Cortisol levels and suicidal behavior: A meta-analysis

In press

Psychoneuroendocrinology

Daryl B. O'Connor, PhD[1*], Eamonn Ferguson, PhD[2,] Jessica A. Green, MSc[1],

Ronan E. O'Carroll, PhD[3], & Rory C. O'Connor, PhD[4*]

[1]School of Psychology, University of Leeds, Leeds UK

[2]School of Psychology, University of Nottingham, Nottingham, UK

[3]Department of Psychology, University of Stirling, Stirling, UK

[4]Suicidal Behaviour Research Laboratory, Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK

Running head: Cortisol and suicide

Correspondence to:

Daryl B. O'Connor	or	Rory C. O'Connor
School of Psychology		Institute of Health & Wellbeing
University of Leeds,		University of Glasgow
Leeds, UK		Glasgow, UK
e: d.b.oconnor@leeds.ac.uk		e: rory.oconnor@glasgow.ac.uk
t: ++44 113 3435727		t: 0141 2113924

ABSTRACT

Suicide is a major cause of death worldwide, responsible for 1.5% of all mortality. The causes of suicidal behavior are not fully understood. Dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity, as measured by cortisol levels, is one potential risk factor. This meta-analytic review aimed i) to estimate the strength and variability of the association between naturally fluctuating cortisol levels and suicidal behavior and ii) to identify moderators of this relationship. A systematic literature search identified 27 studies (N = 2226; 779 suicide attempters & 1447 non-attempters) that met the study eligibility criteria from a total of 417 unique records initially examined. Estimates of effect sizes (r) obtained from these studies were analysed using Comprehensive Meta-Analysis. In these analyses, we compared participants identified as having a past history of suicide attempt(s) to those with no such history. Study quality, mean age of sample and percentage of male participants were examined as potential moderators. Overall, there was no significant effect of suicide group on cortisol. However, significant associations between cortisol and suicide attempts were observed as a function of age. In studies where the mean age of the sample was below 40 years the association was positive (i.e., higher cortisol was associated with suicide attempts; $r = .234$, $p < .001$), and where the mean age was 40 or above the association was negative (i.e., lower cortisol was associated with suicide attempts; $r = -.129$, $p < .001$). These findings confirm that HPA axis activity, as indicated by age-dependent variations in cortisol levels, is associated with suicidal behavior. The challenge for theory and clinical practice is to explain the complete reversal of the association with age and to identify its clinical implications.

Funding: US Department of Defense (US DOD W81XWH-12-1-0007)

1. INTRODUCTION

Suicide is a major cause of death worldwide, responsible for 1.5% of all mortality. The causes of suicidal behavior are not fully understood; however, this behavior clearly results from a complex interplay between many different factors. Numerous models have been proposed that differ in their emphasis on the role of psychological, social, psychiatric and neurobiological factors in predicting risk of suicide and identifying targets for intervention to improve suicide prevention (Mann et al., 1999; O'Connor, 2011; O'Connor & Nock, 2014; van Heeringen and Mann, 2014; van Orden et al., 2010). However, central to many models is a stress-diathesis component which states that suicidal behavior is a result of an interaction between acutely stressful events and a susceptibility to suicidal behavior (a diathesis). Evidence is accumulating from post-mortem, neuroimaging and in-vivo studies that a trait diathesis is not only manifested in impairments of the serotonergic and noradrenergic neurotransmitter systems, in structural brain abnormalities and via epigenetic pathways but also in dysregulation of hypothalamic-pituitary-adrenal (HPA) axis stress response activity (Mann, 2013; Turecki et al., 2012; van Heeringen et al., 2011; van Heeringen and Mann, 2014). Moreover, it has been suggested that biomarkers of a trait-diathesis following serious stressful and traumatic psychosocial events, independent of psychiatric co-morbidities, may be useful predictors of suicide risk (van Heeringen and Mann, 2014). One such potential biomarker is the glucocorticoid, cortisol.

When we experience stress, the HPA axis is activated and releases cortisol from the adrenal glands. Once released, cortisol has several important functions such as increasing access to energy stores, increasing protein and fat mobilisation, as well as regulating the magnitude and duration of inflammatory responses (Sapolsky et al., 2000). Cortisol has also been found to be associated with impairments in cognitive control, decision-making and emotional processing linked to suicidal behavior (Giletta et al., 2015; Turecki et al., 2012). As such, cortisol is the primary effector hormone of the HPA axis stress response system and has received extensive empirical investigation. As with other aspects of the endocrine system, the HPA axis is regulated by a negative feedback system, whereby the hypothalamus and the pituitary gland have receptors that detect changes in cortisol

levels. For example, cortisol secretion will be inhibited when circulating levels rise or it will be stimulated when levels fall. However, if the HPA axis is repeatedly activated, this will trigger increased cortisol output, thereby exposing bodily tissues to excessive concentrations of the hormone (McEwen, 1998; McEwen, 2000; Miller et al., 2007). Over time, such repetitive activation may lead to tissue damage and contribute to future ill health by placing excessive pressure on various bodily systems including the HPA axis (known as allostatic load; McEwen, 1998). Nonetheless, the precise effects of psychological stress on HPA axis regulation in relation to the *diurnal* cortisol profile and how this relates to suicidal behavior remains unclear.

The majority of previous research on cortisol and suicidal behavior relations has focused on assessing HPA axis functioning through pharmacological manipulation of the stress system (Mann and Currier, 2007; Pompili et al., 2010). The Dexamethasone Suppression Test (DST; Carroll et al., 1968) has been commonly employed to assess HPA axis dysregulation by measuring cortisol inhibition after the administration of the synthetic glucocorticoid Dexamethasone. Failure to suppress cortisol is evidence for HPA-axis hyperactivity and has consistently been found to predict completed suicide in patients with mood disorder for example (Coryell and Schlesser, 1981; Coryell et al., 2006; Jokinen and Nordstrom, 2008; Jokinen and Nordstrom, 2009; Jokinen et al., 2009; Norman et al., 1990). However, whilst DST research has contributed enormously to knowledge regarding HPA axis dysregulation and suicide vulnerability, findings remain inconsistent and contradictory (McGirr et al., 2011). Pharmacological manipulation has also been criticised as it may not adequately mimic the size of the endogenous HPA response to naturally occurring stressors (Burke et al., 2005). In addition, more recent studies have begun to explore other aspects of the cortisol response, such as the diurnal cortisol rhythm (including morning and afternoon/evening cortisol levels) and cortisol reactivity to stressors (for example, see McGirr et al., 2010).

Studies that have explored the relationship between naturally fluctuating cortisol and suicidal behavior have yielded inconsistent findings. For example, Westrin et al. (1999) found elevated cortisol levels in patients who had recently attempted suicide compared to healthy controls, while Lindqvist and colleagues (2008) found that cortisol levels were significantly lower in suicide

attempters compared to controls. A number of methodological factors may account for these mixed findings including the timing of the cortisol sampling (morning vs afternoon/evening) and study quality (both of which are examined in the current meta-analysis). However, age is another important variable that has been found to be associated with cortisol levels *and* suicidal behavior (Hawton et al., 2012; Hawton and van Heeringen, 2009). For example, cortisol levels have been shown to increase as part of normal aging (possibly mediated by diminished negative feedback inhibition), but normal-to-low levels of cortisol have also been observed in older Holocaust survivors with posttraumatic stress disorder (PTSD) and in patient groups with different stress-related disorders such as fibromyalgia (Ferrari et al., 2000; Fries et al., 2005; Yehuda et al., 2005). Taken together, these data suggest that the relationship between age and cortisol levels is far from straightforward and it is likely moderated by stress-related factors. In terms of suicidal behavior, age has been found to be differentially associated with suicide. In most regions in the world, suicide rates are highest in individuals aged 70 years and older (World Health Organization, 2014). However, in some countries, the highest levels of suicide are among the young (15-29 year olds) and in more wealthy countries, men are three times as likely to die by suicide. However, it is worth noting that age has also been found to be inversely associated with suicide *attempt*, such that greater levels of suicide attempt have been observed in younger people (e.g., Nock et al., 2008). Therefore, for these reasons, the mean age of the sample and percentage of males in each sample will be also explored as potential moderators of the relationship between cortisol and suicide attempter status (Hawton et al., 2012; Hawton and van Heeringen, 2009). Therefore, the goal of this review was to synthesize findings from all existing research that has compared participants with at least one prior suicide attempt with a comparison group with no suicide attempt history in order: i) to estimate the strength and variability of the association between naturally fluctuating cortisol levels and suicidal behavior and ii) to identify moderators of this relationship.

2. METHOD

2.1. Search Strategy

PubMed, ISI Web of Science (ISI WOS) and PsycINFO were searched for full published reports from 1958 until the end of February 2015. The following search terms were used; (i) suicid* AND cortisol. Initially all abstracts were examined to identify studies meeting the study inclusion

criteria, before the full text was assessed for eligibility. The search strategy was inclusive, including studies of inpatient, outpatient and non-clinical samples.

The following eligibility criteria were used: (1) published in a peer-reviewed journal and written in English, (2) levels of naturally occurring cortisol were reported, assayed from either cerebral spinal fluid, urine, saliva, or blood, (3) a measure or report of suicide attempt history was described, (4) the sample included a case group of participants who had made at least one prior suicide attempt and comparison participants with no history of suicide attempt, and (5) the association between cortisol and suicide history was reported, or a statement that an association did not exist was specified. Studies which only reported cortisol levels after the introduction of an exogenous substance (e.g. dexamethasone) were excluded. Studies which carried out a challenge test but reported pre-manipulation cortisol levels were included, but only those findings relating to cortisol measured prior to manipulation were used.

2.2. Data Extraction

The following information was taken from each published report: the study design, sample demographic information and any exclusion criteria, the primary sample diagnoses and method used to assess psychopathology, the methodology used to ascertain suicide history, procedural details relating to the assessment of cortisol, controlled variables, details relating to longitudinal designs (duration, follow up procedure, attrition rate) and the main findings or related statistical information between cortisol and suicide group.

2.3. Quality Assessment

Each study was assessed for methodological quality using a six item index developed *a priori* by the authors. A score from 0-2 (with the exception of suicide attempt history assessment scored 0-3) was given for each item, and then a total quality score was calculated ranging from a score of 0 to a maximum of 13. The six methodological criteria points can be found in Table 1 in the Supplementary Materials.

2.4. Statistical Analysis

We compared participants identified as having a past history of suicide attempt(s) to individuals with no such history. If multiple case groups existed within these categories (e.g. violent

and non-violent attempters), an average value was used. Due to the majority of studies assaying cortisol from blood, if within studies there were multiple analytical methods (e.g. blood and urine samples), only blood data was included in the analyses in order to not "double count" any one study. However, in those studies where cortisol was only sampled from non-blood substances (e.g. saliva, cerebrospinal fluid) we extracted the available data.

Data were available for cortisol at various time points. Although the majority of studies only sampled morning cortisol (before midday), we did not want to exclude data collected at different time points. Therefore, an overall analysis was conducted which included all data regardless of the time of day. However, acknowledging the importance time of day has on cortisol levels, separate analyses were carried out only including cortisol samples collected before midday (AM) and cortisol collected in the afternoon or evening (PM).

The correlation coefficient was used as the index of effect size for the reasons specified by Roberts et al., 2007). Other effect size estimates, such as odds ratios (OR) and risk ratios (RR), can make small effects appear bigger than they are in absolute terms. Second, compared to indices like ORs, the correlation has an upper and lower limit for judging the relative size of the effect.

All analyses were conducted in Comprehensive Meta-Analysis (CMA) version 2©. All effects were coded to indicate if cortisol was higher in the suicide attempters versus the non-attempters, with random effects models estimated.

3. RESULTS

3.1. Study Information

In total, 854 records were initially identified. After the removal of duplicates, the abstracts of 491 unique records were examined (see Figure 1 in supplementary materials). The main reasons for excluding studies at this stage were that the subject matter did not relate to cortisol or suicidality, or the record was not a research article reporting primary data. Research studies measuring HPA functioning using pharmacological challenge tests (e.g. the DST) were retained at this stage if it could not be determined from the abstract alone whether they also measured pre-manipulation cortisol levels. After the exclusion of 365 records, the full texts of 126 articles were screened for eligibility.

Twenty-seven studies published between 1980 and 2013 were identified as meeting the inclusion criteria.

3.2. Descriptive Statistics

The characteristics of the 27 studies included in the meta-analysis are presented in Table 1. The combined sample totalled 2269 participants, including 798 suicide attempters and 1471 non-attempters. The median sample size was 56 with a range of 22 to 359 participants. The mean age in the individual studies ranged from 17.62 to 55.80 years, giving a combined mean age of 39.42 years (SD = 8.60). The average proportion in the combined sample reported as male was 50.1%. In terms of study quality, there was a broad range of scores allocated to studies extending from a low score of 2 to a high score of 11.

Of the 24 studies that reported the specific time cortisol was assayed, 16 measured morning cortisol (66.6%), 4 only assayed during the afternoon or evening (16.6%) and four measured cortisol at multiple time points throughout the day (16.6%). The remaining three studies either did not report the time of day cortisol was assayed (Kim et al., 2013), or measured 24 hour cortisol from urine (Ostroff et al., 1982; van Heeringen et al., 2000).

3.3. *Meta-analysis*

The results of the random effects meta-analysis are shown in Table 2. Overall, no association was found between suicide group and cortisol for all 27 studies, the 24 studies that reported time of assay, or when analysing the AM and PM data separately (Table 2, upper panel). However, there was a significant moderation effect for the mean age of the samples for all 27 studies and in each of the subgroup analyses (Table 2, upper panel). Meta-regression of *r* on age found a significant negative effect for age. At approximately 39-40 years there is a reversal of the direction of the effect size (see Figure 2 Supplementary Materials). Prior to 40 years the association is mostly positive (higher cortisol is associated with suicide attempts), whereas after 40 years this becomes generally negative (lower cortisol associated with suicide attempts). To examine this further we recoded average age into less than 40 years and equal to and greater than 40 years. We ran mixed effects models to examine whether there was a significant difference in the association between cortisol and suicide across this age split for all 27 studies, for the 24 studies that reported the specific time cortisol was assayed, and

then again separately in AM and PM samples. The results are shown in Table 2, lower panel. As can be seen in all cases, the differences are statistically significant, indicating that where the average age of the sample was below 40 years the association was positive, whereas it was negative for samples where the average age was equal to or above 40 years. A summary of the moderating effects of age are shown in the Forest Plot for the full sample (k = 27; Figure 3 in the Supplementary Materials). If we restrict these analyses just to blood samples the same pattern of results is observed (data not shown). It is also worth noting that the mean absolute levels of cortisol were consistent with the observed associations outlined above. In studies with a mean age less than 40 years, the mean cortisol was 399.19 nmol/L in the attempter group compared to 312.49 nmol/L in the non-attempter group. In studies with a mean age greater than 40 years, the mean cortisol was 367.10 nmol/L in the attempter group compared to 411.71 nmol/L in the non-attempter group.

There was no evidence that the association between suicide attempts and cortisol level was moderated by sex (Table 1, upper panel) or year of publication (data not shown). However, study quality was found to significantly influence the relationship. For the all (k = 27) analyses there was a significant effect of study quality (B = -0.03, p = .013) indicating that as quality improved the effect size becomes smaller. Similar results were found in the AM + PM (k = 24) analyses (B = -0.033, p = .007) and the AM only (k = 20) analyses (B = -0.05, p = .0005), but not for the PM only (k = 8) analyses (B = -0.02, p = .22).

Nine studies were identified where the participants were diagnosed as having unipolar depression, major depressive disorder or depression (Ayuso-Gutiérrez and Cabranes, 1987; Brown et al., 1986; Brunner et al., 2002; Inder et al., 1997; Karlović et al., 2012; Kim et al., 2013; Pitchot et al., 1995; 2005; Westrin et al., 1999). Therefore, we also explored whether the moderating effects of age was observable in this sub-group. Meta-regression showed a significant negative effect of age -0.013 (p = .004) consistent with the analysis of the whole sample. Categorical moderation for age (average sample age below or above 40 years) demonstrated an effect approaching significant (Q = 3.34, p = .08), with a significant negative association between cortisol and suicide in samples older on average than 40 (r = -0.09, p = .018, *k* = 5) and a positive, but non-significant association, for samples under 40 (r = 0.18, p = .238, *k* = 4). Thus the general pattern of results replicates the main findings.

3.4. Publication bias

There was no evidence for publication bias (Table 1). Edger's intercept was non-significant for all four analyses and Duvall and Tweedie's Trim and Fill analysis indicated that there were no missing studies that would alter the result. However, Cochran's Q was found to be significant for the overall analysis, and for the time subgroup analyses, suggesting considerable heterogeneity in study outcomes. The I^2 statistic revealed that 79% to 83% of the variation in study outcomes was due to true heterogeneity, thereby confirming the need to examine the potential effects of moderating variables on the suicide attempts-cortisol association.

3.5. Time between suicide attempt and assessment of cortisol

One potential methodological confound is the time between the suicide-related event and the assessment of cortisol. We examined this by initially coding if temporal data were available or not and found that 14 of the 27 studies reported the timing of cortisol assessment. The association between cortisol and suicidal behavior did not vary systematically across reporting or not reporting temporal information ($p = .17$) and was non-significant in studies that did not report timing ($p = .95$) and those that did ($p = .074$). In addition, these temporal parameters (time recorded or not) did not influence the reversal in association around the 40 year age split, such that the observed effects remained in both groups but stronger in the group that did record temporal data.

4. DISCUSSION

The results of this meta-analysis confirm that HPA axis activity, as indicated by age-dependent variations in naturally occurring cortisol levels, are associated with suicide attempt. Generally in younger samples, less than 40 years old, the association was positive, such that suicide attempts were associated with greater cortisol levels, but for older samples the effect was reversed, with suicide attempts associated with lower cortisol levels. Moreover, the moderating effects of age were also significant in studies that assessed cortisol in the morning and afternoon/evening. The relationship between cortisol and suicide attempts was not influenced by percentage of males in study

samples or year of publication. However, as frequently observed in meta-analyses, the study quality influenced the associations, such that, smaller effect sizes were observed in better quality studies.

These findings indicate clearly that a reversal in the association between cortisol and suicidal attempt occurs when the average age of the sample is 40 years or older. This is not to imply that for any individual the shift would happen at 40 years, this is on average. Nonetheless, what these analyses do demonstrate is that for older people the association is negative and for younger people it is positive and that the relationship between cortisol and suicide attempts is more complex than previously acknowledged. In addition, these findings may have implications for research studies that have assessed HPA axis functioning using pharmacological manipulation of the stress system such as the DST and raise the interesting question as to whether age moderates the extent to which cortisol is suppressed following manipulation.

What may account for this reversal of the association between cortisol levels and suicide attempts? The short answer is we do not know. We are mindful that there is huge variation in the studies, their designs and in cortisol and suicidal attempt assessments (see shortcomings section below). Nevertheless, with these caveats notwithstanding and the obvious associated "noise" linked to meta-analyses generally, we feel these findings are worthy of dissemination and may be important to inform future research. Therefore, within this context, we feel there are a number of plausible explanations that may account for the observed effects.

Broadly speaking, the findings are consistent with McEwen's notion of allostatic load, whereby if the HPA axis is repeatedly activated (by stress) the immune, cardiovascular and the endocrine systems are potentially exposed to excessive demands that over time can lead to dysregulation of these systems (McEwen, 1998; 2000). For example, a recent large scale prospective study, using a comprehensive measure of allostatic load (including cortisol levels), found that participants with higher allostatic load scores had a greater risk of having died 10 years later from all-cause mortality (Hwang et al., 2014). Therefore, in the current context, naturally fluctuating cortisol levels may provide an index (or proxy) for the amount of stress exposure that individuals have encountered. This view is also consistent with an influential account of the development of hypocortisolism, which suggests that the latter phenomenon occurs after a prolonged period of

hyperactivity of the HPA axis due to chronic stress (see Fries et al., 2005) for detailed discussion of precise mechanisms). As such, younger individuals (less than 40 years), who have been exposed to serious stressful and psychosocial events, are likely to continue to exhibit an adaptive HPA axis stress response in the short to medium term (by releasing high levels of cortisol in response to their adverse and stressful environment). In contrast, in individuals who are older (40 years or older) and who have likely been exposed to stressful and traumatic events over a longer, more sustained period, their HPA axis may have become dysregulated leading to lower secretion of circulating cortisol levels. Indeed, lower circulating levels of cortisol have been observed in older Holocaust survivors with PTSD compared to those without PTSD (Yehuda et al., 1995). Furthermore, time course effects have also been found in studies of suicide attempters with major depressive disorders (MDD) (e.g., Ehnvall et al., 2004; Lindqvist et al., 2008). For example, Lindqvist et al. (2008) found that greater suicidal intent was associated with lower post DST cortisol levels. Indeed, these authors speculated that this finding reflected an association between the chronicity of the illness, high suicidal intent and a "worn-out" HPA axis (p. 205), such that the prolonged depressive illness alters the HPA axis feedback system, moving it from a hyperactive state to a more normal like state (see also Ehnvall et al., 2004). Moreover, in the current meta-analysis, the differences in *absolute* cortisol levels between the groups support this theorizing with under 40 year olds who had attempted suicide exhibiting higher cortisol levels compared to under 40 year olds who had not attempted suicide. In contrast, over 40 year olds who had attempted suicide exhibited lower cortisol levels compared to over 40 year olds who had not attempted suicide.

This possible explanation is also in keeping with the findings by Miller et al., 2007). In their review, Miller and colleagues highlighted the importance of the temporal features of stressors and showed that time of onset of stress was negatively associated with HPA axis activity. More specifically, they found that the greater the amount of time that had passed since the stressor was encountered, the lower participants' morning cortisol and total daily cortisol output. These authors argued that the HPA axis exhibits initial activation in the form of elevated cortisol release (as observed in studies here with a mean age of less than 40 years). However, following prolonged exposure to the stressors, they theorized that, this activity reduces and cortisol secretion rebounds to

less than normal. As a result, it is possible that in individuals over 40 years old, that the more they fail to mount an appropriate cortisol response, the greater their suicide risk. For example, hyporesponsivity of the HPA axis to acute stressors (as well as hyperresponsivity) has been found to impair decision-making processes and emotional reactivity, aspects of cognitive functioning that are associated with suicidal behavior (Giletta et al., 2015; Jollant et al., 2011; Turecki et al., 2012; van Honk et al., 2003).

As well as identifying the importance of age as a moderator of the cortisol and suicide attempt relationship, the results of this meta-analysis may help to clarify the mixed and inconsistent findings observed to date in this literature. Previous studies have shown that suicidal attempts are associated with elevated cortisol (or hypercortisolism) as well as blunted or low cortisol levels (or hypocortisolism) (e.g., Mann and Currier, 2007; Lindqvist et al., 2008). The current results reveal that both types of observations may be valid and true, but may be accounted for by age-dependent exposure to stress overtime. However, this meta-analysis does not shed any additional light on the relationship between HPA axis functioning and completed suicide (as distinct from suicide attempt). Existing evidence from prospective DST studies suggests that HPA hyperactivity is more consistently associated with completed suicide compared to suicide attempt (Mann and Currier, 2007). For example, Coryell and Schlesser (2001) reported that there was a 14 fold higher risk of completed suicide in DST non-suppressors compared to suppressors. In contrast, the evidence for a clear relationship between HPA hyperactivity, as assessed using the DST, and suicide attempt is mixed. Some studies have shown that DST suppression status is unable to distinguish between individuals who will attempt suicide and those who will not. Yet other research findings have demonstrated DST suppression is associated with a higher rate of suicide attempts (see Mann & Currier, 2007 for a review). Mann and Currier suggest that an important reason why non-suppression on the DST is predictive of completed suicide may be because it is also associated with "a failure to respond to antidepressant treatment or a tendency for early relapse such as shortly after discharge" (p. 10). Therefore, within this context, future research ought to attempt to synthesise existing prospective studies investigating the relationship between naturally fluctuating levels of cortisol and completed suicide and to examine the potential moderating role of age.

We recognize that there are a number of shortcomings and limitations of this meta-analysis that require further comment. There was a great deal of variability across the studies in terms of how suicide attempt was assessed, the timing and measurement of cortisol samples and in relation to controlling for confounding variables. As a result, conclusions about the precise nature of the relationship between cortisol and suicide attempt remain unknown. Therefore, future investigators ought to improve the quality of their studies in this area by utilising longitudinal designs (over many years) that incorporate assessments of suicidal behavior using clinical interviews or validated scales and ensure cortisol is sampled at numerous time points across the day (morning, afternoon, evening) over multiple days. In addition, it is incumbent on researchers to investigate *why* age moderates the relationship between fluctuating cortisol levels and suicide attempt and to explore the role played by different, traumatic and stressful psychosocial events (including psychiatric co-morbidities) within the context of allostatic load, PTSD, hypocortisolism and chronic stress models. We acknowledge also that the current meta-analysis did not include studies that utilised a pharmacological manipulation of cortisol levels and that approaches such as the DST have a number of important advantages over studies that have included one or more naturally occurring assessments of cortisol. We are cognizant that the former research designs allow for carefully controlled experimental investigation of how the HPA responds to challenge as well as permitting important variables such as time of day to be held constant. Nevertheless, given the DST and suicide literature has been successfully reviewed elsewhere (Jollant et al., 2011; Mann and Currier, 2007) and because of the concerns raised that the DST may not accurately mimic how the HPA axis responds to naturally occurring stressors (McGirr et al., 2011), we were motivated to synthesis the existing studies that has been conducted outside the laboratory. Nevertheless, to our mind, in order to fully and accurately characterise how the HPA axis responds to stress in vulnerable individuals, future research ought to integrate pharmacological, laboratory-based stress challenges and naturally occurring approaches that assess the cortisol awakening response as well as cortisol levels throughout the day (see Gartland et al., 2014; O'Connor et al., 2009).

In summary, these findings confirm that HPA axis activity, as indicated by age-dependent variations in cortisol levels, is associated with suicidal behavior. The challenge for theory and clinical

practice is to explain the complete reversal of the association with age and to identify its clinical implications.

Authors' contributions

All authors contributed equally

Role of the funding source

This research was supported in part by a research award from the US Department of Defense (Award No. W81XWH-12-1-0007). Opinions, interpretations, conclusions and recommendations are those of the authors and are not necessarily endorsed by the funder. The funder had no role in the writing of the manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare

Ethics committee approval

The manuscript describes the results of a meta-analysis, therefore, it did not require ethical approval

REFERENCES

Ayuso-Gutiérrez, J., Cabranes, J., 1987. Pituitary-adrenal disinhibition and suicide attempts in depressed patients. Biol Psychiatry. 22, 1409–1412.

Brown, R., Mason, B., Stoll, P., Brizer, D., 1986. Adrenocortical function and suicidal behavior in depressive disorders. Psychiatry Res. 17, 317–323.

Brunner, J., Keck, M.E., Landgraf, R., Uhr, M., Namendorf, C., Bronisch, T., 2002. Vasopressin in CSF and plasma in depressed suicide attempters: preliminary results. Eur Neuropsychopharmacology 12, 489–94.

Brunner, J., Stalla, G.K., Stalla, J., Uhr, M., Grabner, A., Wetter, T.C., Bronisch, T., 2001. Decreased corticotropin-releasing hormone (CRH) concentrations in the cerebrospinal fluid of eucortisolemic suicide attempters. J Psychiatric Res. 35, 1–9.

Burke, H.M., Davis, M.C., Otte, C., Mohr, D.C., 2005. Depression and cortisol responses to psychological stress: a meta-analysis. Psychoneuroendocrinology 30, 846-856.

Carroll, B., Martin, F., Davies, B., 1968. Resistance to suppression by dexamethasone of plasma 11-OHCS levels in severe depressive illness. BMJ 3, 285.

Chatzittofis, A., Nordström, P., Hellström, C., Arver, S., Asberg, M., Jokinen J., 2013. CSF 5-HIAA, cortisol and DHEAS levels in suicide attempters. Eur Neuropsychopharmacology 23, 1280–7.

Coryell, W., Schlesser, M.A., 1981. Suicide and the dexamethasone suppression test in unipolar depression. Am J Psychiatry 138, 1120-1121.

Coryell, W., Schlesser, M.A. 2001. The dexamethasone suppression test and suicide prediction. Am J Psychiatry 158, 748-753.

Coryell, W., Young, E., Carroll, B., 2006. Hyperactivity of the hypothalamic-pituitary-adrenal axis and mortality in major depressive disorder. Psychiatry Res. 142, 99-104.

Ehnvall, A., Sjogren, M., Zachrisson, O.C., Agren, H., 2004. HPA axis activation determined by the CRH challenge test in patients with few versus multiple episodes of treatment-refractory depression. Eur Arch Psychiatry Clin Neurosci. 254, 349-355.

Ferrari E, Arcaini A, Goranti R, Pelanconi L, Cravello L, Fioravanti M, Solerte SB, Magri F., 2000. Pineal and pituitary-adrenocortical function in physiological aging and in senile dementia. Exp Gerontol. 35,1239-1250.

Fries, E., Hesse, J., Hellhammer, J., Hellhammer, D.H., 2005. A new view of hypocortisolism. Psychoneuroendocrinology 30, 1010-1016.

Gartland, N., O'Connor, D.B. Lawton, R., Bristow, M., 2014. Exploring day-to-day dynamics of daily stressor appraisals, physical symptoms and the cortisol awakening response. Psychoneuroendocrinology 50, 130-138.

Giletta, M., Calhoun, C.D., Hastings, P.D., Rudolph, K.D., Nock, M.K., Prinstein, M.J., 2015. Multi-level risk factors for suicide ideation among at-risk adolescent females: The role of hypothalamic-pituitary-adrenal axis responses to stress. J Abnorm Child Psychol. 43, 807-820.

Gmitrowicz, A., Kołodziej-Maciejewska, H., 2002. Dysfunction of the hypothalamic-pituitary-adrenal axis in adolescents after a suicide attempt. Psychiatria Polska 35, 803–18.

Hawton, K., Saunders, K.E.A., O'Connor, R.C., 2012. Self-harm and suicide in adolescents. Lancet 379, 2373-2382

Hawton, K., van Heeringen, K., 2009. Suicide. Lancet 373, 1372-81.

Hwang, A., Peng, L., Wen, Y., Tsai, Y., Chang, L., Chiou, S., Chen L., 2014. Predicting all-cause and cause specific mortality by static and dynamic measurements of allostatic load: A 10-year population-based cohort study in Taiwan. J Amer Med Dir Assoc. 15, 490-496.

Inder, W.J., Donald, R.A., Prickett, T.C., Frampton, C.M., Sullivan, P.F., Mulder, R.T., Joyce, P.R., 1997. Arginine vasopressin is associated with hypercortisolemia and suicide attempts in depression. Biol Psychiatry 42, 744–7.

Jokinen, J., Nordstrom, P., 2009. HPA axis hyperactivity and attempted suicide in young adult mood disorder inpatients. J Affect Disord. 116, 117-120.

Jokinen, J., Nordstrom, P., 2008. HPA axis hyperactivity as suicide predictor in elderly mood disorder inpatients. Psychoneuroendocrinology 33, 1387-1393.

Jokinen, J., Nordstrom, A.L., Nordstrom, P., 2009. CSF 5-HIAA and DST non-suppression--orthogonal biologic risk factors for suicide in male mood disorder inpatients. Psychiatry Res. 165, 96-102.

Jokinen, J., Ouda, J., Nordstrom, P., 2010. Noradrenergic function and HPA axis dysregulation in suicidal behaviour. Psychoneuroendocrinology 35, 1536-1542.

Jollant, F., Lawrence, N.L., Olie, E., Guillaume, S., Courtet, P., 2011. The suicidal mind and brain: a review of neuropsychological and neuroimaging studies. World J Biol Psychiatry 12, 319-339.

Kamali, M., Saunders, E.F.H., Prossin, A.R., Brucksch, C.B., Harrington, G.J., Langenecker, S., McInnis, M.G., 2012. Associations between suicide attempts and elevated bedtime salivary cortisol levels in bipolar disorder. J Affect Disord. 136, 350–8.

Karlović, D., Serretti, A., Vrkić, N., Martinac, M., Marčinko, D., 2012. Serum concentrations of CRP, IL-6, TNF-α and cortisol in major depressive disorder with melancholic or atypical features. Psychiatry Research 198, 74–80.

Keilp, J.G., Oquendo, M.A., Stanley, B.H., Burke, A.K., Cooper, T.B., Malone, K.M., Mann, J.J., 2010. Future suicide attempt and responses to serotonergic challenge. Neuropsychopharmacology 35, 1063–72.

Kim, B., Kang, E-S., Fava, M., Mischoulon, D., Soskin, D., Yu, B-H.… Jeon, H.J., 2013. Follicle-stimulating hormone (FSH), current suicidal ideation and attempt in female patients with major depressive disorder. Psychiatry Res. 210, 951–6.

Lindqvist, D., Isaksson, A., Träskman-Bendz, L., Brundin, L., 2008. Salivary cortisol and suicidal behavior--a follow-up study. Psychoneuroendocrinology 33, 1061–8.

Lindqvist, D., Traskman-Bendz, L., Vang, F., 2008. Suicidal Intent and the HPA-axis characteristics of Suicide Attempters with Major Depressive Disorder and Adjustment Disorder. Arch Suicide Res. 12, 197-207.

Mann, J.J., 2013. The serotonergic system in mood disorders and suicidal behaviour. Philos Trans R Soc Lon B Bio Sci. 368, 20120537.

Mann, J.J., Currier, D., 2007. A review of prospective studies of biologic predictors of suicidal behavior in mood disorders. Arch Suicide Res. 11, 3-16.

Mann, J.J., Waternaux, C., Haas, G.L., Malone, K.M., 1999. Toward a clinical model of suicidal behavior in psychiatric patients. Am J Psychiatry 156, 181-189.

Marcinko, D., Martinac, M., Karlović, D., Filipcić, I., Loncar, C., Pivac, N., Jakovljević, M., 2005. Are there differences in serum cholesterol and cortisol concentrations between violent and non-violent schizophrenic male suicide attempters? Collegium Antropologicum 29, 153–7.

Markianos, M., Tripodianakis, J., Istikoglou, C., Rouvali, O., Christopoulos, M., Papageorgopoulos, P., Seretis, A., 2009. Suicide attempt by jumping: a study of gonadal axis hormones in male suicide attempters versus men who fell by accident. Psychiatry Res. 170**,** 82–5.

McEwen, B.S., 1998. Protective and damaging effects of stress mediators. NEJM 338, 171-179.

McEwen, B.S., 2000. Allostasis and allostatic load: Implications for neuropsychopharmacology. Neuropsychopharmacology 22, 108-124.

McGirr, A., Diaconu, G., Berlim, M.T., Pruessner, J.C., Sable, R., Cabot, S., Turecki, G., 2010. Dysregulation of the sympathetic nervous system, hypothalamic-pituitary-adrenal axis and executive function in individuals at risk for suicide. J Psychiatry Neurosci. 35, 399-408.

McGirr, A., Diaconu, G., Berlim, M.T., Turecki, G., 2011. Personal and family history of suicidal behavior is associated with lower peripheral cortisol in depressed outpatients. J Affect Disord. 131, 368–373.

Miller, G.E., Chen, E., Zhou, E.S., 2007. If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychol Bull. 133, 25-45.

Nock, M.K., Borges, G., Bromet, E.J., Alonso, J., Angermeyer, M., Beautrais, A., Bruffaerts, R., TatChiu, W., de Girolamo, G., Gluzman, S., de Graaf, R., Gureje, O., Haro, J.M., Huang, Y., Karam, E., Kessler, R.C., Lepine, J.P., Levinson, D., Medina-Mora, M.E., Ono, Y., Posada-Villa, J., Williams, D., 2008. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. Br J Psych. 192, 98-105.

Norman, W.H., Brown, W., Miller, I.W., Keitner, G.I., Overholser, J., 1990. The dexamethasone suppression test and completed suicide. Acta Psychiatrica Scandinavica 81, 120-125.

O'Connor, D.B., Hendrickx, H., Dadd, T., Talbot, D., Mayes, A., Elliman, T., Willis, T., Dye, L., 2009. Cortisol awakening rise in middle-aged women in relation to chronic psychological stress. Psychoneuroendocrinology 34, 1486-1494.

O'Connor, R.C., 2011. Towards an Integrated Motivational-Volitional of Suicidal Behaviour. In R O'Connor, S Platt, & J Gordon (Eds.) International Handbook of Suicide Prevention: Research, Policy and Practice. Wiley Blackwell. pp181-191.

O'Connor, R.C., Nock, M., 2014. The psychology of suicidal behaviour. Lancet Psychiatry 1, 73–85.

Ostroff, R., Giller, E., Bonese, K., 1982. Neuroendocrine risk factors of suicidal behavior. Am J Psychiatry 139, 1323–1325.

Pitchot, W., Hansenne, M., Pinto, E., Reggers, J., Fuchs, S., Ansseau, M., 2005. 5-Hydroxytryptamine 1A receptors, major depression, and suicidal behavior. Biol Psychiatry 58, 854–8.

Pitchot, W., Hansenne, M., Gonzalez Moreno, A., Ansseau, M., 1995. The dexamethasone suppression test in violent suicide attempters with major depression. Biol Psychiatry 37, 273–4.

Płocka-Lewandowska, M., Araszkiewicz, A., Rybakowski, J.K., 2011. Dexamethasone suppression test and suicide attempts in schizophrenic patients. *Eur Psychiatry* 16, 428–31.

Pompili, M., Serafini, G., Innamorati, M., Moller-Leimkuhler, A.M., Giupponi, G., Girardi, P.... Lester, D., 2010. The hypothalamic-pituitary-adrenal axis and serotonin abnormalities: a selective overview for the implications of suicide prevention. Eur Arch Psychiatry Clin Neurosci. 260, 583-600.

Roberts, B.W., Kuneel, N.R., Shiner, R., Caspi, A., Goldberg, L.E., 2007. The power of personality. Perspectives in Psychological Science 2, 313-345

Roy, A., 1992. Hypothalamic-pituitary-adrenal axis function and suicidal behavior in depression. Biological Psychiatry 32, 812–6.

Saiz, P., Bobes, J., Gonzalez, M., 1997. Searching for a predictive peripherical biological model in parasuicidal behavior. Eur Psychiatry 12, 75-81.

Sapolsky, R.M., Romero, L.M., Munck, A.U., 2000. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Reviews 21, 55-89.

Secunda, S.K., Cross, C.K., Koslow, S., Katz, M.M., Kocsis, J., Maas, J.W., 1986. Landis H. Biochemistry and suicidal behavior in depressed patients. Biol Psychiatry 21, 756–67.

Traskman, L., Tybring, G., Asberg, M., Bertilsson, L., Lantto, O., Schalling, D., 1980. Cortisol in the CSF of depressed and suicidal patients. Arch Gen Psychiatry 37, 761 – 767.

Tripodianakis, J., Markianos, M., Sarantidis, D., Leotsakou, C., 2000. Neurochemical variables in subjects with adjustment disorder after suicide attempts. Eur Psychiatry 15, 190–5.

Turecki, G., Ernst, C., Jollant, F., Labonte, B., Mechawar, N., 2012. The neurodevelopmental origins of suicidal behavior. Trends Neurosci. 35, 14-23.

van Heeringen, K., Audenaert, K., Van de Wiele, L., Verstraete, A., 2000. Cortisol in violent suicidal behavior: association with personality and monoaminergic activity. J Affect Disord. 60, 181–9.

van Heeringen, C., Bijttebier, S., Godfrin, K., 2011. Suicidal brains: A review of functional and structural brain studies in association with suicidal behaviour. Neurosci Biobehav Rev. 35, 688-98

van Heeringen, K., Mann, J.J., 2014. The neurobiology of suicide. Lancet Psychiatry 1, 63-72.

van Honk, J., Shutter, D.J., Hermans, E.J., Putman, P., 2003. Low cortisol levels and the balance between punishment sensitivity and reward dependency. Neuroreport 14, 1993–1996.

van Orden, K.A., Witte, T.K., Cukrowicz, K.C., Braithwaite, S.R., Selby, E.A., Joiner, T.E. Jr., 2010. The interpersonal theory of suicide. Psychol Rev. 117, 575–600.

Westrin, A. Ekman, R., Träskman-Bendz, L., 1999. Alterations of corticotropin releasing hormone (CRH) and neuropeptide Y (NPY) plasma levels in mood disorder patients with a recent suicide attempt. Eur Neuropsychopharmacology 9, 205–11.

World Health Organization, 2014. Preventing suicide: A global imperative. Geneva, Switzerland.

Yehuda, R., Golier, J.A., Kaufman, S., 2005. Circadian rhythm of salivary cortisol in Holocaust survivors with and without PTSD. Am J Psychiatry 162, 998-1000.

Yehuda, R., Kahana, B., Binder-Brynes, K., Southwick, S.M., Mason, J.W., Giller, E.L., 1995. Low urinary cortisol excretion in Holocaust survivors with posttraumatic stress disorder. Am J Psychiatry 152, 982-986.

Table 1. Study Characteristics

Authors	Year	Mean Age (yrs)	Sex (% male)	Analytic Method	Sample Time	N	Effect Size	Diagnosis	Time since attempt	Type of control	Quality score
Ayuso-Gutiérrez et al.	1987	55.8	14.08	Blood Plasma	morning	117	-.031	Major Affective Disorder	Unreported	Non-attempters	6
Brown et al.	1986	55.8	33.0	Blood Plasma	morning	64	-.165	MDD	Recent suicide attempt ≤ 4 weeks ago; past suicide attempt > 4 weeks ago (groups collapsed)	Non-attempters	7
					afternoon	57	-.292				
Brunner et al.	2002	38.33	23.97	Blood Plasma	morning	28	.190	Depressive spectrum disorder	5 – 23 days, mean time interval: 16 days	Depressed non-attempters & neurological controls	3
Brunner et al.	2001	35.35	50.75	Blood Plasma	morning	34	.080	Mixed	Shortly before admission	Non-suicidal psychiatric patients & neurological controls	2
Chatzittofis et al.	2013	37	63.73	Blood Plasma	morning	43	.305	Mixed; 50% depressive disorder	“recent suicide attempt”; time-frame	Healthy controls	9

									unreported		
Gmitrowicz & Kolodziej-Maciejewska	2002	17.62	63	Blood Serum	morning	114	.060	Mixed	Prior to hospitalisation; biochemical tests carried out 2-6 days after admission	Non-attempters	8
Inder et al.	1997	32.5	54.43	Blood Plasma	afternoon	56	.185	Unipolar depression	Within 1 month	Depressed non-attempters	5
Jokinen et al.	2010	47	37.25	Blood Plasma	morning	50	-.343	Mood disorder	Patients had attempted suicide just before the admission; 71% had biological tests within 8 days of admission	Non-attempters	7
Kamali et al.	2012	38.95	32.33	Saliva	morning	165	-0.73	Bipolar spectrum	Unreported	Bipolar non-attempters & healthy controls	11
					evening	164	.174				
Karlovic et al.	2012	47.55	63.64	Blood Serum	morning	55	-.057	MDD	Unreported	MDD non-attempters	7

Kelip et al.	2010	43.3	54.76	Blood	morning	53	-.131	Depression	Unreported	Non-attempter patients & healthy controls	8
Kim et al.	2013	43.76	0	Blood	n/a	359	-.091	MDD	Within 1 month	Non-attempters	6
Lindqvist et al.	2008	48.95	39.91	Saliva	morning	51	-.167	Mixed	Unreported	Non-attempters	11
					afternoon	51	-.181				
					evening	51	-.276				
Marcinko et al.	2005	26.47	100	Blood Serum	morning	46	.583	Schizophrenia	Soon after admission, exact duration unreported	Non-attempters	6
Markianos et al.	2009	37.6	100	Blood Plasma	morning	73	.258	Mixed	Within 1 week	Accident patients & healthy controls	5
McGirr et al.	2011	42.01	37.16	Blood Plasma	morning	148	-.244	Mixed	Unreported	Non-attempters	8
Ostroff et al.	1982	32.0	100	Urine	24 hour	21	.144	Mixed	Prospective; Last cortisol sample 1-3 weeks prior attempt	Non-attempters	8
Pitchot et al.	2005	40.66	60	Blood Plasma	morning	60	-.166	Major depression	Unreported	Non-attempters	10

Pitchot et al.	1995	39.7	69.70	Blood Plasma	morning	66	-.160	Unipolar depression	Within current episode of depression	Non-attempters	9
Plocka-Lewansdowska et al.	2001	38	65.63	Blood Plasma	afternoon	32	.368	Schizophrenia	Unreported	Non-attempters	4
Roy	1992	44.2	22.22	Blood Plasma	afternoon	44	-.015	Major depressive episode	Unreported	Non-attempters	6
Saiz et al.	1997	31.72	17.19	Blood	morning	256	.188	Unreported	Minimum of 3 months after an attempt	Non-attempters	7
Secunda et al.	1986	44.95	49.67	Blood Plasma	morning	80	-.224	MDD	Mean duration 34.2 weeks	Non-attempters	8
					evening	73	-.069				
Traskman et al.	1980	46.33	-	CSF	morning	61	.143	Mixed	Unreported	Depressed non-attempters	6
Tripodianakis et al.	2000	26.25	35.38	Blood Plasma	morning	103	.365	Adjustment disorder	24 hours	Non-attempters	8
Van Heeringen et al.	2000	35.45	75.96	Urine	24 hour	40	.375	Unreported	8 cases prior to the current admission, 9 historical suicide	Non-suicidal psychiatric controls	6

									attempt		
Westrin et al.	1999	37	38.88	Blood Serum	afternoon	72	.452	Depressive disorder	Inpatients: Mean 14 days (Range 5 -42 days). Outpatient: 3 months	Non-attempters	10

Note. In some studies the N for AM and PM assessments on the same samples vary. In all the meta-analysis where AM and PM were combined for these studies the average r and mean age (rounded down if there was a decimal) were entered into the specific analyses. When AM and PM are assessed separately the actual AM and PM Ns were used.

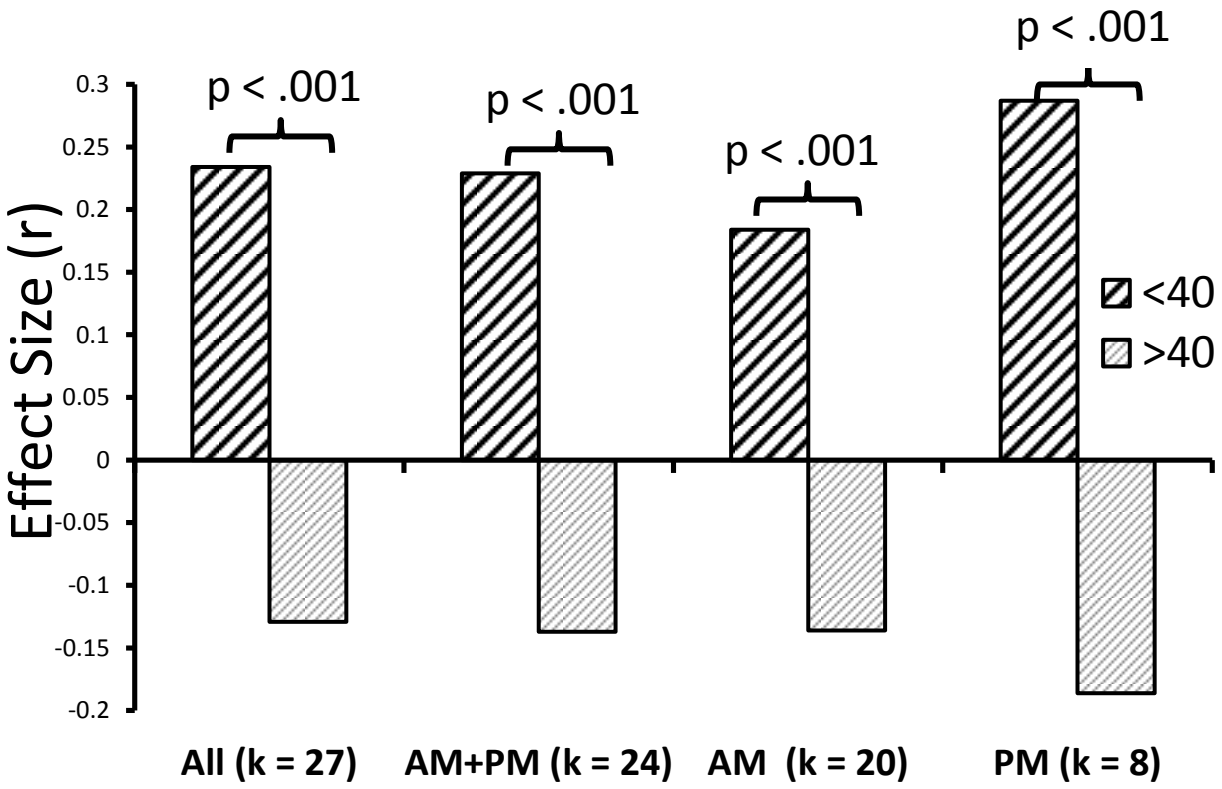
Note: MDD = Major Depressive Disorder; Mixed = Mixed psychopathology

Table 2. Meta-analysis results

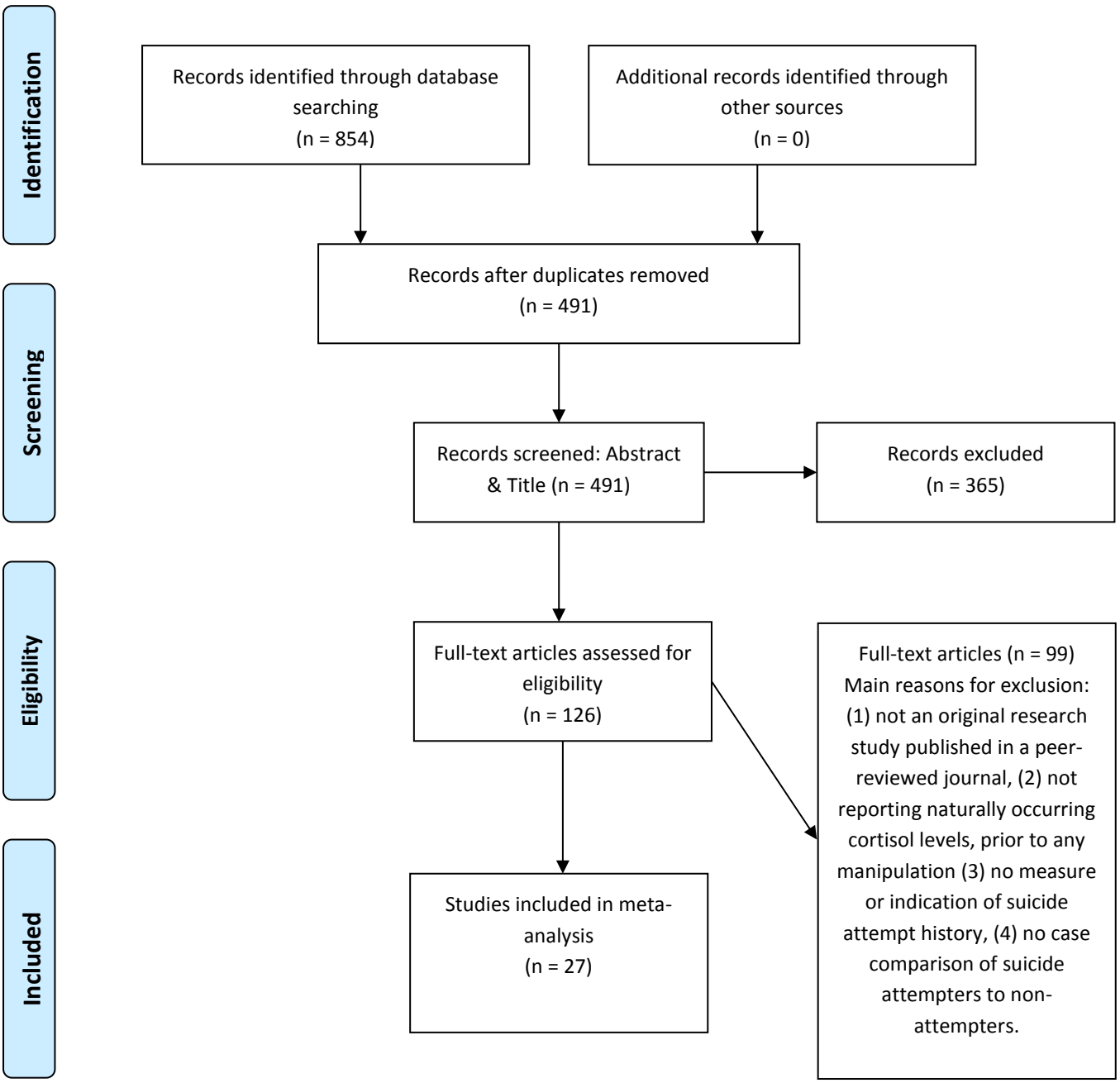
	Basic Stats					**Publication Bias**		**Moderation**	
	k	r	95% (CI)	p	I^2	Egger's Intercept	Trim and Fill Adjusted	Moderation by Age (Regression)	Moderation by sex (ANOVA)
Overall (all)	27	.071	-.02, .16	.132	79.56	1.47, p = .24	-.002 (4 to the left)	-0.015, p < .001	p = .058
Overall (AM & PM)	24	.066	-.03, .16	.201	79.96	0.60 p = 71	.066 (no adjustment)	-0.014, p <.001	P = .145
AM	20	.027	-.08, .132	.621	78.53	-0.28, p = .87	.027 (no adjustment)	-0.013, p <.001	P = .456
PM	8	.065	-.13, .26	.517	82.95	-0.25, p = .95	.065 (no adjustment)	-0.027, p < .001	P = .129
	Moderation by Age								
	k	r	95% (CI)	p		Q			
< 40 (all)	15	.234	.135, .329	< .001		34.5, p < .001			
≥ 40 (all)	12	-.129	-.194, -.063	= .004					
< 40 (AM + PM)	13	.229	.121, .332	< .001		28.33. p < .001			
≥ 40 (AM + PM)	11	-.137	-.214, -.059	= .001					
< 40 (AM)	10	.184	.046, .315	= .009		15.12, p < .001			
≥ 40 (AM)	10	-.136	-.215, -.055	= .001					
< 40 (PM)	4	.287	.131, .429	< .001		21.96, p < .001			
≥ 40 (PM)	4	-.186	-.279, -.070	= .002					

AM = early morning and before 12pm, PM = after 12pm. Three studies reported no time or utilised 24 hr assessments (Kim et al., 2013; Ostroff et al., 1982; van Heeringen et al., 2000). These were included in the analyses of all samples (all), but excluded from AM and PM analyses, therefore AM + PM has an N of 24 studies

Figure 1: Summary of moderating effects of age

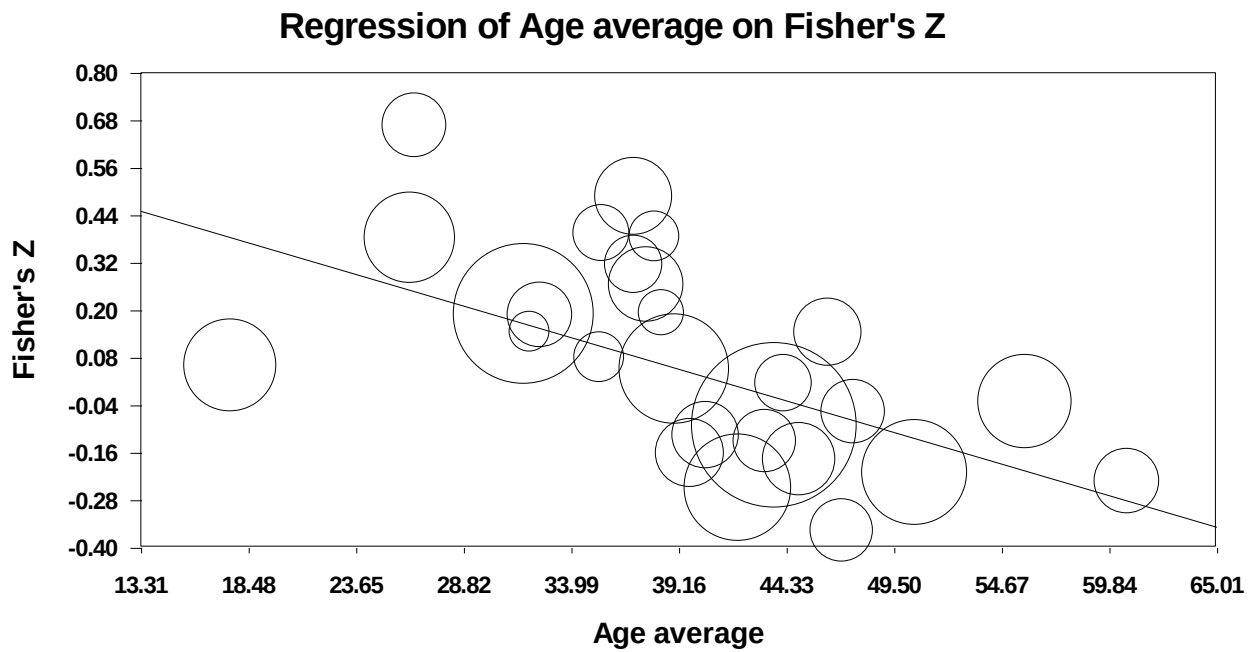


Supplementary Materials
Figure 1: PRISMA 2009 Flow Diagram



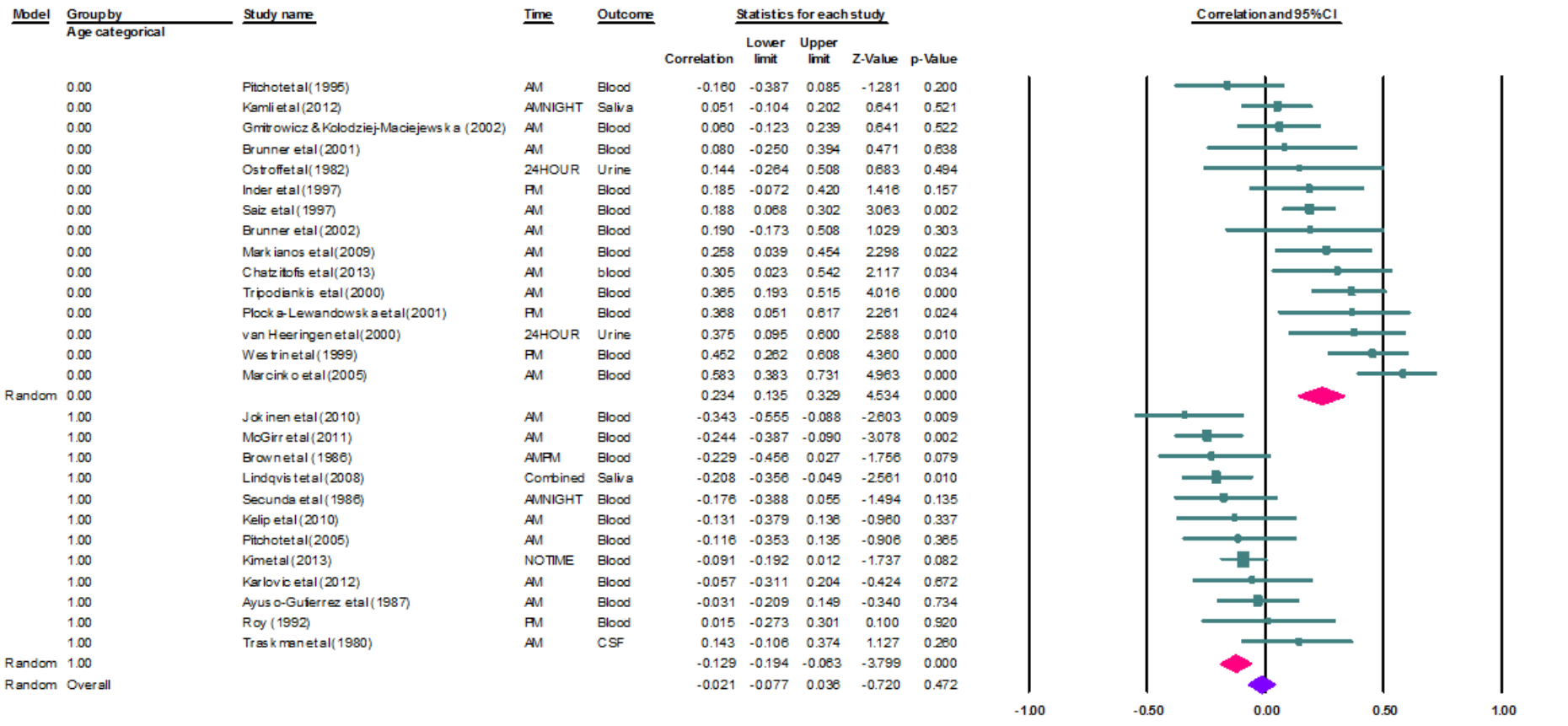
Supplementary Materials

Figure 2: Meta-regression of the mean age on Fisher's Z (k = 27)



Supplementary Materials

Figure 3. Forest plot of the observed association between suicide attempt and cortisol when studies were grouped by categorical age (n=27)



Model	Group by Age categorical	Study name	Time	Outcome	Correlation	Lower limit	Upper limit	Z-Value	p-Value
	0.00	Pitchot et al (1995)	AM	Blood	-0.160	-0.387	0.085	-1.281	0.200
	0.00	Kamli et al (2012)	AMNIGHT	Saliva	0.051	-0.104	0.202	0.641	0.521
	0.00	Gmitrowicz & Kolodziej-Maciejewska (2002)	AM	Blood	0.060	-0.123	0.239	0.641	0.522
	0.00	Brunner et al (2001)	AM	Blood	0.080	-0.250	0.394	0.471	0.638
	0.00	Ostroff et al (1982)	24HOUR	Urine	0.144	-0.264	0.508	0.683	0.494
	0.00	Inder et al (1997)	PM	Blood	0.185	-0.072	0.420	1.416	0.157
	0.00	Saiz et al (1997)	AM	Blood	0.188	0.068	0.302	3.063	0.002
	0.00	Brunner et al (2002)	AM	Blood	0.190	-0.173	0.508	1.029	0.303
	0.00	Markianos et al (2009)	AM	Blood	0.258	0.039	0.454	2.298	0.022
	0.00	Chatzitofis et al (2013)	AM	blood	0.305	0.023	0.542	2.117	0.034
	0.00	Tripodiankis et al (2000)	AM	Blood	0.365	0.193	0.515	4.016	0.000
	0.00	Plocka-Lewandowska et al (2001)	PM	Blood	0.368	0.051	0.617	2.261	0.024
	0.00	van Heeringen et al (2000)	24HOUR	Urine	0.375	0.095	0.600	2.588	0.010
	0.00	Westrin et al (1999)	PM	Blood	0.452	0.262	0.608	4.360	0.000
	0.00	Marcinko et al (2005)	AM	Blood	0.583	0.383	0.731	4.963	0.000
Random	0.00				0.234	0.135	0.329	4.534	0.000
	1.00	Jokinen et al (2010)	AM	Blood	-0.343	-0.555	-0.088	-2.603	0.009
	1.00	McGirr et al (2011)	AM	Blood	-0.244	-0.387	-0.090	-3.078	0.002
	1.00	Brown et al (1986)	AMPM	Blood	-0.229	-0.456	0.027	-1.756	0.079
	1.00	Lindqvist et al (2008)	Combined	Saliva	-0.208	-0.356	-0.049	-2.561	0.010
	1.00	Secunda et al (1986)	AMNIGHT	Blood	-0.176	-0.388	0.055	-1.494	0.135
	1.00	Kelip et al (2010)	AM	Blood	-0.131	-0.379	0.136	-0.960	0.337
	1.00	Pitchot et al (2005)	AM	Blood	-0.116	-0.353	0.135	-0.906	0.365
	1.00	Kim et al (2013)	NOTIME	Blood	-0.091	-0.192	0.012	-1.737	0.082
	1.00	Karlovic et al (2012)	AM	Blood	-0.057	-0.311	0.204	-0.424	0.672
	1.00	Ayuso-Gutierrez et al (1987)	AM	Blood	-0.031	-0.209	0.149	-0.340	0.734
	1.00	Roy (1992)	PM	Blood	0.015	-0.273	0.301	0.100	0.920
	1.00	Traskman et al (1980)	AM	CSF	0.143	-0.106	0.374	1.127	0.260
Random	1.00				-0.129	-0.194	-0.063	-3.799	0.000
Random	Overall				-0.021	-0.077	0.036	-0.720	0.472

Supplementary Table 1. Quality assessment tool and scoring guide

Score **Criteria**	0	1	2	3
Design	Cross-sectional *Groups not adequately matched.*	Cross-sectional *Minimum age and gender matched.*	Longitudinal. *Requires details of follow-up procedure.*	
Sample Size *Median sample size 56*	Total sample < 56.	Total sample >56 but unequal group sizes *(if applicable).*	Total sample >56 participants, approximately equal group sizes (if applicable).	
Suicide Assessment	No mention of how suicide attempt history was assessed.	Non-validated scale or other means of self-report *(e.g. single question)*	Hospital admission where intent has not been established; suicide items from a validated diagnostic/ mood rating scale *(e.g. HDRS, BDI, SADS).*	Clinical interview; validated suicide scale *(e.g. SIS, SAS);* hospital admission where intent has been established; death certificate/cause of death register
Cortisol Assessment[1] *(Frequency)*	Cortisol sampled at one time point. *e.g. morning*	Cortisol sampled at two or more time points, on one day. *e.g. morning and evening*	Cortisol sampled over multiple days.	
Psychiatric Assessment	No mention of how diagnosis was established.	Validated scale *(e.g. HDRS, MADRS, BDI)*	Clinical/diagnostic interview *(e.g. SCID-I; SCID-II; SADS)*	
Confounding variables *To what extent has there been an attempt to account for confounding variables*	No attempt to account for potential confounding variables in recruitment or analysis.	Accounts for basic confounding variables either during recruitment or analysis *E.g. Age, Gender*	Accounts for additional confounding variables either during recruitment or analysis. *E.g. Substance abuse, physical illness, childhood trauma, medication*	

[1] Rated based on what cortisol data was included in the analysis