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Effects of childhood adversity and cortisol levels on suicidal ideation and behaviour: Results from a general population study

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ABSTRACT

Childhood trauma is known to increase the risk of suicidal ideation and behaviours, and has also been linked to hypothalamic pituitary adrenal (HPA) axis dysregulation measured in cortisol levels. Recent evidence has shown that adverse childhood experiences are associated with lower cortisol reactivity to stress and diminished cortisol levels upon awakening in individuals vulnerable to suicide. The present study aimed to investigate whether less traumatic long term difficulties during childhood produced a similar effect on suicidal ideation/behaviour and cortisol levels in a general population sample. Participants (N = 1094; mean age 53 years, 53.7% female) from a large cohort study completed retrospective measures of long-term difficulties during childhood and adolescent years and a measure of history of suicidal thoughts, plans and actions together with a measure of current psychological distress. 24-hour urinary free cortisol samples were collected over two days. The results showed that experiencing childhood long-term difficulties were associated with 21% higher odds of reporting suicidal thoughts or plans in adulthood. Early childhood and adolescent difficulties were equally important predictors of suicide thoughts and plans. However, childhood difficulties were not found to be associated with adult urinary free cortisol, nor were adulthood suicidal thoughts, plans and behaviour associated with adult urinary free cortisol levels. Future research should explore the extent to which childhood difficulties and stressors are related to other indicators of HPA axis functioning. The current findings have implications for clinicians and for the development of future suicide prevention interventions.

Keywords: Childhood difficulties, cortisol, urinary free cortisol, HPA axis, suicidal ideation, suicidal behaviour

1. INTRODUCTION

There is strong evidence that childhood trauma increases the risk of suicidal ideation and behaviours later in life, as well as depression and psychopathology in adulthood (e.g., Heim et al., 2008; Carr et al., 2013; Marshall et al., 2013). For example, a large retrospective cohort study showed that adverse childhood experiences (e.g., abuse, neglect) increased risk of attempted suicide 2- to 5-fold throughout the lifespan (Dube et al., 2001). A systematic review found that childhood trauma triggers, maintains and increases the recurrence of psychiatric disorders (Carr et al., 2013). Furthermore, in a prospective cohort study, Marshall and colleagues (2013) found that severe sexual, physical and emotional childhood abuse conferred a substantial increased risk of suicide in illicit drug users. The relationship is graded, such that the risk of suicidal ideation and attempt increased with the number of adversities faced during childhood, and this effect was only partially mediated by mental disorders (Enns et al., 2006). Psychobiological mechanisms underlying this effect are beginning to be explored, with evidence emerging to suggest that the hypothalamic pituitary adrenal (HPA) axis may be dysregulated in individuals who have been exposed to childhood adversity (O'Connor et al., 2018; 2020).

Childhood trauma has been linked clearly to altered dynamics of the HPA axis and to persistent sensitization of the stress response system within the context of major depression (Heim et al., 2000; Heim et al., 2008). The HPA axis has two modes of operation: it coordinates acute stress responses through a cascade of actions which result in the release of cortisol, but it also manages the diurnal rhythm and regulation of circulating cortisol (de Kloet et al., 2005). While the majority of HPA axis research focusses on salivary or serum cortisol, studies using urinary-free cortisol (UFC) also support these broad findings. The amount of (free) cortisol excreted in urine during a 24h period is thought to reflect overall diurnal cortisol production and has been used as a proxy for HPA-axis functioning. Evidence suggests that while 24h UFC measurement is affected by multiple factors including urine volume and glomerular filtration rate (an indicator of kidney function), it is moderately stable on a day-to-day basis and over the long term (2- years; Rosmalen et al., 2014). Therefore, UFC provides a

useful summative measure of HPA-axis functioning. Roy (2002) assessed the effects of childhood trauma on UFC in withdrawn cocaine dependent patients with no current psychiatric disorder or major depressive episode, and reported that both childhood emotional neglect and sexual abuse were independently associated with lower levels of UFC. In a study of the children of Holocaust survivors, Yehuda and colleagues (2001) found lower UFC levels in individuals reporting emotional abuse compared to those who did not report emotional abuse (no differences were found for emotional neglect, physical abuse/neglect or sexual abuse). A review by Meewisse and colleagues (2007) did not find differences in UFC levels between people with post-traumatic stress disorder and controls. However, only six studies measured UFC and the findings relating to plasma/serum cortisol demonstrated that the association between PTSD and cortisol was only observed in certain subgroups (including studies on physical or sexual abuse, in female-only samples, and in afternoon samples). Therefore, further research with UFC is warranted to disentangle these effects and is the focus of the current study.

The effect of childhood trauma on depression has also been explained by changes in glucocorticoid resistance, increased central corticotropin-releasing factor (CRF) activity, immune activation, and reduced hippocampal volume. However, the results are mixed in the context of childhood trauma and cortisol stress reactivity. For example, Heim et al. (2000) showed that women who had a history of childhood abuse, with and without major depression, exhibited increased cortisol to an acute laboratory stressor. In contrast, a study by Carpenter et al. (2007) found that childhood maltreated men who had never been depressed exhibited decreased cortisol levels in response to a laboratory stressor. In a later study, Carpenter et al. (2011) replicated this finding and showed that women reporting childhood physical abuse displayed a blunted cortisol response to the TSST compared to women without physical abuse. Other studies have begun to emerge suggesting that early life adversity is associated with blunted cortisol reactivity to stress (e.g., Lovallo et al., 2012; Lovallo, 2013). Data from the Oklahoma Family Health Patterns Project showed that experience of adversity predicted reduced cortisol response to laboratory stress challenge, but was not associated with diurnal cortisol levels (Lovallo et al., 2012). More recently, O'Connor and colleagues (2018) demonstrated

that childhood trauma was a significant predictor of blunted cortisol reactivity to stress *and* resting cortisol levels, such that higher levels of trauma were associated with lower cortisol levels in those with a suicidal history. In another study, the same team found that childhood trauma was associated with lower cortisol levels in the morning and a tendency towards a flatter diurnal slope across the day (O'Connor et al., 2020).

A range of measures has been used to quantify childhood trauma in this area of research (including the Childhood Trauma Questionnaire; Bernstein et al., 2003), measuring physical or sexual assault or parental separation (Lovallo et al., 2012; Lovallo, 2013), and the Early Trauma Inventory (used by Heim et al., 2000). However, all these measures have focused on specific and explicit childhood trauma (e.g. physical and sexual abuse). The work by Lovallo and colleagues (2012; Lovallo, 2013) highlights the importance of different aspects of early life adversity, and raises the question: is it only traumatic events which trigger HPA changes and an increase in suicide risk? Stress in childhood can vary both in chronicity, where discrete life events are contrasted with chronic adversity (Allen et al., 2008), but also in the severity of events. Furthermore, evidence is mixed regarding the association between traumatic events and diurnal cortisol levels. The present study focussed on exploring a range of long-term difficulties, or chronic stressors, experienced during childhood. Childhood and adulthood difficulties were measured with the Long-Term Difficulties Inventory (LDI), a chronic stress measure that has been shown to have sufficient stability and validity for cohort studies (Rosmalen et al., 2012). Examples of these chronic stressors include: having negative relationships with family and friends, chronic illness, not having enough support, too much/not enough free time, financial hardship, housing issues. These experiences are not as extreme as trauma, but may still have a strong impact on children. The aim of the present study was to determine whether retrospective measurement of these childhood difficulties significantly influence diurnal cortisol levels and suicidal behaviour in adulthood, in a larger sample than has been tested previously. In addition, research into the role of childhood trauma in suicidal behaviour has often specifically recruited vulnerable samples and compared with control groups (e.g. Marshall et al., 2013; O'Connor, Gartland & O'Connor, 2020). Therefore, we used data collected from a large general population study to determine whether these

effects are observed along the wider scale of suicidal behaviour seen in the general population. Specifically, this study aimed to answer the following research questions:

1. Do childhood difficulties predict suicidal ideation and behaviour in adulthood?
2. Do childhood difficulties predict levels of UFC in adulthood?
3. Is UFC related to suicidal ideation and behaviour?

2. METHODS

2.1 Population

This cross-sectional study was performed as a secondary analysis of a cohort derived from the Prevention of Renal and Vascular End Stage Disease (PREVEND) study. The recruitment of participants has been described elsewhere (Pinto-Sietsma et al., 2000). All inhabitants of the city of Groningen between the ages of 28 and 75 years (N=85,421) were invited to take part. A total of 40,856 people (47.8%) responded, and 8592 participants completed the total screening programme, making up the PREVEND study cohort. In the 2001–2002 wave, 2554 participants were invited to participate in a sub-study, for which additional psychiatric and psychosocial data were collected. Of these 2554 participants, 1094 (43%) completed the additional measurements, forming the cohort for the current study. The sample of participants was 53.7% female, 97.6% Caucasian, and had a mean age of 53 years (range 33-79). Height and weight were measured and body mass index was calculated as the ratio between weight and the square of height (kg/m2). The study was approved by the local medical ethics committee and all participants gave written informed consent to participate.

2.2 Cortisol measurement

Urinary cortisol was the sole measure of cortisol available for the entire cohort and participants followed a standard urine collection procedure. Specifically, they were asked to collect urine samples on two consecutive days. They were instructed to urinate into a poly-propylene container during each 24-hour collection period, starting at 10:00pm, and store in the fridge until delivery to the laboratory. Suspected non-compliant participants were excluded based on a comparison of observed and expected creatinine levels in the urine samples: (urinary creatinine [mmol/d] × 113)/(21 × body weight [kg]) of

<0.7 (Knuiman et al., 1986). This was shown to be the method of choice in a comparison of exclusion strategies (Murakami et al., 2008). This resulted in the exclusion of 244 (day 1) and 229 (day 2), with an overlap of 143. Urinary free cortisol was measured by liquid chromatography-tandem mass spectrometry (LC-MS/ MS) analysis (Taylor et al., 2002). The lower detection limit of the assay was 0.3 nmol/l. At low, middle, and high concentrations, intra-assay variation ranged from 1.3% to 2.4% and inter-assay variation ranged from 3.8% to 7.8%.

2.3 Suicidal behaviour

The instrument used to measure suicidal behaviours was based on Kessler and colleagues (1999). This 8-item self-report measure asked participants about wanting to be dead, thoughts about attempting suicide, concrete plans for attempting suicide, as well as details about any previous suicide attempts. Respondents indicated how frequently they experienced the relevant aspect on a 3-point scale: 1=never, 2=sometimes, 3=often. This was done for a response category covering the past year and also for each of the following age categories: 0-12, 13-18, 19-39, 40-60, and >60 years.

2.4 Long-Term Difficulties

Childhood and adulthood difficulty were measured with the Long-Term Difficulties Inventory (LDI; Hendriks et al., 1990; Rosmalen et al., 2012). This is a 12-item retrospective self-report measure that has been used to assess different domains of chronic stress, including housing, work, social relationships, free time, finances, health, school/study and religion. Respondents indicated how they experienced these aspects on a 3-point scale: 0=not stressful, 1= slightly stressful, 2=very stressful. This was done for a response category covering the past year and also for each of the following age categories: 0–12, 13–18, 19–39, 40–60 and >60 years. Respondents were instructed not to include the past year when scoring the age categories because this period was covered by a separate response category. We used the 0-12 year age bracket as a measure of 'early childhood' and the 13-18 year age bracket as a measure of 'adolescence', as well as the 0-18 year age range as a measure of 'childhood'; item scores for 0-12 years and 13-18 years were averaged and then summed to derive a total score for this 'childhood' category. Factor analysis revealed that the two items relating to offspring and work

did not perform well in this scale for these age categories, and thus were removed. The resulting 10-item scale demonstrated good internal consistency (Cronbach's alpha = .77). We were also interested in the 18+ year age range as a measure of 'adulthood', so the remaining response categories were averaged and then summed to give a total score for the 18+ year bracket. The full 12-item measure was employed for this age category (Cronbach's alpha = .77). Total scores for the childhood categories can range from 0 to 20 and for the adulthood category from 0 to 24, with higher scores indicating more difficulty.

2.5 Medication use

Information on drug use was obtained from the InterAction database, which contains dispensing information from 55 community pharmacies in the Netherlands, covering on average 500,000 persons annually (www.IADB.nl) (Visser et al., 2013). The database's pharmacy information includes, among others, name of the drug, anatomic-therapeutic-chemical (ATC) classification and date of prescription. With the exception of over-the-counter drugs and in-hospital prescriptions, all prescriptions are included regardless of prescriber, insurance, or reimbursement status. Medication records of patients are virtually complete because of high patient pharmacy commitment in the Netherlands (Monster et al., 2002). We extracted information on drug prescriptions from 100 days prior until 100 days after the date of the visit to the study research facilities. We excluded participants using inhalation, local, gastrointestinal, or systemic glucocorticosteroids from the analyses (N = 201).

2.6 Psychological distress

Psychological distress was assessed with the Symptom Checklist (SCL-8). The SCL-8 is an abbreviated version of the SCL-25, which consists mainly of items from the depression and anxiety subscales of the SCL-90-R (Jorgensen et al., 2000). Items were scored on a five-point Likert scale ranging from 1 (not at all) to 5 (very much). Item scores were recoded (0 to 4) and summed to give the SCL-8 total score (range 0–32). The scale showed good reliability (Cronbach's alpha = .88).

2.7 Renal function

Renal function and urine volume can influence 24-hour UFC excretion (Chan et al., 2004; Mericq and Cutler, 1998). If information on 24-hour urinary creatinine excretion is available, creatinine clearance can provide an estimate for true glomerular filtration rate (GFR; Traynor et al., 2006). Therefore, GFR was estimated using creatinine clearance ((1000/1440) * mean((urine volume day 1 * urinary creatinine concentration day 1), (urine volume day 2 * urinary creatinine concentration day 2))/serum creatinine concentration). Creatinine clearance tends to slightly overestimate true GFR because of tubular secretion of creatinine; however, this is a systematic error of fairly stable magnitude over the range of renal function, until advanced renal failure is reached (Traynor et al., 2006). Creatinine was assessed as described previously (Verhave et al., 2004). Fasting blood samples were taken the morning after the second 24-hour urine collection period.

2.8 Statistical analysis

All analyses were performed using IBM SPSS Statistics version 25. The 2-day average of total 24hr UFC was calculated based on compliant days (if only one compliant day was available, this value replaced the two-day average). Due to positive skew, all cortisol values were log-transformed after which outliers which differed more than 3 standard deviations (SD) from the mean were removed [N = 23 (day 1), 21 (day 2), and 14 (2 day average)]. LDI scores were also log-transformed due to negative skew (Rosmalen et al., 2014). LDI scores relating to different age ranges were included in analyses to investigate age specific effects: 'early childhood' represents 0-12 years, 'adolescence' represents 13-18 years, 'childhood' represents 0-18 years, and 'adulthood' reflects 18+ years. Correlations between key study variables were assessed using Pearson's Product Moment correlations.

Logistic regression was used to investigate the effect of childhood long-term difficulties on adulthood suicidal thoughts and plans due to the low frequency of suicidal thoughts and plans in this population. Suicidal thoughts and plans were dichotomised to create a variable which showed if an individual had reported any experience of suicidal thoughts or plans at any point during their life after the age of 18 years. We adjusted for the potentially confounding effects of age, sex, and psychological distress.

Suicide attempt was not assessed due to low incidence within the sample. Note that the model was originally run with log-transformed LDI scores, and then again with untransformed LDI scores; as these models were insubstantially different, the model with untransformed data is presented here for ease of interpretation.

Multiple hierarchical regressions were used following procedures outlined by Kenny et al. (1998), to test whether childhood long-term difficulties were associated with levels of UFC in adulthood. In order to control for age, sex, BMI, psychological distress, renal function, and urine volume, these variables were entered in step 1 of the equation (as outlined by Rosmalen et al., 2014). The Childhood long-term difficulty score was entered in step 2. In order to determine if any effects remained when taking into account more recent difficulties, Adulthood (18+ years) long-term difficulty score was entered at step 3. Finally, in order to test the interactive effects of childhood and adulthood long-term difficulty on cortisol levels, a multiplicative interaction childhood x adulthood long-term difficulty term was entered at step 4. Mean centred variables were used when testing the interactive effects. The same analytic procedure was used to test whether suicidal behaviours were associated with levels of UFC in adulthood.

3. RESULTS

3.1 Descriptive statistics

Descriptive statistics for the main study variables are presented in Table 1. In terms of suicidal ideation and behaviour, 305 (28%) participants reported some suicidal thoughts or plans during their adult life, and 34 (3.1%) had attempted suicide during adulthood.

Table 1. Descriptive statistics for all study variables (N = 1094).

	Descriptive Statistics
	Mean (SD)
Age (years)	53.12 (11.33)
Sex (% female)	53.7
BMI (kg/m^2)	26.52 (4.12)
Psychological distress (SCL)	4.66 (5.03)

Long Term Difficulties	Median (IQR)
Early childhood (0-12 years)	0.00 (2.00)
Adolescence (13-18 years)	1.00 (3.00)
Overall childhood (0-18 years)	1.00 (2.00)
Adulthood (18+ years)	5.3 (3.83)
Suicide Variables	% of population
Wishing for Death	27.2
Suicidal Thoughts	15.6
Suicidal Plans	6.7
Suicide Attempt	3.1
	Median (IQR)
Urinary Free Cortisol (nmol/24hr)	70.85 (65.43)
	Mean (SD)
GFR (ml/min)	102.83 (23.76)
2-day average of urine volume (l)	1.83 (.63)

Note: IQR = Interquartile range; GFR = Glomerular filtration rate

3.2 Effects of childhood difficulties on suicidal thoughts and plans in adulthood.

The effect of overall childhood difficulties on the likelihood of experiencing suicidal thoughts or plans in adulthood was examined using logistic regression (see Table 2). Age, sex and psychological distress were entered as covariates in the model. The logistic regression model was statistically significant $\chi^2(4) = 230.40$, $p<.001$; the model explained 28.4% (Nagelkerke R^2) of the variance in the presence versus absence of suicidal thoughts or plans in adulthood and correctly classified 76.8% of cases. In both unadjusted and adjusted analyses, the strongest evidence for an association was found for overall childhood difficulties. Experiencing childhood difficulties was associated with 21% higher odds of reporting suicidal thoughts or plans in adulthood (adjusted odds ratio [OR] 1.21, 95% CI 1.13-1.30, $p<.001$). Current psychological distress was also significantly associated with suicidal thoughts or plans in adulthood (1.18, 1.14-1.22, $p<.001$), as were age (.97, .97-.98, $p<.001$) and sex (.62, .45-.84, $p=.002$).

Table 2. Logistic regression analyses testing the effects of childhood long-term difficulties on the reporting of any adulthood suicidal thoughts/plans (N=1094).

	Variable	β	**Odds Ratio**
Overall	Constant	-2.27**	-

Childhood	Age	-.03**	.97
	Sex	-.49**	.62
	Psychological Distress	.16**	1.18
	Overall childhood LDI score	.19**	1.21
	Nagelkerke pseudo r-square		28.4%
	Chi-square		230.40, df=4, p<.001
Early Childhood	Constant	-2.09**	-
	Age	-.03**	.97
	Sex	-.50**	.61
	Psychological Distress	.17**	1.18
	Early childhood LDI score	.19**	1.21
	Nagelkerke pseudo r-square		28.0%
	Chi-square		222.52, df=4, p<.001
Adolescence	Constant	-1.95**	-
	Age	-.03**	.97
	Sex	-.47**	.62
	Psychological Distress	.16**	1.18
	Adolescence LDI score	.16**	1.17
	Nagelkerke pseudo r-square		28.2%
	Chi-square		228.58, df=4, p<.001

Note: The coefficients for sex are contrasts, with the female group as the reference category. *p<0.05, **p<.01

In addition, we investigated the distinct effects of early childhood (0-12 years) and adolescent (13-18 years) difficulties on suicidal thoughts or plans in adulthood; the effects of long-term difficulties were similar for these two age ranges (early childhood OR 1.21, 95% CI 1.12-1.31, p<.001; adolescence OR 1.17, 95% CI 1.10-1.25, p<.001).

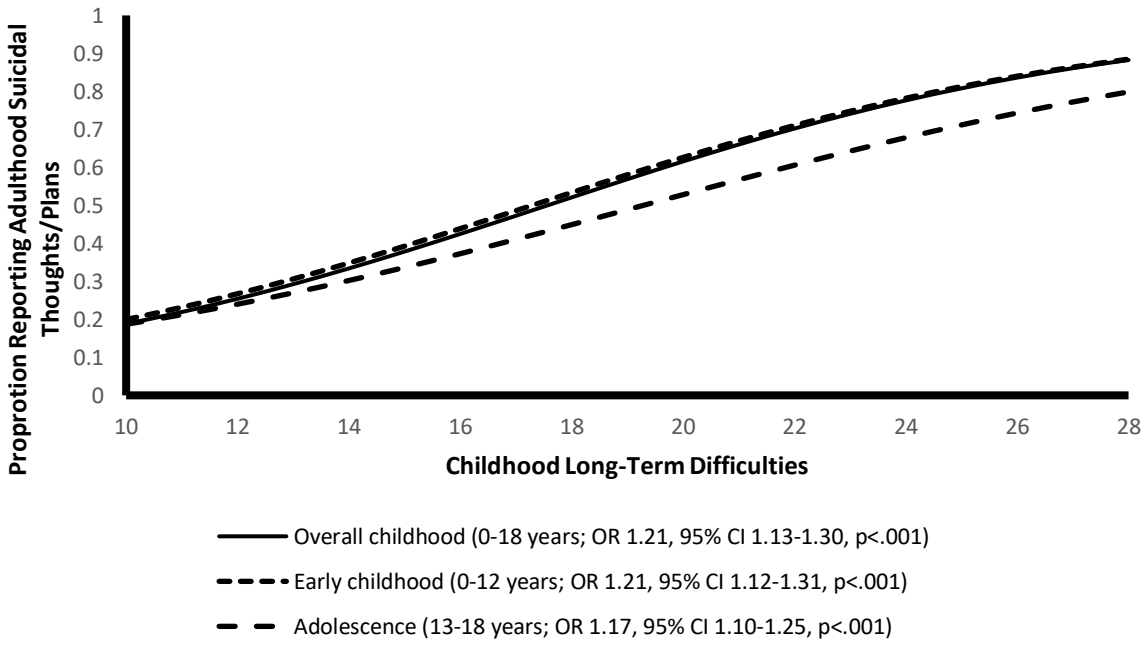

Figure 1. Logistic regression graph showing the prediction of reporting suicidal thoughts or plans in adulthood for different levels of childhood long-term difficulties, as well as the levels associated specifically with early childhood and adolescence.

3.3 Effects of childhood difficulties on urinary free cortisol in adulthood.

A hierarchical multiple regression model was used to examine the effects of childhood long-term difficulties on cortisol levels. As shown in Table 3, at step 1, the covariates significantly entered the equation, accounting for 20.8% of the variance in UFC, $F(6, 592) = 25.89$, $p < .001$. At step 2, childhood long-term difficulties did not enter the equation, and nor did adulthood long-term difficulties at step 3. In the final step, the interaction between childhood long-term difficulties and adulthood long-term difficulties did significantly enter the equation, $F(1, 589) = 4.91$, $p = .03$, accounting for 0.7% of the variance in 24h UFC. However, this effect was marginal, and when decomposed for higher (+1SD), mean, and lower (-1SD) levels of childhood long-term difficulties using simple slopes analyses (Preacher et al., 2006), no significant associations were found for any of the long-term difficulty levels.

Table 3. Hierarchical regression analyses testing the effects of childhood long-term difficulties on 24h UFC levels (N=1094).

		β **Step 1**	β **Step 2**	β **Step 3**	β **Step 4**	Δ R^2 for step	Total R^2
24 h UFC							
Step 1	Age	-.053	-.049	-.058	-.063	.208*	
	Sex	-.002	-.003	.000	.003		
	BMI	.075	.077	.077	.074		
	Psychological Distress	-.050	-.060	-.046	-.046		
	Urine Volume	.453*	.446*	.446*	.438*		
	GFR	-.070	-.068	-.069	-.067		
Step 2	Childhood LDI		.042	.061	.005	.002	.209
Step 3	Post-18 LDI			-.045	-.050	.001	.211
Step 4	Childhood/Post-18 LDI interaction term				.101*	.007*	.217

Note: *p<0.05

3.4 Relationship between adulthood suicidal thoughts, plans and behaviour and adulthood UFC.

Correlational analysis demonstrated no significant association between suicidal thoughts, plans or behaviour and adult UFC levels. Regression analyses controlling for age, sex, BMI, psychological distress, renal function, and urine volume revealed no significant relationship between suicidal ideation and behaviour and adult UFC levels (data not shown). This was the case for suicidal thoughts, plans and behaviour reported at any point after the age of 18, but also for suicidal thoughts, plans and behaviour reported for the prior 12 months.

4. DISCUSSION

The current study found that the experience of childhood difficulties was associated with an increased risk of suicidal thoughts and plans in adulthood. In particular, experiencing childhood difficulties was associated with 21% higher odds of reporting suicidal thoughts or plans in adulthood. The results also showed that early childhood and adolescent difficulties were equally important predictors of suicide thoughts and plans in adulthood. However, childhood difficulties were not found to be associated with adult UFC levels, nor were adulthood suicidal thoughts, plans and behaviour associated with adult

UFC levels. Therefore, the results provide evidence of a link between the experience of long-term difficulties and stress during childhood and self reports of suicidal ideation and behaviour in adulthood; importantly, these effects were independent of current levels of depression and anxiety as well as age and sex.

The current study is important as it contributes to the existing literature by highlighting, that in a large general population sample, less traumatic events such as stress and difficulties surrounding housing, relationships, finances and school during childhood can have long lasting effects that track into adulthood. This finding is consistent with previous research that has demonstrated that early life adversity is associated with suicide risk later in life as well as a range of mental disorders (Enns *et al*., 2006; Dube *et al.,* 2001; Carr *et al.,* 2013). For example, a large retrospective cohort study showed that adverse childhood experiences (e.g., abuse, neglect) increased risk of attempted suicide 2- to 5-fold throughout the lifespan (Dube et al., 2001). Another study by Marshall and colleagues (2013) found that severe sexual, physical and emotional childhood abuse conferred a substantial increased risk of suicide risk in illicit drug users. In a related meta-analysis, Howarth et al. (2020) found that stressful life events (including childhood events) were associated with 37% higher odds of subsequently reporting suicide ideation and behaviour. However, the current study provides evidence in support of widening the scope of this area of research to include a broader range of challenges in childhood. An important next step for research in this area would be to investigate the pathways through which childhood difficulties lead to this increased risk of suicide. Wanner and colleagues (2012) have suggested that early life adversity may lead to the development of anxiousness and/or disruptiveness trajectories for children that subsequently increases the risk of suicide in adulthood. Further work is urgently needed to help understand the developmental pathways that play a role in explaining the relationship between childhood difficulties and suicide vulnerability in adulthood.

The current research has implications for clinicians and for the development of interventions. First, the findings suggest that there may be utility in exploring childhood long-term low level difficulties and stressors as part of suicide risk assessments, in addition to individual traumatic events. One

approach might involve incorporating the Long-Term Difficulties Inventory within the therapeutic setting and using the evidence around these measures to guide a clinician's approach. For example, using the tool to aid information gathering, with the ability to seek further contextual and appraisal information as necessary, may allow the clinician to better assess the individual's risk of suicide ideation and behaviour. Second, the results highlight the need for psychological interventions to include a component which focuses on developing resilience and adaptive coping for future stressful life events. Increasing the range of responses and appraisals available to an individual when stressful events or difficulties are experienced may reduce vulnerability to suicide ideation and behaviour in the future (Howarth et al., 2020; O'Connor et al., 2021). These approaches are in keeping with the majority of models of suicide ideation and behaviour, which place the experience of stressful life events as the initiating stressor or precipitating event, but focus on the interpretation and appraisal of these events (Johnson et al., 2008; Branley-Bell et al., 2019).

Long-term difficulties were not found to be associated with any differences in adult UFC levels and UFC was also not associated with suicidal thoughts, plans and behaviour. UFC measures give a summative measure of HPA-axis functioning and have been demonstrated to be moderately stable on a day-to-day basis and over a 2 year period (Rosmalen et al., 2014). The current results do not support a relationship between childhood difficulties and this measure of HPA axis function. These null findings are surprising given that naturally fluctuating levels of cortisol including UFC (as distinct from cortisol reactivity to stress) have been found to be associated with other measures of adverse childhood experiences (e.g., Roy, 2002; O'Connor et al., 2018). Roy (2002) found that childhood emotional neglect and sexual abuse were independently associated with lower levels of UFC in a sample of withdrawn cocaine dependent patients and O'Connor et al. (2018; 2020) found that childhood trauma was associated with lower resting cortisol levels and upon awakening. The differences could reflect the utility and sensitivity of UFC as a measure of HPA axis function. Research has demonstrated that UFC was a stronger predictor of physical health variables (such as chronic pain and BMI), while different aspects of diurnal salivary cortisol measures were associated with well-being variables (Rector *et al*., 2019). Alternatively, the absence of a relationship between

childhood difficulties and HPA axis functioning may reflect the fact that the effects of childhood difficulties are much less potent physiologically than childhood trauma, and as a result they are less likely to lead to observable dysregulation of the HPA axis as measured by UFC (Roy, 2002). This is particularly relevant given that the concept of allostatic load has been hypothesised to be central to understanding how adverse life experiences may lead to altered dynamics of the HPA axis. Specifically, it has been argued that if the HPA axis is repeatedly activated (by chronic stress caused by trauma) the immune, cardiovascular and the endocrine systems will become exposed to excessive demands that over time will lead to dysregulation of these systems (McEwen, 1998; O'Connor et al., 2021). Therefore, it remains a possibility that the absence of associations may reflect the milder nature of adverse life experiences captured by the Long-Term Difficulties Inventory in a general population sample, compared to other measures of childhood trauma in more specific populations. Nevertheless, it is worth noting that the childhood difficulties measure was still found to predict future suicide thoughts, plans and behaviour. Future research ought to investigate the extent to which childhood difficulties and stressors are related to other indicators of HPA axis functioning (e.g., cortisol reactivity to stress). Longitudinal research would be valuable, as it would allow for mediation analysis to test whether the relationship between childhood difficulties and adult suicidal behaviour may be explained by alterations in HPA axis function (as potential mediation pathways cannot be ruled out with the current results and study design).

There are a number of limitations of this study that ought to be considered. Firstly, the data was collected cross-sectionally with retrospective reporting of childhood experiences. This presents issues of biased recollection, which may disproportionately affect those who have reported suicidal thoughts, plans and behaviours. That said, current psychological distress was adjusted for in the current analysis and it has been suggested that retrospective self-report tools may lead to an underestimation of actual occurrence of adverse childhood experiences (Hardt & Rutter, 2004). Nevertheless, causal relationships cannot be disentangled with such data. Longitudinal and life-course studies are essential to further our understanding of the short and long-term effects of childhood experiences. Relatedly, we are aware that there was low variability in LDI scores in the current data; while this is expected

because the sample was drawn from the general population, it highlights the value of large sample sizes to investigate these relationships. Secondly, this study was a secondary analysis of an existing dataset, and therefore there were limitations in the availability of data; alternative measures of childhood experience such as the Stress and Adversity Inventory for Adolescents (STRAIN; Slavich et al., 2019) could have permitted further insight into the relationships between childhood experience, adulthood suicidal behaviours and HPA function, but were not available in the current study. Thirdly, UFC measures are limited in their demonstration of the functionality of the HPA-axis; however, shortcomings of the current dataset precluded exploration of alternative cortisol indices. Further research assessing the associations between diurnal salivary cortisol patterns, childhood long-term difficulties and suicidal behaviour over multiple days will provide a more detailed view of the role of the HPA-axis in these relationships (Gartland et al., 2014). In addition, given the mixed findings for the effect of childhood trauma and adversities on cortisol levels associated with stress reactivity (Carpenter et al., 2007, 2011; Heim et al., 2000; Lovallo et al., 2012), it would be valuable to further explore the effects of childhood difficulties on this aspect of HPA function to refine the understanding of these effects.

4.1 Conclusion

In conclusion, this study provides confirmatory evidence that experiencing chronic difficulties during childhood can have long-term effects into adulthood, with a 21% greater chance of reporting suicidal thoughts and plans. Early childhood and adolescent difficulties were equally important predictors of suicide thoughts and plans in adulthood. No associated differences in cortisol levels were detected through urinary cortisol measurement, therefore not supporting the hypothesis that this aspect of HPA axis functioning is affected by childhood long-term difficulties or suicidal thoughts and plans. Future research should explore the extent to which childhood difficulties and stressors are related to other indicators of HPA axis functioning.

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