Associations between baseline cortisol and trajectory of symptom improvement in depressed adolescents receiving psychological therapy

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Word Count
Abstract: 233
Main text: 2040

Abstract

Background: Cortisol hypersecretion in depressed adolescents and adults is associated with more persistent illness and may signal a lower response to psychological therapies. A meta-analysis of small and heterogenous studies demonstrated that higher pre-treatment basal cortisol levels were associated with poorer response specifically to psychological therapy for depression. The objective of this study was to investigate the relationship between both morning and evening salivary cortisol levels and response to psychological therapy in depressed adolescents participating in one large randomised controlled trial.

Methods: We tested the association between morning and evening salivary cortisol levels at baseline and improvement in depressive symptoms in response to psychological therapies in depressed adolescents at 6 time points: baseline, 6, 12, 36, 52- and 86-weeks post-randomisation, using the self-reported Mood and Feelings Questionnaire (MFQ).

Results: High evening cortisol was associated with a slower initial decline in depressive symptoms (cortisol x quadratic time $p = .022$); however it was not associated with total change in depressive symtoms over the whole course of the study. Morning cortisol was not associated with change in depressive symptoms. These effects were not significantly different across the three psychological therapies.

Limitations: Results may not generalize to adolescents receiving other treatments (medication) or no treatment, and may not generalize to adults. Only a minority of eligible participants collected valid cortisol samples.

Conclusions: Higher pretreatment evening cortisol may impair a depressed adolescent's ability to use psychological therapy.

1. Introduction

Depressed adolescents display variable rates of symptom reduction to psychological therapies, posing the question of what underlies individual differences in differential treatment response (Weersing et al., 2017). The hormone cortisol contributes to regulating physiological response to stressors, altering metabolism and mobilising energy resources (Herbert et al., 2006). At the neural level higher cortisol levels may impair cognitive processing, including recall memory (Wolf, 2008). A meta-analysis by Fischer and colleagues (Fischer et al., 2017b) found that higher pre-treatment basal cortisol levels were associated with poorer response to psychological therapy for depression. The authors proposed that high cortisol causes cognitive impairment, making it harder for patients to utilize this treatment.

However, the aforementioned meta-analysis only identified five studies with a total of 138 participants. Studies included used a range of different cortisol collection techniques/times, participant ages and psychotherapies. Cortisol levels vary through the day, with a peak in the morning. When both are measured, evening cortisol has a greater effect on reducing improvement in depressive symptoms than morning cortisol (Goodyer et al., 2001; Holland et al., 2013).

To overcome the limitations of the previous studies, our study aimed to investigate the relationship between both morning and evening salivary cortisol levels and response to psychological therapy in depressed adolescents participating in a randomised controlled trial. We also tested whether effects of baseline cortisol were greater in adolescents receiving more cognitively-demanding psychological therapies (cognitive-behaviour therapy (CBT) and short-term psychoanalytical psychotherapy (STPP)) than the reference treatment of Brief Psychosocial Intervention.

2. Methods

2.1 Participants

Participants were recruited from the IMPACT trial (Goodyer et al., 2011; Goodyer et al., 2017), a multicenter, pragmatic, observer-blind, randomised controlled trial investigating the relative effectiveness of two specialist psychological treatments (CBT and STPP) and a brief psychosocial intervention (BPI) for 465 adolescents, aged 11-17, with major depressive disorder. Self-reported depressive symptoms were measured at 6 nominal time points: baseline, 6, 12, 36, 52- and 86-weeks post-randomisation, using the self-reported Mood and Feelings Questionnaire (MFQ, Daviss et al., 2006).

300/465 (65%) IMPACT participants were asked to take part in the hormone component of IMPACT. Of these, some (7.0%, n=21) participants were excluded due to medications that would alter cortisol mechanisms (19 corticosteroids, and 2 antipsychotics).

2.2 Procedures

Participants were asked to collect 3 saliva samples on two consecutive school or working days. Participants were instructed to provide the first sample as soon as they woke up, which acted as their "waking" cortisol measure. The second sample was collected 30 minutes after waking to capture the cortisol waking response. The highest value of these two was taken as the "morning peak" cortisol. The final "evening" sample was provided at 10pm. Patients were asked to collect three saliva samples on two consecutive school or working days; mean across the two days was used for analysis. Participants were also asked to avoid collecting saliva samples within 20 minutes of eating, smoking or brushing teeth, and to avoid collecting samples within 8 hours of alcohol consumption or the use of recreational drugs. For further details on cortisol collection protocol, please see supplementary materials.

Basal cortisol measurements are known to show significant within-subject fluctuation such that it is standard practice to derive an average cortisol value for each individual over a number of time-points (Harris et al., 2000). Plasma and salivary cortisol are highly correlated; salivary cortisol is more closely related than plasma cortisol to free cortisol (which is transmitted across the blood-brain barrier)(Pruessner et al., 1997). Cortisol data was only valid if there were samples taken on both days. The mean value was taken across both days.

2.3 Measures

2.3.1 Salivary Cortisol

Salivary cortisol levels were measured by competitive enzyme immunoassay (EIA) using a Salimetrics Europe Ltd kit. Cortisol was measured in micrograms per decilitre. Intra-assay precision was 9.6% at 0.106 μg/dL and 9.8% at 1.058 μg/dL. Inter-assay precision was 3.7% at 0.097 μg/dL and 3.4% at 0.999 μg/dL.

2.3.2 Mood and Feelings Questionnaire (MFQ)

This is a 33-item Questionnaire of depressive symptomatology covering the past 2 weeks (Daviss et al., 2006). MFQ items were measured on a 3-point scale (almost never, sometimes,

often/almost always). Total scores (range of 0-66) were used in analyses. Higher scores indicated more severe depressive symptoms (Goodyer et al., 2017).

2.3.3 Medication Usage

Taking an antidepressant at baseline or starting a new antidepressant during follow-up could potentially confound results. Sensitivity analyses added antidepressant status to the primary regression models. Participants were asked about medication taken at present (baseline) and since the last assessment (all follow-ups). All baseline antidepressants were SSRIs. All follow-up antidepressants except two (amitriptyline) were SSRIs.

2.4 Statistical Analysis

The analytic strategy was to determine if mean baseline morning peak or evening cortisol levels moderated the trajectory of depressive symptoms (measured using the mood and feelings questionnaire, MFQ). Log_{10} of cortisol values and the vce(robust) estimator were used due to skewed distributions. Longitudinal linear mixed-effects regression analyses with maximum likelihood estimation were performed using xtmixed on Stata 14. This allows exact times of assessment to be modelled and enabled inclusion of participants with some missing data, important when times since baseline varied widely and some data points were missing. Age and gender were added as baseline covariates. Linear and quadratic effects of time were modelled in separate models.

2.4.1 Sensitivity/Secondary Analyses

The first sensitivity analyses taking medication into account added antidepressant at baseline (yes/no) as a covariate; the second only included participants with no antidepressant at baseline and added new antidepressant started during follow-up (yes/no) as a covariate. For the latter, data were only used if there were data on antidepressant usage at baseline and at least one follow-up. To test whether the effects of cortisol were different across therapies, time x cortisol x treatment (CBT/STPP combined vs BPI) interaction terms were added to models.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by Cambridgeshire 2 REC (09/H0308/137). Written informed consent was given by patients and/or parents.

3. Results

3.1 Descriptive Data

112 (24%) IMPACT participants had valid data for morning cortisol, whereas 166 (36%) participants had valid data for evening cortisol. Demographic information on participants with and without valid cortisol data are in table 1. Those with evening cortisol were 75% female, mean(s.d.) age was 15.6(1.4) and mean(s.d.) MFQ was 45.6(10.5). Participants with valid cortisol data were significantly more likely to be white (Morning: χ^2 =7.14, p = .008; evening: χ^2 =6.62, p = .010); otherwise there were no significant differences between IMPACT participants with and without valid cortisol data (all p >.05, table 1). Median (IQR) mean morning peak cortisol was 0.59(0.47-0.77) μg/dl. Median (IQR) evening cortisol was 0.07(0.04-0.11) μg/dl. Baseline cortisol was not correlated with baseline depressive symptoms (morning peak: Spearman's r =-0.02, p = .90; evening: Spearman's r = -0.02, p = .80). MFQ data were available for 65-73% of participants at each follow up point (supplementary table 1).

TABLE 1

3.1 Primary Analysis: Association between Baseline Cortisol and Trajectory of Depressive Symptoms

There were no significant linear (p = .24) nor quadratic (p = .87) interactions between time (ie: change in MFQ) and morning peak cortisol (table 2). Although high evening cortisol was not associated with linear MFQ slope (p = .11), it was significantly associated with a slower initial decline in depressive symptoms (quadratic time x cortisol interaction p = .022). See figure 1 for MFQ trajectories, separate for low and high baseline cortisol, by median split.

TABLE 2, FIGURE 1.

3.2 Sensitivity/Secondary Analyses

In those patients taking antidepressants, baseline morning peak cortisol was significantly lower in those taking an antidepressant at baseline compared to those not taking an antidepressant at baseline (p = .033). Baseline evening cortisol was significantly higher in those who went on to take an antidepressant during follow-up (p = .004, supplementary table 2). Sensitivity analyses controlling for antidepressant use (at baseline and started during follow-up) made no material difference to results

(evening cortisol x time quadratic interaction: baseline antidepressant, $n = 158$, $p = .018$; starting new antidepressant, $n = 118$, $p = .0040$; supplementary table 3).

There were no significant interactions between time, cortisol and treatment type for morning (linear: $p = .25$; quadratic: $p = .15$) nor evening cortisol (linear: $p = .089$; quadratic: $p = .32$; supplementary table 4).

4. Discussion

Our study is the highest-powered study to date demonstrating that increased levels of evening cortisol at baseline predict slower initial improvement of depressive symptoms regardless of the type of psychological treatment received. This effect is particularly strong over the shorter-term. This finding fits with the meta-analysis of smaller studies conducted by Fischer and colleagues (Fischer et al., 2017b), but with the added specificity that this effect pertains only to evening, not morning, cortisol. Such a finding for evening cortisol only is consistent with a clinic study of adolescents with uncontrolled treatment, in which high evening but not morning cortisol was associated with persistence of depression at 72 weeks (Goodyer et al., 2001). These effects may be due to illness-related loss of diurnal variation and 'escape' of the evening cortisol levels from negative feedback.

One possible explanation is that higher cortisol causes cognitive dysfunction leaving these patients less able to engage in psychological therapies. However, there was no interaction between evening cortisol and treatment type. This suggests that any effects of evening cortisol on attention, concentration, and memory adversely influence therapeutics regardless of psychological therapy type. This supports the notion that all therapies require the activation of cognitive resources and so all are affected. A second putative mechanism is that higher evening cortisol is associated with reduced motivation (via its effects on dopamine release at the nucleus accumbens, Lemos et al., 2012). High cortisol has been found to be associated with sleep disturbance, melancholia, dysthymia and childhood abuse all of which may be associated with impaired treatment response (Goodyer et al., 2001; Wilkinson and Goodyer, 2011; Juruena et al., 2018;). Further studies need to study inter-relationships between these phenotypes, cortisol, cognition, and outcomes.

Baseline evening cortisol was higher in participants who were prescribed an antidepressant in the course of the study. However, high evening cortisol continued to predict poor response to treatment when this was controlled for, suggesting that antidepressant prescription was a response to poor response to treatment (in keeping with NICE guidelines (NICE, 2020)), rather than a confounder. Data on antidepressant use was not fine-grained enough to allow us to test whether use of antidepressants

led to greater subsequent reduction in depressive symptoms, nor whether baseline cortisol predicted response to antidepressant treatment. However a prior meta-analysis has demonstrated that high baseline cortisol is a predictor of poor response to antidepressants (Fischer et al., 2017). This suggests that high cortisol is a general predictor of poor response to all treatment for depression, rather than a marker suggesting one treatment is better than another.

Of note, high cortisol has not been found to predict response to psychological therapy in patients with anxiety disorders (Fischer and Cleare, 2017). If cortisol mechanisms were via cognitive impairment, it would be expected that cortisol would impair cognitive therapy response across disorders. This suggests other mechanisms specific to depression (eg motivation), as stated earlier.

Limitations and Conclusion: Results may not generalize to adolescents receiving other treatments (medication) or no treatment, and may not generalize to adults as most have recurrent illness with a potential differing pathophysiology. The low proportion of adolescents collecting cortisol may mean results could be due to selection bias (although the sample was representative of the whole study sample). As this was part of a larger clinical trial, we were reliant on self-reported times of waking and cortisol collection; it was only feasible to collect samples over two days; dynamic cortisol testing was not possible. We did not collect data on cognition, which would have allowed us to test whether cognition indeed mediated effects of cortisol on outcome. Further studies are needed, collecting a wider range of potential mediators for the effects of cortisol. Nonetheless, the present study provides the best evidence to date of the role of evening cortisol in impairing a depressed adolescent's ability to use psychological therapy.

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PW and IG conceived and designed the cortisol collection. IG, PF and NM co-designed the main IMPACT study. PW, SN and AC conducted the data analysis. All authors co-wrote the paper and approved the final manuscript.

Role of the funding Source: IMPACT was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project no 06/05/01), the Department of Health and local NHS trusts. Cortisol collection and analysis were funded by the Evelyn Trust. Funders had no role in the analysis nor the writing of this paper.

Data Availability: The data that support the findings of this study are available on request from the corresponding author, PW. The data are not publicly available due to consents in place at the time the study was designed.

Declaration of Competing Interest: None

Acknowledgements:
We wish to thank all participants, therapists and researchers involved with this study. We wish to thank the other senior members of the IMPACT Consortium: Shirley Reynolds, Barbara Barrett, Sarah Byford, Bernadka Dubicka, Jonathan Hill, Fiona Holland, Raphael Kelvin, Chris Roberts, Rob Senior, Marget Target, Barry Widmer.

Table 1. Baseline Demographics, Comparing IMPACT Participants with and without Valid Cortisol Data

	Morning Peak Cortisol				**Evening Cortisol**			
	With valid cortisol	Without valid cortisol	Comparison	*P*	With valid cortisol	Without valid cortisol	Comparison	*P*
Sample size:, *n*	112	353			166	299		
Female: *n* (%)	83 (74.1%)	265 (75.0%)	$X^2 = 0.04$	0.838	125 (75.3%)	125 (44.0%)	$X^2 = 0.03$	0.864
Age, years: mean (s.d.)	15.6 (1.5)	15.6(1.4)	t = 0.27	0.785	15.6 (1.4)	15.6 (1.4)	*t* =0.20	0.842
White ethnicity: *n* (%)	103 (92.0%)	287(81.3%)	$X^2 = 7.14$	**0.008**	149 (89.8%)	241 (80.6%)	$X^2 = 6.62$	**0.010**
IMD	19.4	25.3	W = 22156	0.054	20.5	25.3	W = 26602	0.199
Baseline MFQ: mean (s.d.)	45.8(10.8)	46.0(9.8)	MW Z = 0.4	0.7	45.6(10.5)	46.1(10.6)	MW Z=0.5	0.6
Baseline SSRI use: mean (%)	20 (17.9%)	61 (17.3)	$X^2 = 0.02$	0.888	23 (13.5%)	58 (19.4%)	$X^2 = 2.28$	0.131
Treatment arm: *n* (%) BPI CBT STPP	31 (27.7%) 40 (35.7%) 41 (36.6%)	124 (35.1%) 114 (32.3%) 115 (32.6%)	$X^2 = 2.1$	0.345	55 (33.1%) 61 (36.7%) 50 (30.1%)	100 (33.4%) 93 (31.1%) 106 (35.5%)	$X^2 = 1.9$	0.380

IMD: Index of Multiple Deprivation; MFQ: Mood and Feelings Questionnaire; SSRI: Selective Serotonin Re-Uptake Inhibitor; BPI: Brief Psychosocial Intervention; CBT: Cognitive-Behaviour Therapy; STPP: Short-Term Psychoanalytical Psychotherapy

Table 2. Longitudinal Mixed Effects Models Demonstrating Effects of Baseline Cortisol on Trajectory of Depressive Symptoms

	Cortisol x time interactions	Coefficient	95% CI	*P*
Morning peak cortisol: *n* = 112	Linear term	1.1×10^{-2}	-7.4×10^{-3} to 3.0×10^{-2}	0.24
	Quadratic term	7.3×10^{-6}	-7.9×10^{-5} to 9.3×10^{-5}	0.87
Evening cortisol *n* = 166	Linear term	8.6×10^{-3}	-1.8×10^{-3} to 1.9×10^{-2}	0.11
	Quadratic term	-4.5×10^{-5}	-8.4×10^{-4} to -6.0×10^{-6}	**0.022**

Covariates included in models: age, gender

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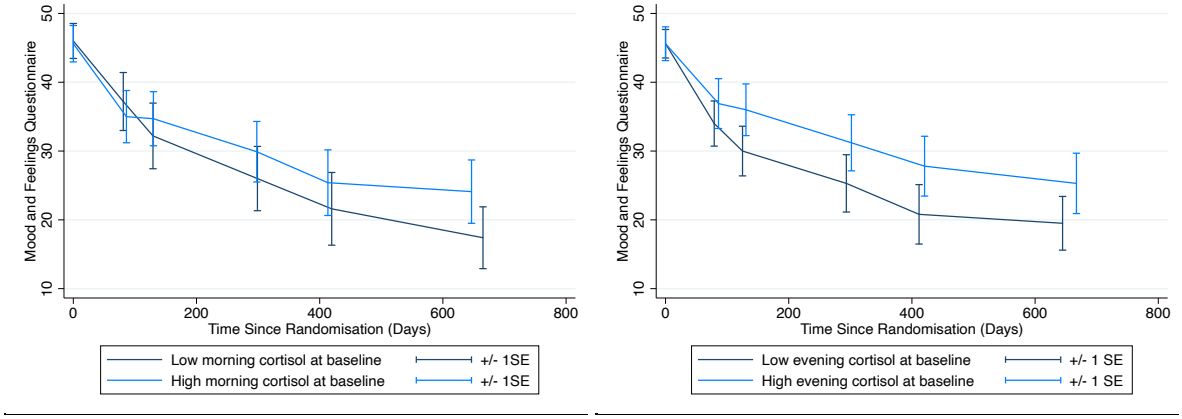

Fig 1. Growth trajectories of depressive symptoms, with sample split by median cortisol at baseline at morning peak (a) and evening (b). Each point on the graph shows mean depressive symptoms and mean time since randomization for that group at that planned assessment point.

Associations between baseline cortisol and trajectory of symptom improvement in depressed adolescents receiving psychological therapy.

Supplementary Material

Methods: Further Details on Cortisol Collection Protocol

Participants were asked to note the exact time cortisol measures were provided, in relation to them waking. This helped us to assess compliance with study protocol. Patients also noted any medication taken in the previous week. Valid morning samples were collected between 0400 and 1159. A peak sample was only valid if at least one of the morning samples was collected between 20 and 40 minutes of waking, given the normal peak cortisol at 30 minutes (Adam et al., 2010). If the other morning cortisol level was higher than that at the normal peak time, the higher number was taken as the peak. Evening cortisol values were considered valid if saliva was collected between 1900 and 0100.

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Supplementary Table 1. Completeness of Depressive Symptom Data at Each Time Point

Assessment Point	Planned Assessment Time (weeks)	Morning Peak Cortisol		Evening Cortisol (n=166)	
		Number with valid data: *n (%)*	Assessment time, weeks: mean (s.d.)	Number with valid data: *n (%)*	Assessment time, weeks: mean (s.d.)
0	0	112 (100%)	0 (0)	166 (100%)	0 (0)
1	6	77 (69%)	12.0 (4.7)	119 (72%)	11.8 (4.1)
2	12	81 (72%)	18.5 (5.0)	120 (72%)	18.2 (4.5)
3	36	82 (73%)	42.6 (4.7)	113 (68%)	42.5 (4.4)
4	52	74 (66%)	59.5 (6.2)	108 (65%)	59.4 (5.6)
5	86	75 (67%)	93.8 (6.5)	113 (68%)	93.7 (6.8)

Supplementary Table 2. Associations between Cortisol and Antidepressant Usage

	Baseline Antidepressant			Follow-up New Antidepressant		
	No	Yes	Mann-Whitney Z (*P*)	No	Yes	Mann-Whitney Z (*P*)
Morning peak cortisol	n = 85	n = 21		n = 58	n = 21	
	0.615 (0.485-0.77)	0.505 (0.395-0.685)	Z=2.1 **P=0.033**	0.62 (0.485-0.795)	0.615 (0.505-0.76)	Z=0.3 P=0.8
Evening cortisol	n = 131	n = 27		n = 81	n = 37	
	0.065 (0.04-0.115)	0.0425 (0.035-0.103)	Z=0.07 P=0.9	0.055 (0.04-0.09)	0.09 (0.055-0.145)	Z=2.9 **P=0.004**

Cortisol is given as median (inter-quartile range)

Supplementary Table 3. Longitudinal Mixed Effects Models Demonstrating Effects of Baseline Cortisol on Trajectory of Depressive Symptoms, Controlling for Antidepressant Usage

	Antidepressant (AD) Variable	Cortisol x time interactions	Coefficient	95% CI	*P*
Morning peak cortisol	AD at start, n = 106	Linear term	$1{,}1 \times 10^{-2}$	-9.9×10^{-3} to 3.2×10^{-2}	0.30
		Quadratic term	5.7×10^{-6}	-6.8×10^{-5} to 7.9×10^{-5}	0.88
	New AD over F/U, n = 79	Linear term	1.4×10^{-2}	-1.1×10^{-2} to 3.9×10^{-2}	0.26
		Quadratic term	-4.2×10^{-5}	-1.2×10^{-4} to 4.1×10^{-5}	0.32
Evening cortisol	AD at start, N = 158	Linear term	7.4×10^{-5}	-3.3×10^{-3} to 1.8×10^{-2}	0.18
		Quadratic term	-4.8×10^{-5}	-8.8×10^{-5} to -8.3×10^{-6}	**0.018**
	New AD over F/U, n = 118	Linear term	9.8×10^{-3}	-1.7×10^{-3} to 2.1×10^{-2}	0.096
		Quadratic term	-0.000061 -6.1×10^{-5}	-1.0×10^{-4} to 2.0×10^{-5}	**0.004**

Covariates included in models: age, gender, antidepressant use

Supplementary Table 4. Longitudinal Mixed Effects Models Demonstrating Whether Treatment Modifies the Effects of Baseline Cortisol on Trajectory of Depressive Symptoms

	Treatment x Cortisol x time interactions	Coefficient	95% CI	*P*
Morning peak cortisol *n* = 112	Linear term	-2.3×10^{-2}	-6.2×10^{-2} to 1.6×10^{-2}	0.25
	Quadratic term	1.3×10^{-4}	-2.9×10^{-5} to 4.3×10^{-5}	0.15
Evening cortisol *n* = 166	Linear term	-1.8×10^{-2}	-3.9×10^{-2} to 2.8×10^{-3}	0.089
	Quadratic term	3.6×10^{-5}	-3.5×10^{-5} to 1.1×10^{-4}	0.32

Treatment Contrast: CBT/STPP(combined) vs BPI. Covariates included in models: age, gender