

The Relationship between Alcohol Consumption and Cortisol Secretion in an Aging Cohort

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Context: Evidence for an association between alcohol consumption and activity of the hypothalamic-pituitary-adrenal (HPA) axis is inconclusive.

Objective: Our objective was to assess the relationship between indices of alcohol consumption and salivary cortisol concentration.

Design: This was a cross-sectional study of alcohol consumption and cortisol secretion from phase 7 (2002–2004) of the Whitehall II study.

Setting: An occupational cohort originally recruited in 1985–1987 was included in the study.

Participants: A total of 2693 men and 977 women had information on cortisol levels and alcohol consumption.

Outcome Measures: Saliva samples were taken on waking, waking + 0.5, 2.5, 8, and 12 h, and bedtime for the assessment of cortisol.

Results: In men there was a positive association between cortisol and units of alcohol intake per week (3% increase in cortisol per unit of alcohol consumed; $P = 0.010$). The slope of cortisol decline over the day in heavy drinkers was reduced (heavy drinkers $\beta = -0.155$, moderate drinkers $\beta = -0.151$), indicating reduced control of the HPA axis in heavy drinkers. In women the cortisol awakening response was greater in heavy drinkers 14.15 nmol/liter (9.12–19.17) compared with moderate drinkers 8.69 nmol/liter (7.72–9.67) ($P = 0.037$).

Conclusions: This study suggests that alcohol consumption is associated with activation of the HPA axis. These results are not due to alcohol consumption on the day, suggesting chronic changes of the HPA axis in heavy drinking groups. (*J Clin Endocrinol Metab* 93: 750–757, 2008)

Excess cortisol levels, a product of the hypothalamic-pituitary-adrenal (HPA) axis, have been shown to be detrimental to health. They are related to hypertension, impairment of immune function, and alteration of metabolism (1–3). Given the recent evidence that the HPA axis may be associated with this broad range of morbidities (4), understanding predictors of HPA axis function assumes increasing importance. The behavioral determinants of HPA axis activity are poorly understood. Recent evidence demonstrates that cortisol secretion is associated with

smoking behavior (5), but the association with alcohol consumption in community populations is not well examined.

The majority of evidence from animal studies suggest a direct effect of alcohol on HPA axis activity (6, 7). The function of the HPA axis in alcohol-dependant people and those going through the withdrawal process has been altered (8–11), but extrapolation from these studies to the general population is difficult. Few studies have looked at the relationship between alcohol consumption and endocrine function in human populations (12).

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Abbreviations: BMI, Body mass index; BP, blood pressure; CAGE, cutting down, annoyance by criticism, guilty feeling, and eye-openers; CAR, cortisol awakening response; GHQ, General Health Questionnaire; HPA, hypothalamic-pituitary-adrenal.

Alcohol consumption is often included as a covariate in analysis when examining the function of the HPA axis (13), but not investigated directly, or it is measured poorly.

We are aware of two epidemiological studies examining the function of the HPA axis in relation to one measure of alcohol consumption in general population samples. The first, in an apparently healthy male working population, found elevated cortisol levels in heavy drinkers (14). The second study also suggests increased HPA axis activity in heavy drinking groups (15), but plasma cortisol was measured once, and covariates were not fully accounted for in the analysis.

Cortisol, a marker of HPA axis activity, can be measured in urine, blood, or saliva (16). The HPA axis has a diurnal rhythm; therefore, repeated measures are needed. The use of salivary cortisol allows measurement in a naturalistic setting (17, 18), with minimal inconvenience for participants. It allows measurement of the activity of the HPA axis capturing the cortisol awakening response (CAR) and levels over the day.

To our knowledge the assessment of the relationship between alcohol consumption and salivary cortisol levels in a naturalistic setting has not been reported. Our study has enough power to investigate different indices of alcohol consumption and account for relevant covariates. In this paper we examine the relation between alcohol consumption and two markers of cortisol secretion (CAR and slope of decline in levels over the day). Furthermore, we examine whether these relationships are independent of a wide number of covariates.

Subjects and Methods

Participants

Data reported here are from phase 7 (2002–2004) of the Whitehall II study. The Whitehall II cohort initially recruited 10,308 participants between 1985 and 1988 (phase 1) from 20 London based civil service departments. The number participating at phase 7 was 6941. Of those participants that attended the screening clinic and were asked to collect saliva samples, 90.1% ($n = 4609$) returned samples. Details of the clinical assessment and cohort profile have been reported elsewhere (19). Ethical approval for the Whitehall II study was obtained from the University College London Medical School committee on the ethics of human research. Informed consent was gained from every participant.

Cortisol analysis

To collect a saliva sample, participants used a device called a Salivette (Sarstedt, Leicester, UK). Participants were recruited by a face-to-face interview at the end of their clinical assessment; they were asked to complete saliva sampling the following day and mail samples back. The participants were instructed to provide six samples at waking, waking + 30 min, waking + 2.5 h, waking + 8 h, waking + 12 h and bedtime. An instruction booklet also recorded information on wake time, smoking, alcohol consumption, and stressful events on the day of sampling. Returned samples were stored at -80°C until assay. Salivette devices were centrifuged at 3000 rpm for 5 min, resulting in a clear supernatant of low viscosity. Salivary cortisol levels were measured using a commercial immunoassay with chemiluminescence detection (IBL Hamburg, Hamburg, Germany). The lower concentration limit of this assay is 0.44 nmol/liter; intraassay and interassay coefficients of variance were less than 8%. Any sample over 50 nmol/liter was repeated.

Alcohol consumption

The frequency of drinking alcohol was assessed in a self-completed questionnaire by asking “In the last 12 months have you taken an alcoholic drink?”, with six response options: “twice a day or more”; “daily or almost daily”; “once or twice a week”; “once or twice a month”; “special occasions only”; or “No.”

Mean alcohol intake was calculated from questionnaire answers to “In the last seven days, how many drinks of each of the following have you had?”; a separate response box for spirits (measures), wine (glasses), and beer (pints) was provided. This was calculated into equivalent units; in the United Kingdom for standard measures, 1 U alcohol is equivalent to 8 g ethanol. Alcohol consumption on the day of sampling was assessed from the response to “Did you drink alcoholic beverages today?”: yes or no.

Heavy drinking was defined using a cutoff of more than or equal to 28 U for men and more than or equal to 21 U for women per week. Problem drinking was assessed using the cutting down, annoyance by criticism, guilty feeling, and eye-openers (CAGE) questionnaire (20), which is a tool for detection of problem drinkers, not a clinical diagnostic tool (21). It includes four questions relating to drinking behavior. Each question has “yes” or “no” options. Persons stating “yes” for two or more questions were classified as “problem drinkers.”

Covariates

Job grade was determined if still in the civil service, or based on their last employment grade if they left the service. For this analysis, civil service grades were collapsed into three categories (22).

Income was determined by “What is the current yearly amount you receive from the above sources added together?”, with eight possible answers ranging from “less than £9,999” to “more than £70,000.” Low income was defined as earning less than £15,000 a year.

Wealth was determined by the question “If you sold all your assets your household owns for example [list of assets] and cashed in savings and investments and paid off all your debts (including your mortgage) how much money do you think you would have?” Low wealth defined as having less than £100,000. Further details on the definitions of income and wealth can be found in the study by Martikainen *et al.* (23).

Financial insecurity was assessed by “Thinking of the next ten years how financially secure do you feel?”, with secure, fairly secure, fairly insecure, and insecure the possible answers. Persons answering fairly

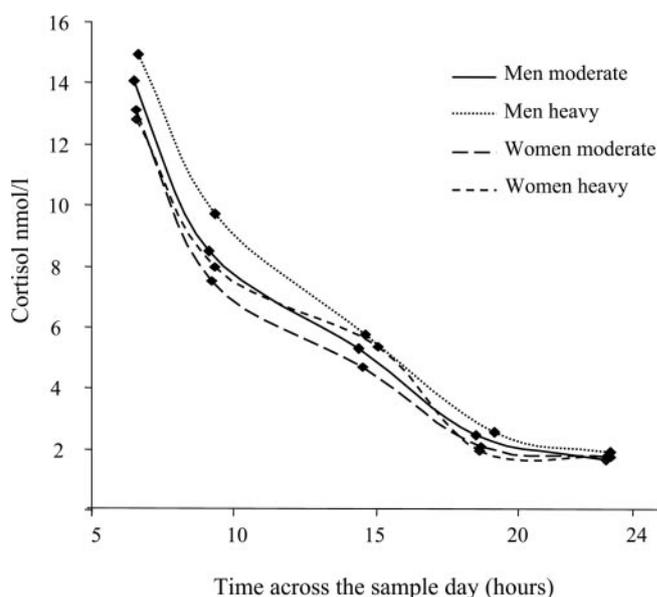


FIG. 1. Unadjusted mean cortisol (nmol/liter) by heavy drinking category in men ($n = 2167$) and women ($n = 738$) by mean time of day each sample was taken. The markers on the lines represent the average cortisol concentration and average time sample taken for samples 1 and 3–6.

TABLE 1. Participants' characteristics for men and women who had data available for indices of alcohol consumption and cortisol secretion

	Men	Women
No. with valid data	2693	977
Mean age (sd) ^a	60.89 yr (5.85)	61.36 yr (6.06)
Social position (%)		
Lowest employment grade ^a	3.3	26.2
Lowest income ^a	11.8	44.1
Lowest wealth ^a	5.4	14.8
Physical characteristics		
Smokers (%) ^a	10.2	9.4
Less than once a week eat fresh fruit/vegetable (%)	1.8	1.5
Mean systolic BP (sd) ^a	128.29 mm Hg (15.85)	126.88 mm Hg (18.33)
Mean diastolic BP (sd) ^a	74.74 mm Hg (10.23)	73.35 mm Hg (10.69)
Mean sleep disturbance score (sd) ^a	5.00 (4.17)	6.56 (4.91)
Mean BMI (sd) ^a	26.6 kg/m ² (3.86)	27.29 kg/m ² (5.61)
Psychological characteristics		
Financial insecurity (%) ^a	8.5	15.4
Mean depression score (sd) ^{a,b}	0.81 (1.69)	1.04 (1.82)
Very stressful experience on the day of sampling (%) ^a	5.4	11.2
More busy or stressed than usual (%) ^a	12.6	17.3
Alcohol consumption		
Frequency (%) ^a		
Twice a day or more	6.5	2.1
Daily or almost daily	44.6	29.2
Once or twice a week	32.3	27.4
Once or twice a month	7.5	11.0
Special occasions only	6.0	21.6
No	4.4	8.6
CAGE score (%) ^a		
0	71.1	82.8
1	17.7	11.4
2	7.7	4.6
3	3.0	0.9
4	0.5	0.2
Problem drinking (CAGE 2+) (%) ^a	11.2	5.8
Mean weekly alcohol intake (sd) ^a	113.01 g (110.17)	48.50 g (60.27)
Drinking \geq 28/21 U (%) ^a	12.8	3.7

^a A significant ($P \leq 0.05$) difference between men and women (χ^2 test used for categorical variables and ANOVA for continuous variables).

^b Defined using the GHQ depression subscale.

insecure and insecure were classed as feeling financially insecure, as in the study by Ferrie *et al.* (24).

Smoking status was categorized as either a current, ex, or never smoker. If any nicotine replacement therapy was listed, they were assigned a smoker ($n = 4$). In terms of healthy eating, participants were classed as having a poor diet if they reported less than once a week consumption of fruit or vegetables.

Systolic and diastolic blood pressure (BP) was measured at the clinical screening after a 5-min rest in a sitting position, using an Omron HEM 907 (Omron Healthcare, Inc., Bannockburn, IL). The measurement was taken twice, and the average was used in this analysis. Sleep disturbance was assessed with the scale described by Jenkins *et al.* (25), consisting of four items regarding sleep quality over the past month. There were six response options ranging from zero (not at all) to five (22–31 d). The total was summed to give a score between zero and 20. Body mass index (BMI) was calculated from measures of height and weight taken at the clinical screening calculated as weight (kg)/height (m)². Depression was measured using the 30-item General Health Questionnaire (GHQ) depression subscale. This consists of four items, all items scored on a Likert scale from zero to three. Respondents scoring three or more were assigned "GHQ depression cases." This is not a clinical definition of depression, but one validated to be used for the 30-item GHQ (26). Stress on the day of sample collection was assessed with the questions "We'd like to know if this was a typical day for you, compared with your usual workdays (or

weekends), in terms of how busy, pressured, or stressed you felt." Options were "Today was typical/greater/lower in terms of my workload or stress level." Participants were asked about the most stressful event and if it made them feel "not at all stressed," "somewhat stressed," "moderately stressed," "very stressed," or "the most stressed I have ever felt." Participants were classified as having a stressful experience if they were "very stressed" or "the most stressed I have ever felt."

Statistical analysis

From the samples returned, 168 individual samples were not taken by participants (0.55% of the number expected). During laboratory analysis, 1002 individual samples were not assayed for technical reasons. Missing cortisol data were imputed for participants missing samples at times 3, 4, or 5 [number imputed for sample 3 ($n = 16$), 4 ($n = 37$), and 5 ($n = 36$)] using the average of the previous and subsequent sample. The analyses were repeated with and without imputation. No statistical differences were observed. The results using imputation are presented here. Outliers were assessed for each time using a box plot [time 1 ($n = 4$), time 2 ($n = 5$), time 3 ($n = 5$), time 4 ($n = 4$), time 5 ($n = 4$), and time 6 ($n = 3$)] and removed from analysis. Any participants taking sample 1 more than 10 min after waking were excluded from analysis ($n = 634$); this is the commonly used cutoff when investigating daytime cortisol levels because the CAR is already substantially under way (27). The distribu-

TABLE 2. CAR nmol/liter (plus 95% confidence interval) by frequency of alcohol consumption, weekly alcohol intake, and CAGE score in men (n = 2167) and women (n = 738), adjusted for covariates

	Men		Women	
	Model 1	Model 4	Model 1	Model 4
Frequency (past 12 months)				
Twice a day or more	4.97 (3.06–6.88)	5.24 (3.25–7.23)	12.23 (5.31–19.15)	13.07 (5.92–20.21)
Daily or almost daily	6.99 (6.25–7.74)	7.22 (6.41–8.03)	8.33 (6.54–10.12)	8.84 (6.76–10.93)
Once or twice a week	8.44 (7.59–9.30)	8.27 (7.38–9.16)	8.82 (7.06–10.59)	8.78 (7.01–10.56)
Once or twice a month	8.26 (6.49–40.03)	7.85 (6.01–9.69)	9.54 (6.64–12.44)	9.22 (6.24–12.19)
Special occasions only	7.15 (5.12–9.18)	6.84 (4.70–8.97)	8.96 (6.90–11.02)	8.51 (6.26–10.77)
No	10.02 (7.09–12.96)	9.96 (6.68–12.71)	9.255 (5.82–12.69)	9.03 (5.39–12.67)
P value for ANOVA	0.005	0.084	0.911	0.910
Heavy drinking ^a				
Moderate consumption	7.75 (7.20–8.26)	7.70 (7.17–8.23)	8.65 (7.65–9.70)	8.69 (7.72–9.67)
Heavy consumption	6.42 (4.91–7.72)	6.42 (5.01–7.83)	14.80 (9.76–19.80)	14.15 (9.12–19.17)
P value for ANOVA	0.085	0.098	0.015	0.037
U/wk				
% Change in cortisol for 1 U increase in alcohol	–25 (–60 to 10)	–3 (–44 to 37)	37 (–96 to 171)	89 (–72 to 251)
P value for linear trend	0.164	0.874	0.583	0.278
CAGE				
<2	7.57 (7.04–8.10)	7.58 (7.04–8.11)	8.96 (7.80–9.94)	8.88 (7.85–9.92)
≥2	7.33 (5.83–8.82)	7.25 (5.72–8.77)	12.10 (7.89–16.42)	11.97 (7.61–16.32)
P value for ANOVA	0.749	0.691	0.150	0.178
Linear regression percent change for one point increase	27 (–599 to 653)	172 (–478 to 821)	–14 (–505 to 476)	4 (–499 to 619)
P value for linear trend	0.932	0.604	0.954	0.890

Model 1 includes age and waking time. Model 4 includes age, waking time, alcohol consumption on the day, BMI, smoking status, depression scale, sleep disturbance, financial insecurity, last known employment grade, very stressful experience, and typical day.

^a Moderate consumption for men is less than 28 U/wk, heavy is more than or equal to 28 U. Moderate consumption for women is less than 21 U/wk, heavy is more than or equal to 21 U.

tion of all alcohol consumption measures and if participants followed the protocol correctly were assessed. Those taking the first sample more than 10 min after waking were more likely to score on the CAGE questionnaire $P < 0.05$ for men and women. Participants taking medications (e.g. glucocorticoids such as prednisolone) affecting cortisol levels were removed from the analysis (n = 236). For this analysis the sample was restricted to those respondents who had data on cortisol levels, alcohol consumption, and covariates included.

The cortisol data were not normally distributed, therefore, all data were log transformed for analysis. The CAR was calculated by subtracting cortisol at time 1 from cortisol at time 2. The slope of the decline in cortisol levels over the day is calculated by regressing cortisol values on time after waking samples were taken for samples 1 and 3–6. To ensure the CAR does not obscure the slope calculation, sample 2 is not included. Figure 1 illustrates the unadjusted cortisol levels in men and women by time of day samples taken for samples 1 and 3–6. The mixed models procedure in SPSS (SPSS, Inc., Chicago, IL) was used, cortisol and time each sample taken are nested within person. Covariates are then added as between-person variables, interaction terms between time samples taken over the day and covariates are entered into the model and used to assess if significant differences in rate of cortisol decline over the day exist between groups. The slope of cortisol decline over the day is a negative coefficient, therefore, the lower (more negative) the slope, the more rapid the decline in cortisol levels, whereas slope values closer to zero reflect flatter diurnal rhythms (28–30). Men and women were analyzed separately as is common for assessment of alcohol consumption.

The main analysis focused on the relationship between cortisol and frequency of consumption, weekly alcohol consumption, and CAGE score. These were analyzed using univariate ANOVA. Linear regression was performed on weekly unit consumption and CAGE score. All analyses were initially run adjusting for age only (model 1), then an indicator of whether alcohol was consumed on the day of saliva sample collection (model 2). A third included BMI and smoking status (model 3). The final

model included sleep disturbance, depressive symptoms, last employment grade, financial insecurity, stressful event on the day, and if it was a typical day (model 4). Assessment of the CAR was also adjusted for wake-up time in all models. To keep tables brief, only models 1 and 4 are displayed. Adjustment for multiple comparisons was made using Bonferroni correction; the statistical package used in all analyses was SPSS version 14.0.

Results

Participants' characteristics are shown in Table 1. A total of 2693 men and 977 women with valid data were available for analysis. Men reported a higher frequency of drinking, consumed more alcohol per week, had higher CAGE score, and had higher BP and mean cortisol production over the day than women. Greater proportions of women were in the lowest social position groups, suffered from depression (GHQ defined), and had sleep problems.

We assessed the distribution of potential confounders across the categories of frequency of drinking (data not shown). In men, less frequent alcohol consumers were in the lowest employment grade, wealth, and income groups, felt more financially insecure, ($P < 0.001$ for all), had higher depressive symptoms ($P = 0.004$), and consumed less fruit and vegetables ($P = 0.006$). In men, more frequent drinkers were older ($P = 0.002$), had higher systolic and diastolic BP ($P = 0.002$ and $P < 0.001$, respectively), and contained a higher proportion of smokers ($P = 0.001$). Frequency of drinking was not associated with sleep disturbance, BMI, stress-

ful event on the day, or if it was a typical day. In women, trends across frequency of consumption mirror those in men for measures of social position, financial insecurity, and age ($P < 0.001$ for all). In addition, in women, more frequent drinkers had higher BMI ($P < 0.001$), were more likely to be smokers ($P = 0.001$), and report a poor diet ($P = 0.035$). Frequency of drinking was not associated with sleep disturbance, BP, depressive symptoms, very stressful event on the day, or if it was a typical day.

The CAR was assessed (Table 2), and no relationships were apparent for men. Interestingly, the nondrinkers had a larger CAR, however, these were nonsignificant relationships. In women an array of effects were apparent; heavy drinking was associated with a larger CAR in fully adjusted models. The CAR in heavy compared with moderate drinkers for men and women is further illustrated by Table 3 and Fig. 2.

The slope of cortisol release was calculated and is displayed in Table 4 for men. A significant relationship exists for heavy drinkers; in the fully adjusted model, heavy drinkers have a flatter slope than moderate drinkers (slopes are closer to zero). The slope of secretion in women is displayed in Table 5. Different rates of decline in cortisol are apparent between the frequency of alcohol consumption groups and these remain significant in the fully adjusted model. There is an indication of flatter slopes of secretion in heavy drinking groups, but this is not significant.

Discussion

The principal aim of the study was to examine the relationship between alcohol consumption and cortisol secretion. The results indicate that, in a large community dwelling population, alcohol consumption has a positive relationship with cortisol release over the day. An increased number of alcohol units consumed per week and heavy drinking are associated with increased cortisol levels. The slope of cortisol decline was flatter in heavy drinkers; this indicates reduced inhibitory control of the HPA axis, as described by Thayer *et al.* (14). A greater array of effects was apparent in women than in men. However, the proportion of heavy and problem drinking women in this cohort is small, and this finding deserves further investigation. This is one of few studies examining the relation between alcohol and cortisol in a large community dwelling population.

Our findings accord with Thayer (14) and Gianoulakis (15) *et al.* The results described in our study are robust to adjustment and are found in a much larger sample than previously described. We were able to investigate a number of different measures of alcohol consumption, and explore the diurnal rhythm of cortisol secretion. Mediators and confounders were

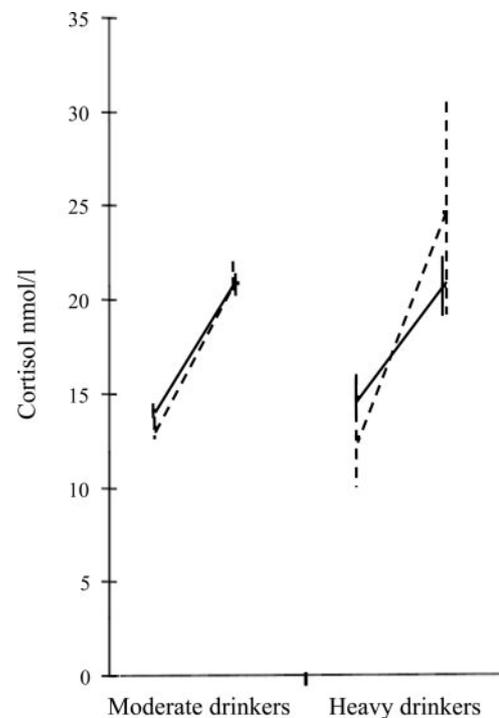


FIG. 2. CAR nmol/liter (plus 95% confidence interval) by heavy drinking category, in men ($n = 2167$) and women ($n = 738$), adjusted for covariates, adjusted for age, waking time, alcohol consumption on the day, BMI, smoking status, depression scale, sleep disturbance, financial insecurity, last known employment grade, very stressful experience, and typical day. Men are the solid line and women the dashed line.

adjusted for, and the results remain statistically significant. Of the four measures of alcohol consumption investigated, the strongest predictor of increased cortisol levels in men was units of alcohol consumed per week. This is in accordance with other studies investigating endocrine function and alcohol consumption (31). In men in this cohort, there is little evidence that frequency of consumption *per se* is detrimental to the function of the HPA axis, but the volume of consumption and heavy drinking are related to poorer endocrine function. The findings in women suggest that all three measures of alcohol consumption are associated with a wider array of effects on the HPA axis, and affect the CAR and slope differently. This could indicate that drinking behavior has different effects on men and women. This has not been described previously, but due to the small number of heavy and problem female drinkers in this cohort, it deserves wider investigation.

The biological basis the association described is not clear. A direct acute effect of alcohol on the HPA axis is theoretically possible, as in animal studies (7), but our finding of a flatter slope after considering the effect of alcohol consumption on the day of

TABLE 3. Mean levels of cortisol (nmol/liter) (plus 95% confidence interval) for samples 1 and 2 by drinking category in men ($n = 2167$) and women ($n = 738$), adjusted for covariates

	Cortisol sample	Moderate drinkers	Heavy drinkers
Men	Sample 1	14.07 (13.69–14.46)	14.75 (13.72–15.86)
	Sample 2	20.84 (20.25–21.44)	20.70 (19.18–22.33)
Women	Sample 1	13.17 (12.58–13.78)	12.68 (10.03–16.02)
	Sample 2	21.07 (20.15–22.04)	24.25 (19.25–30.56)

TABLE 4. Slope of cortisol decline over the day (β) (calculated as log of cortisol level regressed onto time sample was taken), and intercept by frequency of alcohol consumption, weekly alcohol intake, and CAGE score in men ($n = 2141$), adjusted for covariates

	Model 1		Model 4	
	β	Intercept	β	Intercept
Frequency (past 12 months)				
Twice a day or more	-0.043	1.90	-0.146	2.91
Daily or almost daily	-0.156	2.56	-0.165	3.32
Once or twice a week	-0.115	2.92	-0.138	3.16
Once or twice a month	-0.069	1.96	-0.065	1.36
Special occasions only	-0.178	3.41	-0.225	3.36
No	-0.118	3.57	-0.143	3.64
P value for difference in slope	0.136		0.586	
Heavy drinking ^a				
Moderate consumption	-0.125	2.77	-0.155	3.16
Heavy consumption	-0.120	2.64	-0.151	3.12
P value for difference in slope between the groups	0.865		0.784	
P value for difference in slope using units of consumption a week	0.033		0.011	
CAGE				
<2	-0.126	2.74	-0.138	3.08
≥ 2	-0.125	2.66	-0.222	3.27
P value for difference in slope between the groups	0.677		0.764	
P value for difference in slope for CAGE score	0.161		0.519	

Model 1 includes age and waking time. Model 4 includes age, waking time, alcohol consumption on the day, BMI, smoking status, depression scale, sleep disturbance, financial insecurity, last known employment grade, very stressful experience, and typical day.

^a Moderate consumption is less than 28 U/wk and heavy more than or equal to 28 U.

sampling and an alteration in the CAR in women suggest that additional mechanisms are at play. Excess alcohol consumption damages liver function and may, therefore, reduce the bodies' ability to metabolize cortisol (or other active substances of the HPA axis); this would result in altered endocrine function. Impaired inhibitory control of the HPA axis in heavy drinking groups has been the proposed mechanism (14). Our results are

consistent with other studies in men in that alcohol consumption is associated with a change in endocrine function (12).

Although the effects of alcohol consumption on cortisol secretion in this cohort were relatively small, acute differences in cortisol concentration of this magnitude have had a detrimental effect on insulin and glucose function (2). Previously, alcohol intake has predicted the development of type 2 dia-

TABLE 5. Slope of cortisol decline over the day, and intercept by frequency of alcohol consumption, weekly alcohol intake, and CAGE score in women ($n = 724$), adjusted for covariates

	Model 1		Model 4	
	β	Intercept	β	Intercept
Frequency (past 12 months)				
Twice a day or more	-0.004	2.73	-0.124	1.94
Daily or almost daily	-0.210	3.08	-0.245	3.37
Once or twice a week	-0.112	2.54	-0.126	2.57
Once or twice a month	-0.205	3.08	-0.195	3.14
Special occasions only	-0.089	2.52	-0.102	2.54
No	-0.082	2.47	-0.129	2.35
P value for difference in slope	0.014		0.013	
Heavy drinking ^a				
Moderate consumption	-0.144	2.90	-0.167	2.70
Heavy consumption	-0.077	-0.05	-0.015	-0.956
P value for difference in slope between the groups	0.573		0.774	
P value for difference in slope using units of consumption a week	0.244		0.195	
CAGE				
<2	-0.174	2.96	-0.193	3.12
≥ 2	-0.063	0.36	-0.057	1.50
P value for difference in slope between the groups	0.489		0.741	
P value for difference in slope for CAGE score	0.551		0.641	

Model 1 includes age and waking time. Model 4 includes age, waking time, alcohol consumption on the day, BMI, smoking status, depression scale, sleep disturbance, financial insecurity, last known employment grade, very stressful experience, and typical day.

^a Moderate consumption is less than 21 U/wk, and heavy is more than or equal to 21 U.

betes (31–33). Our findings may provide a mechanism for these associations because increased cortisol is related to insulin resistance (34). The analysis of heavy drinking provides some support for the hypothesis that heavy drinking has a more detrimental effect on health than regular drinking, and that the physiological responses to different drinking patterns vary.

The advantages and disadvantages of the current analyses need to be stated. The number of participants with valid data on cortisol levels was 39% of phase 1 of the Whitehall II study. However, of those still participating at phase 7 and asked to complete cortisol collection, 90% returned the samples; there were no differences between participants and those who refused by age, gender, or last known employment grade. This is a cross-sectional study, and salivary cortisol has been measured at one phase only; therefore, the direction of causation cannot be determined. Increased stress can increase cortisol levels and influence a person's health behaviors; however, adjustment for concurrent indicators of stress and alcohol consumption and for items (sleep disturbance, depression, financial insecurity, and last known employment grade) that may represent or be associated with chronic stress failed to explain fully the associations observed. The use of a self-report measure of problem drinking is a limitation, however, the CAGE questionnaire has had high validity (35, 36). Adherence to the protocol was assessed by a self-reported measure (time of taking samples); it is possible that some people who followed the protocol incorrectly might have been included in the analysis. It is also possible, although unlikely, that increased cortisol levels encourage the adoption of detrimental alcohol consumption behaviors. The Whitehall II study was set up as an occupational cohort. At this phase it now represents an older age group (55–72 yr) and, therefore, may not be fully representative of the general population. In our analysis the results are significant, even with the relatively small variation in drinking behavior; this would suggest that the effects within the general population would be greater.

In summary, this study suggests that there is a positive relationship between different indices of alcohol intake and daily release of cortisol. The mechanisms mediating these relationships are not fully elucidated but appear to be independent of the potential confounders and mediators examined. This is the first study of alcohol consumption and diurnal cortisol secretion in a naturalistic setting. This study confirms laboratory work and smaller studies that describe alteration of the HPA axis in heavy drinkers.

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