrane EPOC and Arditi et al. (2016) [23] to expand its scope to non-randomised studies (Fig. 6). Green denotes low risk of bias, red- high risk, and yellow- unclear risk. Where C.S = Comparative Study. R.C.T. = Randomised Control Trial. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.4. Early abstinent AUD

Early abstinence was described as abstinence for more than 2 weeks (to avoid confoundment from withdrawal symptoms) and less than 6 months. Twenty-nine eligible records examining early abstinence were found (Table 3).

3.4.1. The ACTH response to stress

Six studies found that the ATCH response to stress was significantly blunted in early abstinence compared to healthy controls [53,55,56,58,61]. Two studies found that there was no difference between early abstinence and healthy controls [44,64]. Two studies included male and female participants [44,45,60], whilst the rest were males only (Table 3). Participants were majority Caucasian in all studies (where recorded). Nine studies used pharmacological stressors, 4 used a psychological stressor, and 2 used physical (Table 3). Overall, results suggest that the ACTH response to stress in blunted during early abstinence. To reinforce this suggestion, a meta-analysis was performed including studies adhering to the inclusion criteria.

A meta-analysis of 12 studies was performed (Fig. 5). Adinoff et al. (2010) [42] was removed due to leave-one out heterogeneity analysis. The total effect suggests that AUD patients during early abstinence produce significantly less ACTH in response to stress when compared to healthy controls. (SMD = -1.47 [-1.76, -1.19]; Z = -10.1, p = < .001). Analysis of heterogeneity found that variability between studies was moderately low (*Tau* (11) = 0.28, (p = 0.07), I^2: 35.68%). There was high variation between weighting of studies (4.58- 14.46%). Rosenthal's fail-safe n suggests that publication bias was not present (fail-safe n = 655, p < .001) (Fig. 6).

To validate that these differences were due to a blunting of the HPA axis in response to stress, i.e. that these differences do not exist at baseline, another meta-analysis was performed measuring resting ACTH in early abstinence and healthy controls (Fig. 7). George et al. (1994) was removed due to heterogeneity leave-one out analysis. The total effect suggests that AUD patients during early abstinence do not have significantly different resting plasma ACTH levels when compared to healthy controls. (SMD = -0.39 [-0.93, 0.157]; Z = -1.39, p = < .001). Analysis of heterogeneity found that variability between studies was high (*Tau* (11) = 0.8, (p < .001), I^2: 81.11%). Studies were weighted relatively equally (7.04- 11.41%). Rosenthal's fail-safe n suggests that publication bias was not present (fail-safe n = 655, p < .001) (Fig. 8).

Further analysis was performed using the to assess the impact of gender (male or mixed), stress induction type (pharmacological, psychological, or physical), and length of abstinence (less or greater than 6 weeks). Unpaired T-tests with Welch's correction for unequal standard deviations were performed. No significant difference was found for gender in the abstinent group (t (9) = 1.715, p = 0.12) or the control group (t (9) = 2.1, p = 0.12). No significant difference was length of abstinence for in the abstinent group for length of abstinence (t (9) = -0.287, p = 0.78). A one-way ANOVA with Welch's correction for unequal standard deviations was performed to assess stress induction type. No significant difference was found between stress types (F (2, 10,) = 1.252, p = 0.34).

Overall, results suggest that individuals with AUD going through early abstinence have a blunted ACTH response to stress.

3.4.2. The cortisol response to stress

Twelve studies found that the cortisol response to stress in early abstinent AUD was significantly lower than healthy controls [55,56,40,41,46,48–51,57,60,63]. Five studies found that there was no difference in the cortisol response to stress in early abstinent AUD compared to healthy controls [29,56,61,64,42]. One study found an increased cortisol response to stress in early abstinent AUD compared to healthy controls [58]. One studied used only female participants (48). Two used male and female participants [44,45]. The remaining studies used only male participants (Table 3). All studies used majority Caucasian participants (where recorded). Ten studies used pharmacological stressors, three used physical, and five used psychological stressors (Table 3). Overall, results suggest that the cortisol response to stress in blunted during early abstinence. To reinforce this suggestion, a meta-analysis was performed including studies adhering to the inclusion criteria.

A meta-analysis of 9 studies was performed (Fig. 9). Inder et al. (1995) [53] was removed due to leave-one out heterogeneity analysis. The total effect suggests that AUD patients during early abstinence produce significantly less cortisol in response to stress when compared to healthy controls. (SMD = -1.32 [-1.62, -1.02]; Z = -8.7, p = < .001). Analysis of heterogeneity found that variability between studies was moderately low (*Tau* (8) = 0.28, (p = 0.06), I^2: 38.97%). There was high variation between weighting of studies (6.66- 16.99%). Rosenthal's fail-safe n suggests that publication bias was not present (fail-safe n = 410, p < .001) (Fig. 10).

To validate that these differences were due to a blunting of the HPA axis in response to stress, i.e. that these differences do not exist at baseline, another meta-analysis was performed measuring resting cortisol in early abstinence and healthy controls (Fig. 11). Inder et al. (1995) [53] was removed due to heterogeneity leave-one out analysis. The total effect suggests that AUD patients during early abstinence do have significantly higher resting plasma cortisol levels when compared

Table 3
Summary table of each article included under the "Early Abstinence" section.

Reference	n T	n C	Age M + SD	Gender (M:F %)	Race	Length of abstinence	Method of Control	Intervention Method	HPA axis measurements	Summary
Adinoff et al., 2005 [40]	11	10	40.94 (4.9)	Male	60% white	4-6 weeks	healthy	cosynthropin, dexmethasone	Plasma cortisol corticotropin	Cortisol but not corticotropin response blunted in abstinent AUD
Adinoff et al., 2005 [41]	11	10	40.94 (4.9)	Male	60% white	4-6 weeks	healthy	OCRH, naloxone	Plasma cortisol and corticotropin	Cortisol but not corticotropin response to oCRH blunted in AD
Adinoff et al., 2010 [42]	7	10	36.5 (5.2)	Female	Majority White	4-8 weeks	healthy	cosyntropin	Plasma ACTH and cortisol	No significant differences in HPA axis response to stress between abstinent and healthy
Anthenelli et al., 2001 [43]	67	42	39.8 (8.4)	Male	76.5% white	4 months	healthy	fenafluramine	Plasma cortisol and ACTH	AUD have lower baseline cortisol, but greater response to fenafluramine, indicating the damage may be in the 5ht area
Bailly et al., 1989 [44]	10	7	27-47 (n/a)	70:30	n/a	4 weeks	Healthy	CRF, DST	Plasma cortisol and ACTH	AUD group had lower cortisol compared to controls after 4 weeks of abstinence.
Bardeleben et al., 1989 [45]	12	11	38 (9)	75:25	n/a	2-6 weeks	Healthy	H-CRH	Plasma cortisol and ACTH	Blunted ACTH response to CRH in early-abstinence AUD
Bernardy et al., 1996 [46]	40	14	36.2 (1.1)	Male	n/a	4 weeks	Control Group	Math and isometric handgrip exercise	Urinary Cortisol	AUD have lower cortisol reponse to stress but normal prestress values, not affected by a large range of factors such as nicotine use or affective disorder
Chakrabarty et al., 2022 [47]	66	50	35 (6.24)	Male	n/a	3 weeks+	healthy and diseased controls	n/a	cortisol	AUD have lower daily cortisol than healthy
Coiro et al., 2007 [48]	10	10	44 (1.4)	Male	n/a	4-8 weeks	healthy	Exercise	Plasma Cortisol, ACTH, and cardiological variables	HPA axis function during exercise significantly blunted after 4-6 weeks but normalises after 8 weeks of abstinence
Ehrenreich et al., 1997 [49]	11	10	41.1 (6.9)	Male	n/a	Up to 13 weeks	healthy	hCRF, bolis stress test (math, background noise etc)	Plasma cortisol ACTH norepinephrine	ACTH values normalised after 12 weeks of abstinence
Errico et al., 1992 [50]	52	30	39.2 (7.3)	Male	n/a	4 weeks abstinent AUD	healthy	Cold pressor and Math	Serum Cortisol	AUD have diminished cortisol response to stressors
Fox et al., 2009 [51]	42	42	35.7 (8.1)	50:50	56% white	4 weeks	healthy	Guided imagery (stress/ relaxation)	Salivary cortisol, ACTH, norephinephrine and epinepherine	Gender differences in response to stress and cue, Males diminished hpa axis to all cues, feMales only to stress
George et al., 1994 [52]	26	15	36.2 (2.25)	Male	n/a	3 weeks	healthy	2 deoxy-glucose	Plasma cortisol, ACTH	Low dose 2dg (12.5 mg/ kg) did not produce effect, but 25 mg/kg led to increased cortisol and ACTH in AD)
Heinz et al., 1995 [38]	12	14	42.9 (9.5)	Male	n/a	3 weeks	healthy	n/a	luteinizing hormone, follicle-stimulating hormone, testosterone, androstenedione, oestradiol, sex hormone-binding globulin, cortisol, and prolactin	Cortisol fell during abstinence, significantly higher during withdrawal but no significant differences after 3 weeks abstinence
Inder et al., 1995 [53]	9	9	41.4 (3.1)	Male	n/a	6 weeks	healthy	oCRH, naloxone	Plasma Cortisol, ACTH, CRH and AVP	Alcoholics had a blunted ACTH response, no difference in cortisol responses
Iranamesh et al., 1989 [39]	10	7	41 (11)	Male	n/a	4-6 weeks	healthy	n/a	Plasma cortisol	Alterations in the circadian rthym of cortisol persist after 6 weeks of abstienence
Junghaans et al., 2007 [54]	37	12	40 (7.8)	Male	n/a	3 weeks and 4 months	Controlled by long term	n/a	Waking cortisol	Longer abstainers had higher waking cortisol

(*continued on next page*)

Table 3 (*continued*)

Reference	n T	n C	Age M + SD	Gender (M:F %)	Race	Length of abstinence	Method of Control	Intervention Method	HPA axis measurements	Summary
							abstainers (healthy)			
Knudsen et al., 1987 [55]	10	n/a	42 (11)	Male	n/a	4 weeks	Healthy	ACTH stimulation and insulin test	Plasma cortisol ACTH	HPA axis response blunted in insulin stress test, not in ACTH test
Loosen et al., 1993 [56]	28	19	42.4 (7.6)	Male	n/a	2 weeks+	healthy	CRH, TRH	Plasma cortisol, ACTH, TSH	No difference in cortisol response, reduced ACTH response in AUD group
Lovallo et al., 2000 [57]	20	10	40 (2)	Male	n/a	3-4 weeks	community controls	public speaking test	Salivary Cortisol	Blunted response to stress in AUD and substance abusing AUD vs control
Marchesi et al., 1997 [58]	14	12	42.3 (6.2)	Male	n/a	4 weeks	healthy	n/a	cortisol, b endorphin, ACTH	Increased cortisol in abstinent AUD but decreased ACTH and b-endorphin
Price et al., 2019 [59]	62	24	43.1 (8.4)	Male	65% White	4-6 weeks	healthy	oCRH, Cosyntropin, psychostressor	plasma cortisol and ACTH	Black men with AUD exhibited greater cortisol reactivity relative to White men with AUD.
Sinha et al., 2011 [60]	36	36	35.47 (8.74)	70:30	79% White	4 weeks	healthy	Stressful imagery	plasma cortisol and corticotropin	Lack of HPA axis stress response via cortisol seen in abstinent AUD group
Starcke et al., 2013 [29]	23	20	42.13 (13.17)	male	n/a	0 weeks-24 months abstinent, and currently drinking	healthy	TSST	Salivary cortisol, heart rate, and skin conductance levels	Abstinent AUD had comparable cortisol response to controls, actively drinking AUD had a higher cortisol response. Duration of abstinence was positively correlated with cortisol response in abstinent AUD
Vescovi et al., 1997 [61]	48	25	34-56	Male	n/a	5 weeks	healthy	hyperthermic stress	Plasma ACTH cortisol b endorphin and met-enkephalin	Lower ACTH and cortisol and b endrophin in abstinent AUD after hyperthermic stress
Walter et al., 2006 [62]	46	26	42 (9.7)	74:26	n/a	6 weeks, monitored up to 1 year	healthy	n/a	Cortisol	Lower daily cortisol in abstainers than relapsers
Zhang et al., 2020 [63]	70	26	42.6 (9.3)	Male	60% white	4-6 weeks	healthy	OCRH, TSST	Plasma cortisol, ACTH	AUD have a lower cortisol and ACTH response to OCRH (chemical probe) but not as much difference in response to TSST (psychological probe)

Summary of studies included in the early abstinence section. nT = n of AUD group. nC = n of control group. OCRH = Ovine Corticotropin Releasing Hormone. TSST = Trier Social Stress Task.

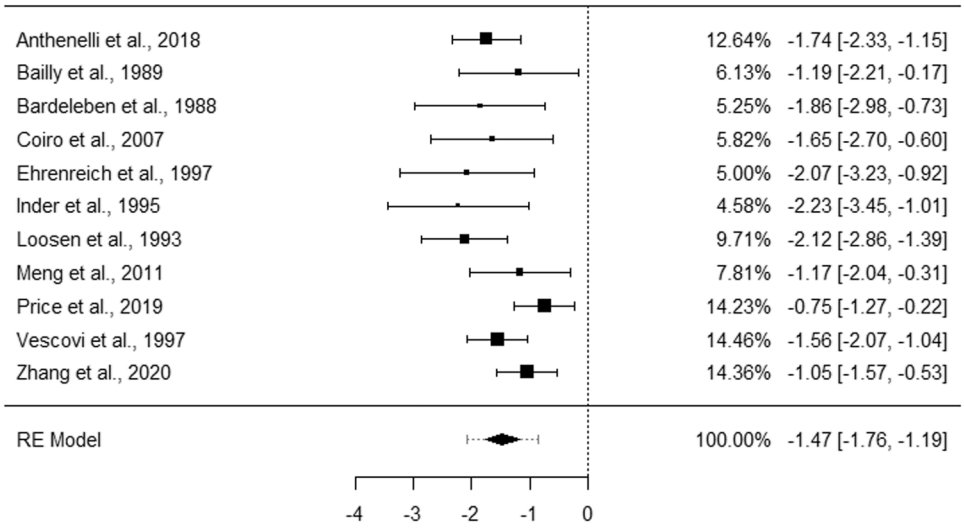

Fig. 5. Forest Plot of Meta-analysis of the ACTH Response to Stress in Early Abstinence in AUD Compared to Healthy Controls
This forest plot shows the weight, precision, and standardised mean difference (SMD) for each study included in the meta-analysis. The total number of studies used in the meta-analysis was (k=11). The Hunter-Schmidt randomised effects model was used. SMDs are the difference in plasma ACTH levels in response to stress in an early abstinent AUD group compared to healthy controls. The data are left of zero, indicating a significant effect. Where C.I = Confidence Intervals, L.B = Lower Bound, U.B = Upper Bound. Data on plot are represented as SMD, 95% confidence intervals, and %weight.

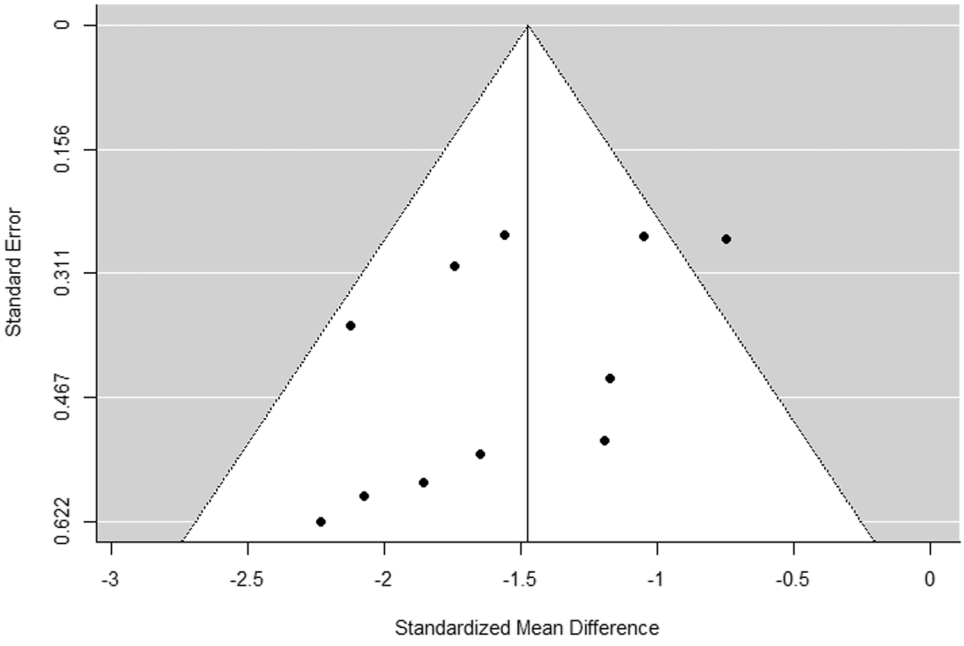

Fig. 6. Publication Bias Funnel Plot of Meta-analysis of the ACTH Response to Stress in Early Abstinence in AUD Compared to Healthy Controls
This funnel plot shows the spread of standardised mean differences (SMD) across the studies included. Total number of studies included in meta-analysis (k = 11). Each black circle is a study's SMD. The horizontal black line in the middle of the white triangle indicates the total effect (-1.47). The large majority of SMDs are inside white triangle, indicating that the risk of publication is low. Rosenthal's fail-safe n was calculated and reinforces the assumption that publication bias was not present (P < .001)

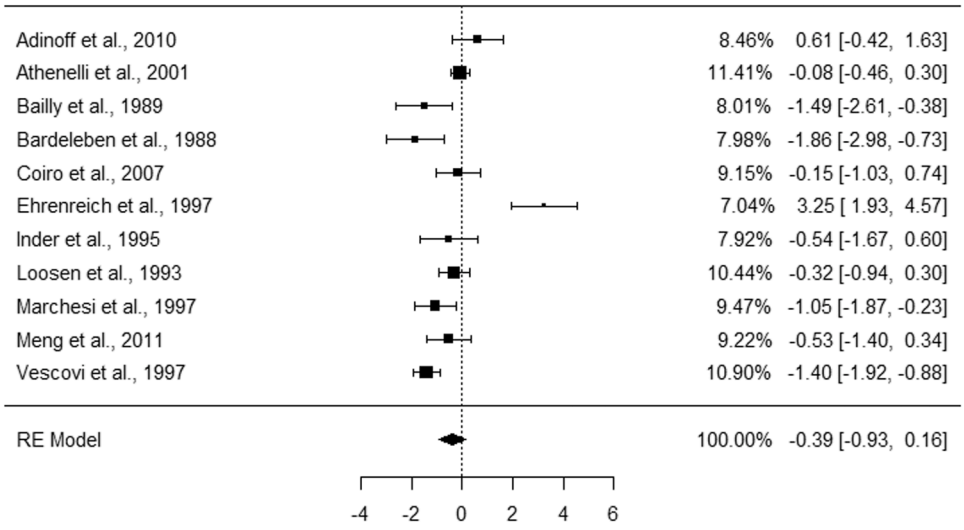

Fig. 7. Forest Plot of Meta-analysis of resting ACTH in Early Abstinence in AUD Compared to Healthy Controls
This forest plot shows the weight, precision, and standardised mean difference (SMD) for each study included in the meta-analysis. The total number of studies used in the meta-analysis was (k=11). The Hunter-Schmidt randomised effects model was used. SMDs are the difference in resting plasma ACTH in an early abstinent AUD group compared to healthy controls. The data are cross zero, indicating a non-significant effect. Where C.I = Confidence Intervals, L.B = Lower Bound, U.B = Upper Bound. Data on plot are represented as SMD, 95% confidence intervals, and %weight.

to healthy controls. (SMD = 0.74 [-0.16, 1.33]; $Z = 2.44$, $p = < .015$). Analysis of heterogeneity found that variability between studies was high (Tau (11) = 0.97, ($p < .001$), I^2: 88.66%). Studies were weighted relatively equally (7.23- 9.34%). Rosenthal's fail-safe n suggests that publication bias was not present (fail-safe n = 280, $p < .001$) (Fig. 12).

Further analysis was performed using the to assess the impact of gender (male or mixed), stress induction type (pharmacological, psychological, or physical), and length of abstinence (less or greater than 6 weeks). Unpaired T-tests with Welch's correction for unequal standard deviations were performed. No significant difference was found for gender in the abstinent group (t (9) = -1.619, $p = 0.129$) or the control group (t (9) = -1, $p = 0.321$). No significant difference was length of abstinence for in the abstinent group for length of abstinence (t (9) = 0.71, $p = 0.49$). A one-way ANOVA with Welch's correction for unequal standard deviations was performed to assess stress induction type. No significant difference was found between stress types (F (2, 10,) = 1.244, $p = 0.32$).

Overall, results suggest that individuals with AUD going through early abstinence have a blunted cortisol response to stress.

3.4.3. *Risk of bias in early abstinence studies*

The risk of bias in studies selected was assessed using the Cochrane Collaboration tool modified by Cochrane EPOC and Arditi et al. (2016) [23] to expand its scope to non-randomised studies. Baseline characteristic differences may have led to confoundment due to a lack of clinical diagnosis, differences in years drinking, and recent poly-substance misuse (Fig. 13). Confoundment chance was increased due to the use of only a public speaking task for stress induction, which would vary between individual participants and was not validated with another stress task (Fig. 13). Most studies did not describe an outcome assessment blinding procedure or address incomplete outcome data (Fig. 13).

3.5. *Long-term abstinence*

Six studies were found to focus on long term abstinence in AUD (greater than 6 months) (Table 4). Of these, Four studies found no differences between long term abstinent AUD patients' cortisol and ACTH responses to stress compared to health controls [29,65–67]. Two studies

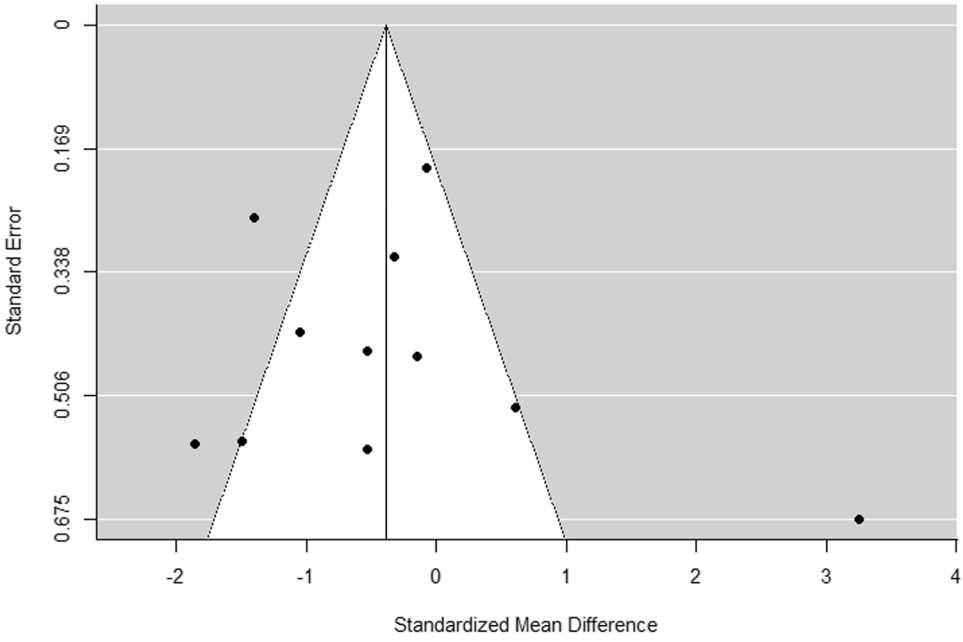

Fig. 8. Publication Bias Funnel Plot of Meta-analysis of the Resting ACTH in Early Abstinence in AUD Compared to Healthy Controls
This funnel plot shows the spread of standardised mean differences (SMD) across the studies included. Total number of studies included in meta-analysis (k = 11). Each black circle is a study's SMD. The horizontal black line in the middle of the white triangle indicates the total effect (-0.39). The large majority of SMDs are inside white triangle, indicating that the risk of publication is low. Rosenthal's fail-safe n was calculated and reinforces the assumption that publication bias was not present (P < .001)

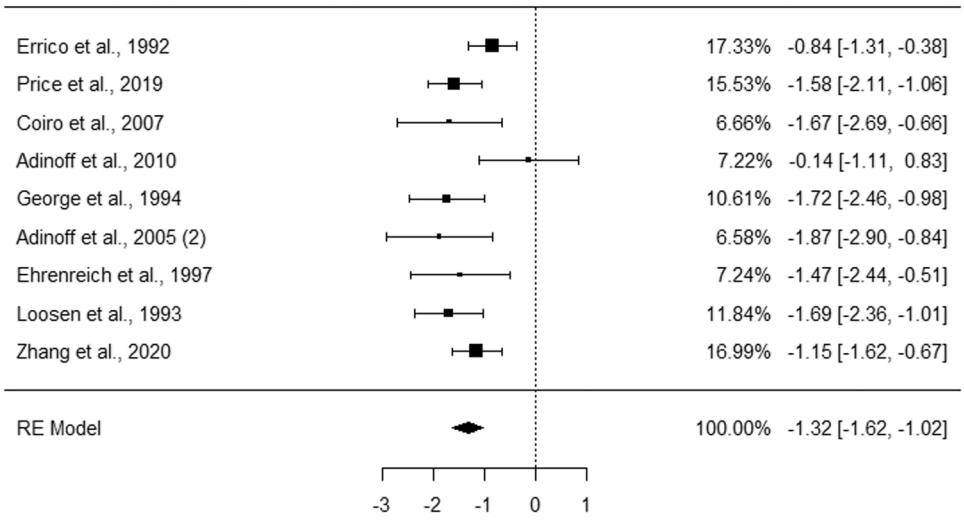

Fig. 9. Forest Plot of Meta-analysis of Cortisol Response to Stress in Early Abstinence in AUD Compared to Healthy Controls
This forest plot shows the weight, precision, and standardised mean difference (SMD) for each study included in the meta-analysis. The total number of studies used in the meta-analysis was (k = 9). The Hunter-Schmidt randomised effects model was used. SMDs are the difference in resting plasma ACTH in an early abstinent AUD group compared to healthy controls. The data are cross zero, indicating a non-significant effect. Where C.I = Confidence Intervals, L.B = Lower Bound, U.B = Upper Bound. Data on plot are represented as SMD, 95% confidence intervals, and %weight.

assessing recovery outcomes found that a lower acth:cortisol ratio in response to stress resulted in a higher risk of relapse [29,47]. Three studies used male and female participants [47,67] whilst the remaining used only males. All studies used majority white participants (where recorded) (Table 4). Two studies used psychological stressors and 4 used pharmacological stressors (Table 4). Overall, the results suggest a recovery of the HPA axis response to stress after 6 months of abstinence from alcohol.

3.6. Risk of bias in long-term abstinence studies

The risk of bias in studies selected was assessed using the Cochrane Collaboration tool modified by Cochrane EPOC and Arditi et al. (2016) [23] to expand its scope to non-randomised studies (Fig. 14). High risk of bias was found in baseline characteristics due to differences in the years spent drinking [65]. Confoundment chance was increased due to the use of only a public speaking task for stress induction, which would vary between individual participants and was not validated with another stress task [66,67]. Most studies did not describe an outcome assessment blinding procedure or how incomplete outcome data was addressed (Fig. 14).

4. Discussion

This review aimed to contextualise the current research focused on HPA axis functioning in all stages of AUD. When an individual is diagnosed with AUD and is drinking, considered here as ongoing AUD, HPA axis activity was shown to be mixed, with some studies resulting in higher activity [27–29], and others low [30,31]. Following the previously discussed theory of allostatic adaption, mixed results may be due to individuals undergoing said process of adaption at different rates as alcohol has been ingested for differing lengths of times in different amounts. Previous reviews reinforce the important role of the individual when examining AUD related adaptations in stress pathways [68,69]. Overall, the current review did not find evidence to suggest that HPA axis functioning is significantly altered in AUD solely in the context of a patient who is still actively drinking.

However, once a patient stops drinking alcohol, results became

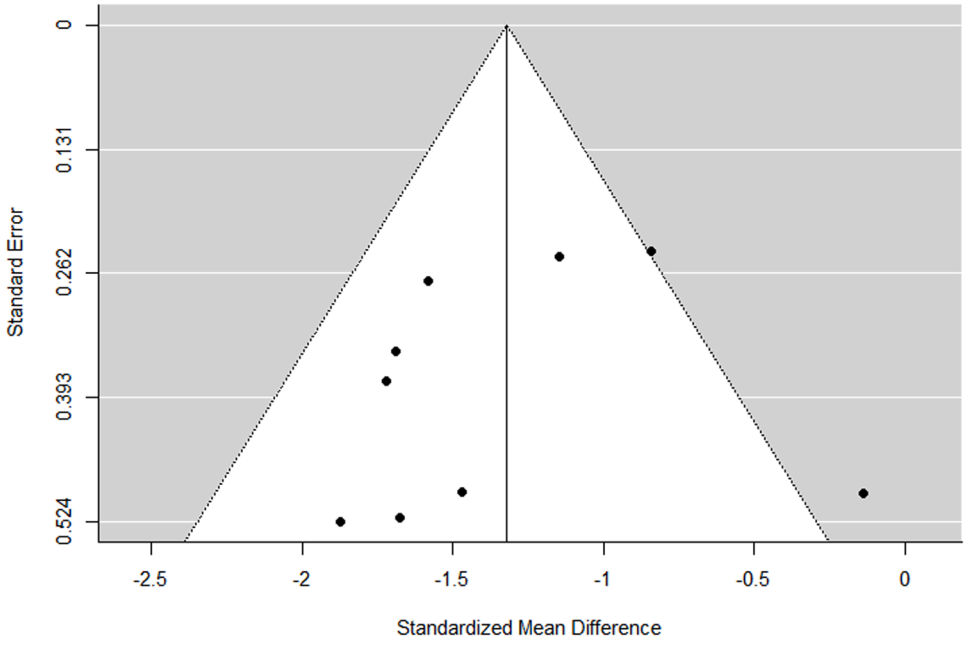

Fig. 10. Publication Bias Funnel Plot of Meta-analysis of the Cortisol Response to Stress in Early Abstinence in AUD Compared to Healthy Controls
This funnel plot shows the spread of standardised mean differences (SMD) across the studies included. Total number of studies included in meta-analysis (k = 9). Each black circle is a study's SMD. The horizontal black line in the middle of the white triangle indicates the total effect (–1.32). The large majority of SMDs are inside white triangle, indicating that the risk of publication is low. Rosenthal's fail-safe n was calculated and reinforces the assumption that publication bias was not present ($P < .001$)

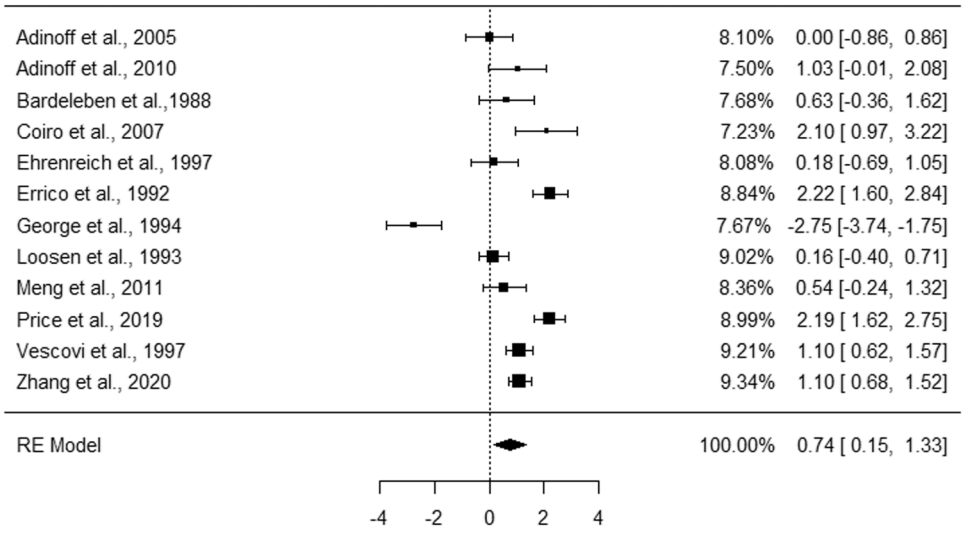

Fig. 11. Forest Plot of Meta-analysis of Resting Cortisol in Early Abstinence in AUD Compared to Healthy Controls
This forest plot shows the weight, precision, and standardised mean difference (SMD) for each study included in the meta-analysis. The total number of studies used in the meta-analysis was (k = 12). The Hunter-Schmidt randomised effects model was used. SMDs are the difference in resting plasma ACTH in an early abstinent AUD group compared to healthy controls. The data are cross zero, indicating a non-significant effect. Where C.I = Confidence Intervals, L.B = Lower Bound, U.B = Upper Bound. Data on plot are represented as SMD, 95% confidence intervals, and %weight.

consistent. During the withdrawal phase, cortisol and ACTH were chronically elevated. Theorising the cause of this, withdrawal is a highly stressful process, both physically and psychologically. Neuroplasticity derived from chronic alcohol exposure during ongoing AUD will have caused the nervous system to expect said alcohol to be present, causing an almost neurological "state of emergency" when it is removed. High levels of glucocorticoids can cause neuropathy, hyperglycaemia, and deficiency of B vitamins [70]. Previous preclinical studies suggest that high cortisol may be a driving factor for the severity of withdrawal syndrome itself [71,72]. Not only can the severity of the withdrawal syndrome affect recovery outcomes, but multiple episodes of withdrawal may also lead to further neurological dysregulation [71,72]. Overall, current evidence suggests that HPA axis activity is heightened to a possibly harmful level during withdrawal [73].

Examination of the period directly following withdrawal, here referred to as early abstinence of 4-6 weeks, revealed a blunting of HPA axis activity. This blunting means that when the patient was exposed to a stressor, they produced less cortisol and ACTH than a control. These chemicals are necessary for an individual to react to stress. Therefore, a lack thereof may help explain why stress is such a major trigger for relapse. The ability to produce sufficient levels of glucocorticoids in times of stress could be considered a form of biological recovery capital, an asset present in some individuals at varying levels, akin to social support or stable accommodation, which may prove advantageous to sustainable recovery. As previous research has shown, the higher the recovery capital, the better the recovery outcome [74]. Therefore, these results highlight a significant aspect of recovery that is not currently addressed in clinical or psychotherapeutic approaches, warranting further research to expand and then incorporate this knowledge into said interventions.

Analysis of HPA axis function in sustained abstinence (6 months+) revealed a normalisation of glucocorticoid levels in response to stress when compared to a control, highlighting an important milestone for the treatment of AUD. This may be due to the modulation of the allostatic state created by chronic alcohol consumption and withdrawal [12,13]. This suggests that early abstinence may be a specific phase of enhanced vulnerability to stress and provides a timeline on where to assert more focus on stress-coping skills during recovery. Studies with longitudinal

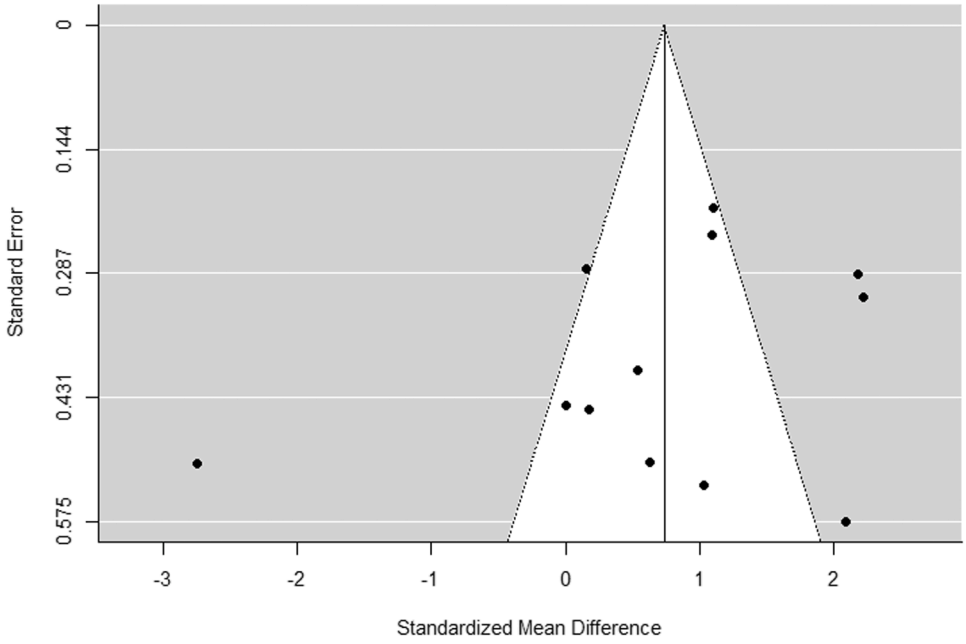

Fig. 12. Publication Bias Funnel Plot of Meta-analysis of the Resting Cortisol in Early Abstinence in AUD Compared to Healthy Controls
This funnel plot shows the spread of standardised mean differences (SMD) across the studies included. Total number of studies included in meta-analysis (k = 12). Each black circle is a study's SMD. The horizontal black line in the middle of the white triangle indicates the total effect (-0.74). The large majority of SMDs are inside white triangle, indicating that the risk of publication is low. Rosenthal's fail-safe n was calculated and reinforces the assumption that publication bias was not present (P < .001)

aspects throughout abstinence suggest that better recovery outcomes are related to a lower degree of HPA axis dysfunctionality in early abstinence [29,62,75]. Previous medications exist to increase cortisol, such as medications commonly used to treat Addison's disease or psychotropic drugs, though more research in an AUD specific population and an abstinence context would be needed [76,77]. While psychotherapy often focuses on lowering feelings of stress, development of novel coping mechanisms for stress may help a patient counteract lower glucocorticoid levels, where exercise has been shown to even raise them [78,79]. Such evidence highlights the importance of HPA axis functioning in recovery and warrants further research into ways to ameliorate dysfunction whether pharmacologically or psychotherapeutically.

Dysfunction of the HPA axis has been previously shown to have been caused by DNA methylation, and in the context of alcohol use, specifically on the FKBP5 gene [80,81]. While previous research suggests FKBP5 may not be the underlying mechanism for lower glucocorticoid levels in early abstinence, research on the offspring of AUD patients indicates there are heritable alterations in HPA axis functioning, in the form of increased glucocorticoid production in response to stress [82–84]. Interestingly, one study found that these HPA axis alterations were normalised by the ingestion of alcohol [84]. This puts forward the idea of a systemic vulnerability to alcohols effects. Other studies have created a gene-environment hypothesis, where a combination of an individual's genetic makeup, specifically in the HPA axis, and environment can lead to a high risk of addictive behaviour [85]. A combination of inherited methylation in a gene other than FKBP5, pre-existing alterations of the HPA axis, or genetic vulnerabilities to addiction may combine to contribute to HPA axis hypoactivity during early abstinence. As this review found a normalisation of HPA axis activity following 6 months of abstinence, the theory that there is an ever-present genetic alteration in the HPA axis does not seem to stand up against the previous research. Further investigation is needed to solidly make that conclusion and identify the underlying mechanisms of HPA axis hypoactivity in AUD and the nature of alcohol reactivity in the offspring. Despite this, a benefit of this knowledge is that examination of family medical history may help inform patients about their risk of addictive behaviour, hopefully leading to less risk of AUD [85].

This study excluded studies where a significant number of participants with psychiatric co-morbidities that would have their own effect on HPA axis activity, as it aimed to solely examine AUDs effect. While this was done to reduce confoundment, a large portion of AUD patients do have a co-morbid psychiatric disorder [86,87]. While research into the HPA axis activity of said populations is necessary, it presents a challenge in determining if any hypo- or hyperactivity is due to alcohol use or a co-morbid psychiatric disorder. While more dated research suggests that alcohol has a similar biochemical effect in said populations and the results of the current review may be applicable to a co-morbid population, many recent studies aim to reduce confoundment by eliminating psychiatric diagnoses or AUD among participants, such as in the research presented by the current review [48,50]. Researching dual-diagnosis psychiatric disorder and AUD would open the avenue for up-to-date approaches to these populations, enabling them to get the most suitable treatment. Considering this, any pharmacological interventions would have to be tested and made cautiously due to the underlying neurochemical differences and pre-existing medications in said population. Interestingly, the commonly used SSRI sertraline has been shown to raise cortisol levels, which may be of benefit in an individual with co-morbid depression and AUD [88].

The current review presented several limitations. High heterogeneity was present in both baseline cortisol and ACTH levels analyses and low to moderate heterogeneity in stress response analyses. High heterogeneity means that the results must be taken with caution. Several factors have been shown to alter cortisol and ACTH levels, increasing heterogeneity, such as the time of day the biomarkers were assessed, the sex of the participants, the experimental environment and interior design, or even the demeanour or attractiveness of the researchers [89,90]. Heterogeneity may have come from the different array of stressors used. Physical, psychological, and pharmacological stressors can vary in the degree to which they exert their effects on the HPA axis, where pharmacological stressors often produce a dose-dependent, higher biomarker response [15–17]. Psychological stressors can increase internal variability, as different participants are more receptive to arithmetic or public speaking tasks [15]. Concerning physical stressors, other participants may be more acclimated to exercise [91]. None of the studies indicated whether participants were undergoing psychotherapeutic treatment, and therefore heterogeneity may have stemmed from differences in the presence or efficacies of different talk-therapies [6]. Future inclusion of a description of the detox program may help isolate different treatment approaches and their respective effects on HPA axis functioning. While heterogeneity can affect the relevance of the results,

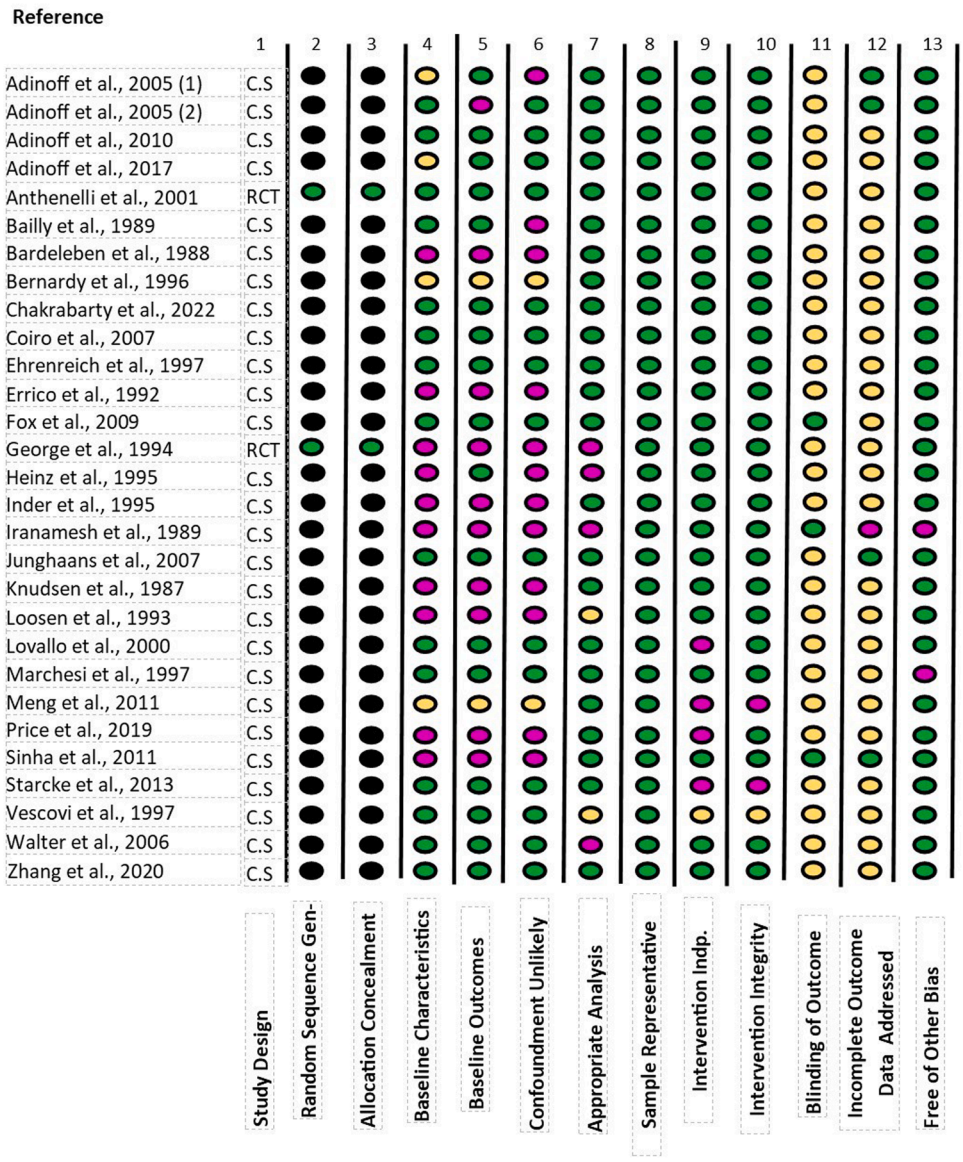

Fig. 13. Risk of Bias Early Abstinence AUD Studies
This infographic shows the risk of bias found in each study for this analysis. Categories of bias are detailed horizontally below. Risk was analysed using Cochrane Collaboration tool modified by Cochrane EPOC and Arditi et al. (2016) to expand its scope to non-randomised studies (Fig. 13). Green denotes low risk of bias, red-high risk, and yellow- unclear risk. Where C.S = Comparative Study. R.C.T. = Randomised Control Trial. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

no significant differences in HPA axis response were found between stressor types in the current review. Studies examining long-term abstinence may contain unintended selection bias whereby only those with recovered or originally relatively unaltered HPA axis functioning had not relapsed, and therefore recovery of said functioning cannot be determined. As most early abstinence studies did not follow up with their participants to assess links between HPA axis functioning and relapse rates, a crucial opportunity to examine potential recovery in the HPA axis or distinguish whether levels of said functioning are predictive of a relapse was missed. Future research with greater methodological consistency and reduced risk of bias is needed to establish a clear consensus on the functioning of the HPA axis in AUD.

A significant limitation of the current review was the demographics of the samples used in the literature. The majority of studies included male identifying participants only. Previous research on sex differences in HPA axis functioning suggests that there is a notable contrast been male and female identifying participants [92,93]. Research on lay female identifying participants' HPA axis suggests that it produces faster and higher levels of glucocorticoids in response to a pharmacological stressor, while no differences were found in response to a psychological or physical stressor [92,93]. This difference may be due to interactions between oestrogen and the serotonin system. Serotonin has been shown to have a stimulatory effect on the HPA axis, which is mediated by the 5-HT1a receptor. In male rats who had this receptor antagonised, there was an increased response to stress [94]. Oestrogen has been shown to decrease the functioning of the 5-HT1a receptor, enabling a higher stimulatory effect of serotonin on the HPA axis [95–97]. In the context of AUD, female identifying participants were physiologically less likely to respond to stress signals, and had less resting plasma ACTH [33,35]. Whilst individuals who identify as female are less likely to be diagnosed with AUD, they represent a major demographic and continuing to only study male identifying participants will reduce the advancement of AUD treatment [98].

Research examining racial differences in HPA axis functioning has revealed there may be differences between certain groups. Using the terminology in the original studies, black men with AUD had a greater cortisol response to stress compared to white men, as well as lower resting glucocorticoids [32,59]. A similar effect is seen in healthy female identifying participants [92,93]. Despite this, another study found that healthy white men had an increased cortisol response to stress [99,100]. These differences may be due to a combination of genetic and societal factors [85]. A previous review of 27 studies on HPA axis activity in minorities found that HPA axis functioning was altered (either increased or decreased), and that this was associated with the participants'

Table 4
Summary table of each article included under the "Long Term Abstinent" section.

Reference	n T	n C	Age M + SD	Gender %	Race	Length of abstinence	Method of Control	Intervention Method	HPA axis measurements	**Summary**
Adinoff et al., 1990 [65]	9	15	53 (11)	male	n/a	1 week, 3 weeks, 3 weeks to 6 months, 6 months +	healthy	OCRH	cortisol, corticotropin	AUD groups corticotropin response to OCRH blunted compared to controls up to 6 months, where the impairment was less noticeable.
Munro et al., 2005 [66]	18	23	43 (6)	male	72% white	Mean of 3.5 (SD = 5.7) years	social drinkers	TSST	acth cortisol prolactin	No difference in response to stress in controls and AUD
Stalder et al., 2010 [67]	25	20	45.6 (8.2)	76:24 M:F	n/a	14 weeks	Healthy	N/A	Hair cortisol	Withdrawal AUD had higher hair cortisol, Abstinent and Controls had no significant differences
Starcke et al., 2013 [29]	31	20	44.39 (8.79)	male	n/a	2 weeks-24 months	healthy	tsst	Salivary cortisol, heart rate, and skin conductance levels	Abstinent AUD had comparable cortisol response to controls, actively drinking AUD had a higher cortisol response. Duration of abstinence was positively correlated with cortisol response in abstinent AUD
Umhau et al., 2001	20	19	n/a	male	n/a	>6 months	healthy	2 deoxyglucose	blood glucose	AUD group had a significant blunted blood glucose response
Walter et al., 2006 [62]	46	26	42 (9.7)	74:26	n/a	Monitored up to 1 year	healthy	n/a	cortisol	Lower cortisol in abstainers compared to relapsers

Summary of studies included in the early abstinence section. nT = n of AUD group. nC = n of control group. OCRH = Ovine Corticotropin Releasing Hormone. TSST = Trier Social Stress Task.

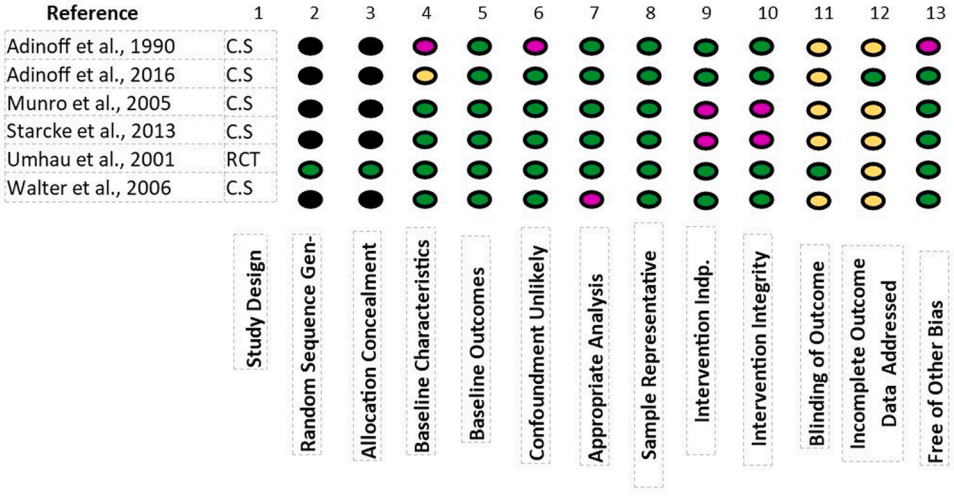

Fig. 14. Risk of Bias in Late Abstinence in AUD Studies
This infographic shows the risk of bias found in each study for this analysis. Categories of bias are detailed horizontally below. Risk was analysed using Cochrane Collaboration tool modified by Cochrane EPOC and Arditi et al. (2016) to expand its scope to non-randomised studies (Fig. 14). Green denotes low risk of bias, red-high risk, and yellow- unclear risk. Where C.S = Comparative Study. R.C.T. = Randomised Control Trial. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

perceived levels of discrimination [101]. Other life experiences like early childhood trauma or the development of mental illness can also lead alteration in HPA axis activity [102–104]. These experiences are often interlinked with societal inequality, disproportionately affecting minorities [105]. A previous review on whether there is a direct link between early-adversity and HPA axis functioning deemed the link inconclusive, requiring further research [106]. Due to the complicated relationship at play between the above factors, further research into HPA axis functioning in AUD among all possible populations is needed.

The current review suggests that HPA dysfunction occurs throughout all stages of AUD, after abstinence following an oscillation from high to low to normalisation. As stress is a major contributor to relapse, and the HPA axis plays a large role in the stress response, this opens opportunities to further dissect the current results in future research, pinpointing underlying mechanisms, examining minority populations, and investigating pharmacological or psychotherapeutic treatments. Increased longitudinal research is needed to examine early and sustained abstinence to isolate the functioning of the HPA axis as a significant contributor to treatment outcomes. Whereby said functioning could be considered as biological recovery capital and improving it could be advantageous to sustainable recovery outcomes. Overall, HPA axis functioning is altered in all stages of AUD, where further research could improve patient wellbeing and recovery outcomes.

5. Outlook

HPA axis functionality in AUD presents a valuable opportunity to examine the physiology of the interwoven relationship between stress and chronic alcohol consumption. Through this examination, novel pharmacological targets can be identified that may ameliorate the high relapse rates currently present in AUD. Future research should look to further dissect current conclusions. If we know that the HPA axis

response to stress is blunted in early abstinence in AUD, we should focus on figuring out how this dysfunctionality occurs- is it temporary allostatic adaption, organic damage, or a previously dormant genetic predisposition? Discovering which areas of the HPA axis are causing this dysfunction may also provide further contextualisation for pharmacological intervention. Examination of long-term abstinence and the associated neuronal recovery or lack thereof is an understudied area. Further research in this area and its conclusions could provide valuable optimism to AUD patients, or help clinicians and psychotherapists prepare patients with specific symptom management for long-term neurological consequences if present. Overall, the outlook for research into the HPA axis in AUD is promising, with many areas and avenues to take that can provide real benefit to patients experiencing an often treatment-resistant disorder.

Author Contributions

ND & JI conceptualized the study, ND & JI designed the methodology. ND & JI validated the studies independently ND carried out data curation. ND carried out writing and visualisation. JI reviewed and edited.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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