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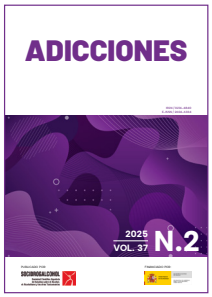

ORIGINAL

Effects of a binge drinking history and an acute episode on the stress response in adolescents: An experimental gender perspective

Efectos de una historia de binge drinking *y de un episodio agudo sobre la respuesta al estrés en adolescentes: Una perspectiva de género experimental*

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Abstract

Adolescence is a period of vulnerability for alcohol binge drinking (BD), being this consumption pattern very common among adolescents and young adults. Furthermore, there is a lack of experimental studies evaluating the effects of alcohol in adolescent population of both sexes. The aim of this study was to evaluate the effects of having a BD consumption history and an acute BD episode on the stress response in male and female adolescents. Participants were 150 adolescents (75 females and 75 males). According to their drinking pattern, subjects were assigned to one of three experimental conditions in each sex: Refrainers-Control (R-Co), Binge Drinkers-Control (BD-Co) or Binge Drinkers-Alcohol (BD-A). After treatment, their stress response was measured throughout the following parameters: cortisol, systolic and diastolic blood pressure (SBP and DBP), heart rate (HR) and perceived stress (PS). A decrease of cortisol levels over time was observed in the present study. Also, the experimental condition was significant for HR, showing the BD-A group higher HR than any other group. Regardless of the experimental condition, sex differences were evident in several measures, males showing higher cortisol levels and higher SBP than females, while females obtaining higher PS scores than males. In conclusion, both the decrease of cortisol levels over time and the gender differences in cortisol, SBP and PS strengthen our previous results, using gender as an experimental variable. Furthermore, an acute BD episode in binge drinkers increases HR without affecting the other stress variables, providing a new finding in this field of research.

Keywords: binge drinking, alcohol, stress response, adolescents, gender

Resumen

La adolescencia es un periodo de vulnerabilidad al binge drinking (BD), siendo este patrón de consumo muy común entre adolescentes y adultos jóvenes. Además, faltan estudios experimentales que evalúen los efectos del alcohol en población adolescente de ambos sexos. El objetivo de este estudio fue evaluar los efectos de tener una historia de BD y de un episodio agudo BD sobre la respuesta al estrés en hombres y mujeres adolescentes. Participaron 150 adolescentes (75 mujeres y 75 hombres). Según su patrón de consumo de alcohol, los sujetos fueron asignados a una de tres condiciones experimentales en cada sexo: Abstemios-Control (A-Co), Binge Drinkers-Control (BD-Co) o Binge Drinkers-Alcohol (BD-A). Después del tratamiento, se midió su respuesta de estrés a través de los siguientes parámetros: cortisol, presión arterial sistólica y diastólica (PAS y PAD), frecuencia cardíaca (FC) y estrés percibido (EP). En el presente estudio se observó una disminución de los niveles de cortisol a lo largo del tiempo. Asimismo, la condición experimental fue significativa para la FC, mostrando el grupo BD-A una FC más alta que cualquier otro grupo. Independientemente de la condición experimental, las diferencias de sexo fueron evidentes en varias medidas: los hombres mostraron niveles más altos de cortisol y PAS más altas que las mujeres, mientras que las mujeres obtuvieron puntuaciones de EP más altas que los hombres. En conclusión, tanto la disminución de los niveles de cortisol a lo largo del tiempo como las diferencias de género en cortisol, PAS y EP refuerzan nuestros resultados previos, utilizando el género como variable experimental. Además, un episodio agudo de BD en con historia BD aumenta la FC sin afectar a las demás variables de estrés, lo que supone un nuevo hallazgo en este campo de investigación.

Palabras clave: consumo intensivo de alcohol, alcohol, respuesta al estrés, adolescentes, género

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Adolescence is a particularly vulnerable neurodevelopmental period for alcohol binge drinking (BD) (Jones & Nagel, 2019), which is associated with accelerated decreases in gray matter and attenuated increases in white matter volume (Lees et al., 2020). Adolescent-specific sensitivity to alcohol's effects may interact with a propensity for greater risk-taking behaviour and peer social environment in contributing to risk for BD during this developmental period (Antón-Toro et al., 2021). The National Institute on Alcohol Abuse and Alcoholism (NIAAA) (2004) has defined BD as a drinking pattern in which the blood alcohol concentration (BAC) rises to 0.8 g/L or higher. This consumption pattern is characterised by the ingestion of large amounts of alcohol in a short period of time (two hours), followed by a period of abstinence that can vary from one week to a month (Parada et al., 2011; Vinader-Caerols & Monleón, 2019); with the intermittency between intakes and the maintenance of this pattern over time being highly influential variables (Petit et al., 2014). The prevalence of BD in Spain is high: 27.9% of Spanish students from 14 to 18 years old admitted to this type of consumption in the previous 30 days at the time of completing the survey (Observatorio Español de las Drogas y las Adicciones, 2021).

Adolescent BD has been associated with multiple acute health damages and long-term adverse effects on stress response (Chung et al., 2018; Hagan et al., 2019). The study of the interactions between alcohol consumption and the physiological response to stress has focused on the functionality of the Hypothalamic-Pituitary-Adrenal (HPA) axis (e.g. Hagan et al., 2019; Weera & Gilpin, 2019) and the main stress hormone, cortisol (Fogelman & Canli, 2018; Price et al., 2019). The HPA axis is a well-known physiological response system that is activated in stressful situations, initiating a hormonal cascade that results in accelerated secretion of cortisol. Activation of the HPA axis triggers the hypothalamus to release corticotropin-releasing hormone (CRH), which in turn leads to the release of adrenocorticotropin hormone (ACTH) from the pituitary, and finally glucocorticoids, including cortisol, from the adrenal glands (Fogelman & Canli, 2018; Hagan et al., 2019). A typical cortisol response to stress involves a period of reactivity (a rise in cortisol levels that are sustained for an appropriate period to meet the demands of the situation) and a period of recovery (a decline in cortisol levels back to baseline) (Chu et al., 2021). Dysregulation of this typical response is observed when cortisol reactivity continues when no longer needed or, conversely, is not of sufficient magnitude to meet the demands of the situation (McEwen, 2007).

In a previous study (Ramírez-Piña, et al., 2021) we measured the stress response throughout several psychophysiological parameters such as cortisol, systolic and diastolic blood pressure (SBP and DBP) and heart rate (HR), as well as psychological parameters such as perceived stress (PS). In line with the literature, we observed that the normal response of the adolescent HPA axis, to a risk-alcohol dose consumption, is an increase in cortisol levels in females, as well as HR in both sexes. In addition, having a history of BD, maintained for at least one year, is associated with HPA axis dysregulation, which is manifested by higher values of cortisol (independently of sex), SBP in male and HR in female healthy adolescents. Several studies have reported that cortisol facilitates an increase in cardiovascular activity, raising heart rate and blood pressure (e.g. Dedovic et al., 2009; Hagan et al., 2019; Ulrich-Lai & Herman, 2009). Studies assessing the relationship between acute alcohol consumption and a history of BD have associated BACs below 0.8 g/l in consumers with a history of low to moderate alcohol consumption (non-binge drinkers) with higher HPA axis response (higher blood cortisol levels) (e.g. Price et al., 2019). Likewise, lower HPA axis response has been linked to these BACs when subjects are binge drinkers (Allen et al., 2011; Blaine & Sinha, 2017). However, as far as we know, there is not information about male and female adolescents' stress response with a BD history under the influence of a BD dose.

It is evident that BD can damage the adolescent brain and that more and more attention is being paid to the sex-dependent effects (e.g. Vinader-Caerols & Monleón, 2021). However, there are still important gaps in our understanding of the effects of BD on the female brain. Experimental results of research performed with only one sex are sometimes extrapolated to both sexes. Sex should be considered an important biological variable in basic and preclinical research before results are applied to both men and women (Lee, 2018). It is crucial that studies address the sex-dependent effects of BD and include both sexes (Cortez et al., 2020). Our previous studies with a gender perspective have assessed the effects of DB on cognitive variables, such as different types of memory (e.g. Vinader-Caerols et al., 2017a), as well as the stress response across the same psychophysiological and psychological parameters assessed here (Ramírez-Piña et al., 2021). Given the scarcity of experimental studies with a biological gender perspective on this topic, the gap to be filled by the present work is to investigate the effects of an acute BD dose (0.9 g of alcohol/kg of body weight for men and 0.8 g of alcohol/kg of body weight for women) according to gender. Thus, the aim of this research is to experimentally evaluate the effects of having a BD consumption history and an acute BD episode on the stress response of adolescent men and women.

Method

Participants

One hundred and fifty healthy 18-19-year-old adolescent students (75 females and 75 males) at the University of Valencia (Spain) participated in this study. The volunteers

were recruited by means of a self-report of their alcohol consumption habits and general health. This self-report was administered to students from several degrees in their classrooms at the beginning of the academic year. Participants were classified as refrainers if they had never previously consumed alcoholic drinks; or as consumers of alcohol with a BD pattern according to the NIAAA criteria for Spain (López-Caneda et al., 2014) if they had drunk six or more SDUs (standard drink unit) of distilled spirits (alcohol content ≥ 40% vol.) in a row in the case of males and five or more SDUs in a row in the case of females on a minimum of three occasions per month during the previous 12 months, according to the BD habits referred by the subjects (Vinader-Caerols & Monleón, 2019).

Strict inclusion/exclusion criteria were applied to the sample selection. The following inclusion criteria were applied: age 18–19 years old; a healthy body mass index (mean of 22.88 ± 0.30 in males and 21.44 ± 0.23 in females) and good health (reporting a state of emotional and physical well-being, without major medical problems or diagnosed pathology). The exclusion criteria were as follows: taking medication; a history of mental disorders (diagnosed by a health professional according to DSM criteria); an irregular sleep pattern (non-restorative sleep and/or an irregular schedule); having consumed, even sporadically, any drug (apart from alcohol or tobacco) or having a history of substance abuse, including caffeine (our criterion: > 2 stimulant drinks/day), tobacco (our criterion: > 10 cigarettes/day) or alcohol; having suffered an intense stressful event within a year of the experiment and having first degree relatives with history of alcoholism. A telephone interview of approximately 15 min was conducted with each subject to confirm the information provided in the self-report and to arrange the date and time of the test. Before the experimental session, the data were again validated. Thus, the chronology related to the subjects' information included 3 steps: 1) self-reported, 2) telephone interview, and 3) experimental session. Participants were told to follow their normal sleep pattern and their usual meal routine and have lunch at one hour before the experimental session.

The data of the female participants' menstrual cycle were registered in the self-report and telephone interview, and the subject's cycle phase was considered in the test to counterbalance this variable in each group, checking that the number of females in each cycle phase was similar in every group. No females taking contraceptives were included in the study.

Tests and Apparatus

Cortisol was registered as the main biochemical marker of the stress response. The activity of the HPA-axis was measured by analysing salivary cortisol levels using a competitive solid phase radioimmunoassay test. Salivette® was employed as a hygienic method of collecting saliva by means of a synthetic swab specially designed for cortisol determination. Three saliva samples were collected from all our subjects: one prior to consumption (COR0'), a second 20 min (COR20') after drink intake, and a third 50 min (COR50') after intake, considering that high levels of BAC are observed at the 20-50 min interval (Vinader-Caerols et al., 2017a; Vinader-Caerols et al., 2017b). The samples were frozen at −18°C until they were sent to the laboratory for analysis by a competitive solid phase radioimmunoassay (tube coated) with the commercial kit Coat-A-Count C (DPC, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). Assay sensitivity was 0.5 ng/mL (1.38 nmol/L). Data were expressed in nanomolar units (nmol/L). All the samples from each participant were analysed in the same trial; the within and inter assay variation coefficients were all below 5.5%. Salivary cortisol levels were determined at Echevarne Analysis Laboratory, Valencia (Spain).

Other parameters of the psychophysiological response (SBP, DBP and HR) and the psychological response (PS) were also recorded. A digital automatic blood pressure monitor (M10-IT, OMRON, Spain) was employed to measure SBP, DBP and HR in all the subjects.

Participants were assessed by means of the Perceived Stress Scale (PSS14) (Cohen et al., 1983), a standardized self-report questionnaire designed to measure stress and which evaluates how unpredictable, uncontrollable and overloaded respondents consider their lives to have been in the previous month (for more details, see Ramírez-Piña et al., 2021). The internal consistency of this scale was calculated for our data, obtaining a Cronbach's alfa coefficient of 0.315 for females and 0.352 for males.

The Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al., 1993) was employed to measure a problematic use of alcohol among the subjects (for more details, see Ramírez-Piña et al., 2021). The internal consistency of this scale was calculated for our data, obtaining a Cronbach's alfa coefficient of 0.636 for females and 0.589 for males.

An alcoholmeter (AlcoQuant® 6020, EnviteCd, Germany) was employed to measure BAC of each participant before and after (20 min and 50 min) intake of a beverage (control drink or alcoholic drink).

Procedure

The experimental procedure was approved by the Research Ethics Committee of the University of Valencia (number: H1485172642673 and 1638361; approved in 2017 and 2022 respectively) and was in accordance with the Helsinki Agreement. The study was carried out by recreating the conditions under which BD occurs: acute consumption of a BD dose (0.9 g of alcohol/kg of body weight for men and 0.8 g of alcohol/kg of body weight for women) in a short time (20 min). All participants pro-

vided written informed consent to take part in the study. According to their drinking pattern (refrainers and binge drinkers) and the beverage received (control drink or alcoholic drink), subjects were assigned to one of three experimental conditions in each sex: Refrainers-Control (R-Co) (refrainers-refreshment intake), Binge Drinkers-Control (BD-Co) (subjects with a history of BD-refreshment intake) or Binge Drinkers-Alcohol (BD-A) (subjects with a history of BD-alcoholic drink intake with BD dose); giving rise to six experimental groups (n = 25 per group). It is important to point out that, for ethical reasons, BD dose alcoholic beverages were not administered to subjects without BD consumption history.

Participants were instructed to abstain from any intake of alcohol, caffeinated beverages, drugs or medication and strenuous exercise for 24 h before the experimental session, and to refrain from eating and smoking at least 1 h prior to the session. At the beginning of the session BAC was measured in all participants of study using the alcoholmeter to ensure that they had not consumed alcohol. None of the subjects was found to be alcohol-dependent by the AUDIT test. All the participants provided a first saliva sample for cortisol determination (COR0') just before the intake. Each subject received a flavoured refreshment (lime, orange or cola, without caffeine) contained in cans of 330 ml, alone or mixed (according to the experimental group) with distilled drinks with an alcohol content of 40% vol. (vodka or gin) in a BD dose according to their body weight (0.9 g of alcohol/kg for males; 0.8 g of alcohol/kg for females). The subjects were instructed to consume their drink within a period of 20 min, during which they ate a light snack (the same for all participants) and the beverages were always consumed in the presence of a research assistant. After finishing the drink, all subjects rinsed their mouths with water and underwent a 20-min waiting period.

After this 20-min waiting interval, the second saliva sample was collected for cortisol determination (COR20') and BAC was measured in all the subjects. Subsequently, we measured SBP, DBP and HR (all were recorded 3 times and their average calculated) and perception of stress by means of the PSS14. Finally, the participants provided a third saliva sample (COR50') after which BAC was measured once again. The duration of the experimental protocol was around 2 hours, and all measurements were performed between 16:00h and 18:00h, during descendent BAC. Members of the groups that received alcohol remained on the premises until their alcohol concentration dropped to legal limits for driving.

The BAC was 0.00 g/L before the alcoholic drink, and 0.76 ± 0.2 g/L after drinking for females and males (no significant differences were found between the BACs of men and women).

Statistical Analyses

Data were subjected to parametric analyses after confirming they met the criteria for normality and homogeneity of variances. Statistically significant differences were established at $p < 0.05$ and the statistical power was calculated using alpha = 0.05. A repeated measures ANOVA was performed for cortisol COR20' and COR50' (COR0' measure was not included in this ANOVA because the first register of cortisol was taken before treatment –alcohol or control drink– was administered). A one-way ANOVA was performed for each measure of stress response (SBP, DBP, HR and PS). Each analysis included the between-subject factors 'Experimental Condition' (Refrainers-Control, Binge Drinkers-Control and Binge Drinkers-Alcohol) and 'Sex' (Males and Females) as independent variables. 'Register' (COR20' and COR50') was also included as intra-subject factor in the repeated measures ANOVA for cortisol. When any interaction between these factors was statistically significant, pairwise comparisons were carried out by Student's t. Cohen's d was the statistical measure of effect size in these analyses. All correlations of stress response measures registered at 20 minutes of treatment were explored. All analyses were performed using the 'SPSS' Statistics software package, version 28 for Windows (IBM, 2021).

Results

A summary of the socio-demographic characteristics and consumption habits for the study population is presented in Table 1.

Cortisol (COR0', COR20' and COR50')

In COR0', the one-way ANOVA showed that neither the factor Experimental Condition ($F_{(2,52)} = 5.76, p = 0.251$) nor the factor Sex ($F_{(1,52)} = 1.35, p = 0.452$) were statistically significant. Similarly, the interaction Experimental Condition X Sex was not statistically significant ($F_{(2,52)} = 0.308, p = 0.581$).

COR20' and COR50': The factor Experimental Condition was not statistically significant ($F_{(2,78)} = 2.029, p = 0.138$). However, the factor Sex was statistically significant ($F_{(1,78)} = 8.588, p = 0.004$), with males showing higher cortisol levels than females [$t(82) = 2.85, p = 0.006$; Cohen's $d = 0.622$] (see Table 2). The interaction Experimental Condition X Sex was not statistically significant ($F_{(2,78)} = 15.742, p = 0.104$).

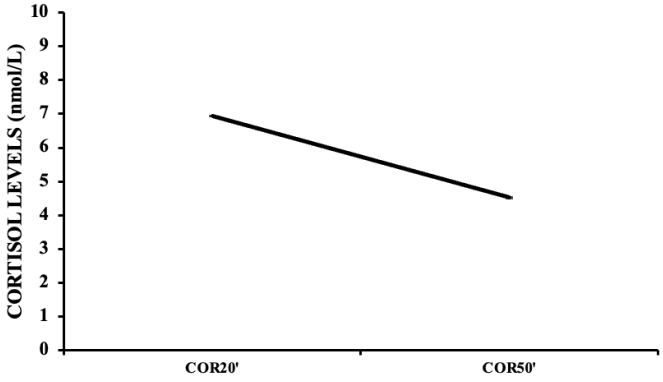
The repeated measures ANOVA revealed that the intra-subject factor Register was statistically significant ($F_{(1,78)} = 45.011, p = 0.001$), showing a decrease in COR50' in comparison to COR20' [$t(83) = 6.693, p < 0.001$; Cohen's $d = 0.730$] (Figure 1).

Table 1
Summary of the socio-demographic characteristics and consumption habits for the study population

	Experimental Condition					
	Refrainers-Control (n = 50)		Binge Drinkers-Control (n = 50)		Binge Drinkers-Alcohol (0.76 ± 0.20 g/L) (n = 50)	
	Females (n = 25)	Males (n = 25)	Females (n = 25)	Males (n = 25)	Females (n = 25)	Males (n = 25)
Age at first alcohol consumption	NA	NA	14.4 ± 0.19	14.68 ± 0.18	14.8 ± 0.25	14.64 ± 0.31
Mean number of BD episodes per month	NA	NA	2.44 ± 0.14	2.64 ± 0.18	3 ± 0.17	3.48 ± 0.2
Mean number of drinks per occasion	NA	NA	6.16 ± 0.41	6.6 ± 0.35	5.84 ± 0.29	7.2 ± 0.21
Mean duration of BD pattern (months) until the beginning of test	NA	NA	11.24 ± 0.52	11.8 ± 0.2	12.36 ± 1.03	13.72 ± 1.16
Smoker: no / yes	25/0	25/0	20/5	21/4	22/3	20/5
Stressful event in the last year: no / yes	20/5	20/5	23/2	23/2	13/12	14/11
Nervous: no / yes	20/5	21/4	22/3	23/2	23/2	23/2
Good Sleep: no / yes	2/23	3/22	3/22	2/23	1/24	2/23
Sports activity: no / yes	23/2	21/4	25/0	19/6	10/15	8/17

Note. The results are expressed as number or mean ± SEM, according to sex, for Refrainers-Control, Binge Drinkers-Control and Binge Drinkers-Alcohol. NA: not applicable.

Figure 1
Salivary cortisol concentrations mean at 20 minutes (COR20') and 50 minutes (COR50') after treatment (females and males together). ### p < 0.001 vs COR20'



Blood Pressure (SBP and DBP)

SBP: No significant differences were observed for the main factor Experimental Condition ($F_{(2,144)}$ = 0.24, p = 0.787), but the factor Sex was statistically significant ($F_{(1,144)}$ = 67.825, p < 0.001), with males showing higher SBP than females [t(148) = 8.21, p < 0.001; Cohen's d = 1.34] (see Table 2). The interaction Experimental Condition X Sex was not statistically significant ($F_{(2,144)}$ = 2.217, p = 0.113).

DBP: Significant differences were not obtained for the main factors Experimental Condition ($F_{(2,144)}$ = 0.464, p = 0.629) and Sex ($F_{(1,144)}$ = 0.003, p = 0.959), or their interaction Experimental Condition X Sex ($F_{(2,144)}$ = 0.376, p = 0.688).

Heart Rate (HR)

HR was statistically significant for the main factor Experimental Condition ($F_{(2,144)}$ = 12.866, p < 0.001), showing the Binge Drinkers-Alcohol group higher HR than the Refrainers-Control group [t(98) = -4.545, p < 0.001; Cohen's d = 0.909] and the Binge Drinkers-Control group [t(98) = -3.384, p < 0.001; Cohen's d = 0.677] (Figure 2). Neither the main factor Sex ($F_{(1,144)}$ = 0.872, p = 0.352), nor the interaction Experimental Condition X Sex ($F_{(2,144)}$ = 1.411, p = 0.247) were statistically significant.

Perceived Stress (PS)

The results obtained for PS were not statistically significant for the main factor Experimental Condition ($F_{(2,144)}$ = 0.312, p = 0.733), but were for the factor Sex ($F_{(1,144)}$ = 14.419, p < 0.001), with females obtaining higher PS scores than males [t(148) = -3.829, p < 0.001; Cohen's d = 0.625] (see Table 2). The interaction Experimental Condition X Sex was not statistically significant ($F_{(2,144)}$ = 0.483, p = 0.618).

Correlations between measures

Positive correlations 20 min after treatment were detected between the following variables: COR20' and SBP (r = 0.318, p = 0.003), SBP and DBP (r = 0.547, p < 0.001), and DBP and HR (r = 0.262, p = 0.016).

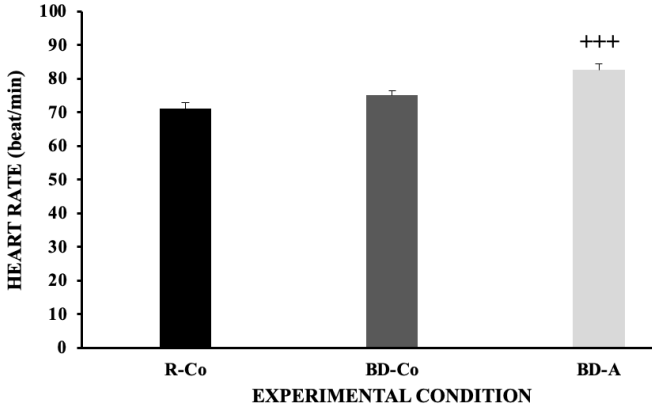
A summary of the stress response variables' scores of the performed experiment is presented in Table 2.

Table 2
Summary of the stress response variables' scores

	Experimental Condition				Gender		
	Refrainers-Control (n = 50) (COR n = 28)	**Binge Drinkers-Control (n = 50) (COR n = 28)**	**Binge Drinkers-Alcohol (0.76 ± 0.20 g/L) (n = 50) (COR n = 28)**	***Statistical Power*[1]**	**Females (n = 75) (COR n = 42)**	**Males (n = 75) (COR n = 42)**	***Statistical Power*[1]**
COR	5.21 ± 0.48	6.59 ± 0.20	5.38 ± 0.48	0.407	4.83 ± 0.47	6.62 ± 0.50 ***	0.825
SBP	112.56 ± 1.86	113.14 ± 2.04	111.62 ± 1.76	0.087	105.00 ± 1.09	119.88 ± 1.44 ***	1.000
DBP	68.22 ± 1.35	69.74 ± 0.98	68.82 ± 0.96	0.125	68.89 ± 0.83	68.96 ± 0.98	0.050
HR	71.10 ± 1.73	75.04 ± 1.26	82.62 ± 1.84 +++	0.997	77.13 ± 1.23	75.37 ± 1.61	0.153
PS	20.26 ± 1.09	21.40 ± 1.15	21.28 ± 1.24	0.099	23.44 ± 0.90	18.52 ± 0.90 ***	0.965

Notes. COR = Salivary cortisol concentrations; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HR = Heart Rate. PS = Perceived Stress.
The results are expressed as mean ± SEM.
[1]The Statistical Power is calculated using alpha = 0.05.
*** $p < 0.005$ ***vs*** females; +++ $p < 0.001$ ***vs*** Refrainers-Control or Binge Drinkers-Alcohol.

Figure 2
Heart Rate (HR) in each experimental condition (males and females together). Values are expressed as means (+SEM). R-Co: Refrainers-Control; BD-Co: Binge Drinkers-Control; BD-A: Binge Drinkers-Alcohol. +++ p < 0.001 vs R-Co or BD-Co



Discussion

The aim of this study was to experimentally evaluate the effects of having a BD consumption history and an acute BD episode on the functionality of the HPA axis (cortisol) and other variables of the stress response (BP, HR, and PS) from a gender perspective in male and female adolescents. The main findings showed a decrease of cortisol levels over time, and that the experimental condition was significant for HR, showing the binge drinkers that received alcohol higher HR than any other group. Furthermore, sex differences were evident in several measures regardless of the experimental condition, males showing higher cortisol levels and higher SBP than females, while females obtaining higher PS scores than males.

The decrease of cortisol levels over time (lower levels of COR50' than COR20') is in line with our previous investigation, where a risk dose of alcohol was administered to male and female adolescents (BAC: 0.38 ± 0.01 g/L) with or without a BD history, showing such a decrease in males and females separately, as well as in both sexes together (Ramírez-Piña et al., 2021). In addition, similarly to that work, we have presently found biological gender differences in cortisol, SBP and PS. In cortisol levels, males showed higher salivary cortisol levels than females. This sex difference is supported by the literature: the typical mean response in males has been shown to range from 200 to 400% with respect to baseline, while changes from 50 to 150% are usually seen in females (Kudielka et al., 2009). The sex difference related to BP has been confirmed in the present study: higher SBP in males than in females. According to previous research, the BP of young females is typically lower than that of young males, even among healthy normotensive people (Joyner et al., 2016). Finally, our female participants also showed higher levels of stress (PS) than males, as reported by other studies (Anbumalar et al., 2017; Michou et al., 2021). These gender differences observed in our studies are baseline: they are not due to the influence of compsumption history, alone or in combination with an acute BD episode, as was the case in the previous study by Ramírez-Piña et al. (2021).

There is a lack of scientific literature evaluating the effects of an acute BD episode on the stress response (cortisol, BP, HR and PS) in BD consumers. In our subjects, cortisol, BP and PS were not affected; these results were similar to those observed with an acute risk dose in binge drinkers. However, an increase in HR was observed with an acute BD episode, which does not occur with a risk dose (Ramírez-Piña et al., 2021). Tolerance would explain the

lack of effect on this measure of stress in BD users at a risk dose (Ramírez-Piña et al., 2021). It may be that when the acute dose is increased to mimic a BD episode, the tolerance to the effects of alcohol on HR in binge drinkers disappears and an increase in this measure is observed. Therefore, tolerance is more sensitive in HR than the other stress measures. Several studies have reported that an acute intake of alcohol, in doses lower than an acute BD episode, increases HR in young adults (e.g. Bau et al., 2011; Vinader-Caerols et al., 2012).

There are few experimental studies on binge drinking in the adolescent population, as ethical and legal aspects limit their research. A strength of the present study is therefore the inclusion of adolescents of both sexes, as they are of legal age, and they can be part of both the experimental control sample and the acute drinking sample in this research. The inclusion of both sexes makes it possible to study gender differences and is more representative of the general population. These differences are important because some are basic physiological differences, and some are differences observed under the influence of alcohol. Both differences should be considered when analysing experimental studies. The fact that our research was conducted by replicating the conditions under which young people typically consume alcohol is also considered a strength.

Among the limitations of this study, it must be mentioned that we measured cortisol levels after treatment, but we did not measure early morning cortisol. Nevertheless, the saliva cortisol samples were within the normal range of basal values (2.76-8.27 nmol/L) at the time they were taken (16:00h-18:00h) (e.g. Kobayashi et al., 2017). Besides, longitudinal studies are necessary in the future in order to study the long-term effects of HPA axis dysregulation.

In conclusion, both the decrease of cortisol levels at 50 min and the gender differences in cortisol, SBP and PS strengthen the previous results obtained by Ramírez-Piña et al. (2021), using gender as an experimental variable. Furthermore, an acute BD episode in binge drinkers increases HR without affecting the other stress variables; this could be because tolerance is more sensitive to HR than the other stress measures. This study provides new insights into the effects of a binge drinking history and an acute BD episode on the stress response in adolescents and may help to develop strategies for implementing more effective prevention programmes from a gender perspective.

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Conflict of interests

The authors declare they have no conflict of interest.

References

Allen, C. D., Lee, S., Koob, G. F. & Rivier, C. (2011). Immediate and prolonged effects of alcohol exposure on the activity of the hypothalamic-pituitary-adrenal axis in adult and adolescent rats. *Brain, Behavior, and Immunity, 25 (Suppl 1),* S50–60. https://doi.org/10.1016/j.bbi.2011.01.016

Anbumalar, C., Dorathy, A. P., Jaswanti, V. P., Priya, D. & Reniangelin, D. (2017). Gender differences in perceived stress levels and coping strategies among college students. *The International Journal of Indian Psychology, 4,* 22–33. https://doi.org/10.25215/0404.103

Antón-Toro, L. F., Bruña R, Suárez-Méndez, I., Correas, A., García-Moreno, L. M. & Maestú, F. (2021). Abnormal organization of inhibitory control functional networks in future binge drinkers. *Drug Alcohol Dependence, 218,* 108401. https://doi.org/10.1016/j.drugalcdep.2020.108401

Bau, P. F., Moraes, R. S., Bau, C. H., Ferlin, E. L., Rosito, G. A. & Fuchs, F. D. (2011). Acute ingestion of alcohol and cardiac autonomic modulation in healthy volunteers. *Alcohol, 45,* 123–129. https://doi.org/10.1016/j.alcohol.2010.08.011

Blaine, S. K. & Sinha, R. (2017). Alcohol, stress, and glucocorticoids: From risk to dependence and relapse in alcohol use disorders. *Neuropharmacology, 122,* 136–147. https://doi.org/10.1016/j.neuropharm.2017.01.037

Chu, B., Marwaha, K., Sanvictores, T. & Ayers, D. (2021). *Physiology, stress reaction*. In StatPearls. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK541120/

Chung, T., Creswell, K. G., Bachrach, R., Clark, D. B. & Martin, C. S. (2018). Adolescent Binge Drinking. *Alcohol Research, 39,* 5–15.

Cohen, S., Kamarck, T. & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24,* 385–396. https://doi.org/10.2307/2136404

Cortez, I., Rodgers, S. P., Kosten, T. A. & Leasure, J. L. (2020). Sex and age effects on neurobehavioral toxicity induced by binge alcohol. *Brain Plasticity, 6,* 5–25. https://doi.org/10.3233/BPL-190094

Dedovic, K., Duchesne, A., Andrews, J., Engert, V. & Pruessner, J.C. (2009). The brain and the stress axis: The neural correlates of cortisol regulation in response to stress. *Neuroimage, 47,* 864–71. https://doi.org/10.1016/j.neuroimage.2009.05.074

Fogelman, N. & Canli, T. (2018). Early life stress and cortisol: A meta-analysis. *Hormones and Behavior, 98,* 63–76. https://doi.org/10.1016/j.yhbeh.2017.12.014

Hagan, M. J., Modecki, K., Tan, L. M., Luecken, L., Wolchik, S. & Sandler, I. (2019). Binge drinking in adolescence predicts an atypical cortisol stress response in young adulthood. *Psychoneuroendocrinology, 100,* 137–144. https://doi.org/10.1016/j.psyneuen.2018.10.002

IBM Corp Released. (2021). *IBM SPSS Statistics for Windows, Version 28.0.* Armonk, New York: IBM Corp.

Jones, S. A. & Nagel, B. J. (2019). Altered frontostriatal white matter microstructure is associated with familial alcoholism and future binge drinking in adolescence. *Neuropsychopharmacology, 44,* 1076–1083. https://doi.org/10.1038/s41386-019-0315-x

Joyner, M. J., Wallin, B. G. & Charkoudian, N. (2016). Sex differences and blood pressure regulation in humans. *Experimental Physiology*, *101*, 349–355. https://doi.org/10.1113/EP085146

Kobayashi, H., Song, C., Ikei, H., Park, B. J., Kagawa, T. & Miyazaki, Y. (2017). Diurnal changes in distribution characteristics of salivary cortisol and immunoglobulin A concentrations. *International Journal of Environmental Research and Public Health,14,* 987. https://doi.org/10.3390/ijerph14090987

Kudielka, B. M., Hellhammer, D. H. & Wüst, S. (2009). Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge. *Psychoneuroendocrinology, 34,* 2–18. https://doi.org/10.1016/j.psyneuen.2008.10.004

Lee, S. K. (2018). Sex as an important biological variable in biomedical research. *BMB Reports, 51,* 167–173. https://doi.org/10.5483/bmbrep.2018.51.4.034

Lees, B., Meredith, L. R., Kirkland, A. E., Bryant, B. E. & Squeglia, L. M. (2020). Effect of alcohol use on the adolescent brain and behavior. *Pharmacology Biochemistry and Behavior, 192,* 172906. https://doi.org/10.1016/j.pbb.2020.172906

López-Caneda, E., Mota, N., Crego, A., Velasquez, T., Corral, M., Rodríguez Holguín, S. & Cadaveira, F. (2014). Neurocognitive anomalies associated with the binge drinking pattern of alcohol consumption in adolescents and young people: A review. *Adicciones, 26,* 334–359. https://doi.org/10.20882/adicciones.39

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews*, *87*, 873–904. https://doi.org/10.1152/physrev.00041.2006

Michou, M., Panagiotakos, D. B., Lionis, C. & Costarelli, V. (2021). Low health literacy and perceived stress in adults: is there a link? *Central European Journal of Public Health*, *29*, 195–200. https://doi.org/10.21101/cejph.a6692

National Institute on Alcohol Abuse and Alcoholism (NIAAA) (2004). The National Institute on Alcohol Abuse and Alcoholism council aproves definition of binge drinking. *NIAAA Newsletter, 3,* 3.

Observatorio Español de las Drogas y las Adicciones (OEDA) (2021). *Encuesta sobre Uso de Drogas en Enseñanzas Secundarias en España (ESTUDES) 1994-2021.* Madrid: Ministerio de Sanidad, Consumo y Bienestar Social.

Parada, M., Corral, M., Caamaño-Isorna, F., Mota, N., Crego, A., Rodríguez Holguín, S. & Cadaveira, F. (2011). Definición del concepto de consumo intensivo de alcohol adolescente (binge drinking). *Adicciones, 23,* 53-63. https://doi.org/10.20882/adicciones.167

Petit, G., Maurage, P., Kornreich, C., Verbanck, P. & Campanella, S. (2014). Binge drinking in adolescents: A review of neurophysiological and neuroimaging research. *Alcohol & Alcoholism, 49,* 198–206. https://doi.org/10.1093/alcalc/agt172

Price, J. L., Frazier, I. R., Lewis, B., Walker, R., Javors, M. A., Nixon, S. J. & Adinoff, B. (2019). Differences in pituitary-adrenal reactivity in black and white men with and without alcohol use disorder. *Psychoneuroendocrinology, 100,* 180–189. https://doi.org/10.1016/j.psyneuen.2018.10.004

Ramírez-Piña, M., Monleón, S. & Vinader-Caerols, C. (2021). Hypothalamic-pituitary-adrenal axis dysregulation initiated by a binge drinking pattern, but not by acute alcohol intake, in female and male adolescents. *Adicciones, 35*, 421–432. https://doi.org/10.20882/adicciones.1665

Saunders, J. B., Aasland, O. G., Babor, T. F., de La Fuente, J. R. & Grant, M. (1993). Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. *Addiction, 88,* 791–804. https://doi.org/10.1111/j.1360-0443.1993.tb02093.x

Ulrich-Lai, Y. M. & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. *Nature Reviews Neuroscience, 10,* 397–409. https://doi.org/10.1038/nrn2647

Vinader-Caerols, C. & Monleón, S. (2019). Binge drinking and memory in adolescents and young adults. In S. Palermo & M. Bartoli (Eds.), *Inhibitory Control Training-A Multidisciplinary Approach* (pp.1–19). IntechOpen. http://dx.doi.org/10.5772/intechopen.88485

Vinader-Caerols, C. & Monleón, S. (2021). Binge drinking, alone or with cannabis, during adolescence triggers different effects on immediate visual memory in men and women. *Frontiers in Psychiatry, 12,* 797221. https://doi.org/10.3389/fpsyt.2021.797221

Vinader-Caerols, C., Monleón, S., Carrasco, C. & Parra, A. (2012). Effects of alcohol, coffee, and tobacco, alone or in combination, on physiological parameters and anxiety in a young population. *Journal of Caffeine Research, 2,* 70–76. https://doi.org/10.1089/jcr.2012.0018

Vinader-Caerols, C., Talk, A., Montañés, A., Duque, A. & Monleón, S. (2017a). Differential effects of alcohol on memory performance in adolescent men and women with a binge drinking history. *Alcohol and Alcoholism, 52,* 610–616. https://doi.org/10.1093/alcalc/agx040

Vinader-Caerols, C., Duque, A., Montañés, A. & Monleón, S. (2017b). Blood alcohol concentration-related lower

performance in immediate visual memory and working memory in adolescent binge drinkers. *Frontiers in Psychology*, *8*, 1720. https://doi.org/10.3389/fpsyg.2017.01720

Weera, M. M. & Gilpin, N. W. (2019). Biobehavioral interactions between stress and alcohol. *Alcohol Research: Current Reviews, 40*, 04. https://doi.org/10.35946/arcr.v40.1.04