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Review article

The dexamethasone suppression test as a biomarker for suicidal behavior: A systematic review and meta-analysis

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ABSTRACT

Background: The dexamethasone suppression test (DST), which measures HPA-axis functioning, is a potential biomarker for suicidal behavior. The current study aimed (a) to synthesize available knowledge on the association between DST non-suppression and suicidal behavior, and (b) to study potential moderators.
Methods: A total of 4236 studies were screened, 43 were included. Suicide attempts and suicide completion were studied separately. The meta-analysis included 37 effect sizes for suicide attempts ($n = 3733$) and 11 effect sizes for suicide completion ($n = 1626$).
Results: DST non-suppression was associated with completed suicide (odds ratio (OR) = 2.10, (95 % CI [1.37, 3.23]). For suicide attempts, we found no evidence that DST status was associated in the overall meta-analysis including all patient samples. However, moderator analysis indicated that the DST status was associated with suicide attempts in patient samples that included psychopathology other than just mood disorders, such as psychotic, substance use and personality disorders (OR = 2.34, 95 % CI [1.39–3.93], $k = 11$).
Limitations: The potential influence of publication bias and exclusion of some relevant published studies (since effect sizes could not be calculated, authors could not supply data or authors could not be reached) are limitations. Furthermore, missing moderator data decreased our ability to explain heterogeneity between studies.
Conclusions: The results of this meta-analysis support the hypothesis that DST non-suppression is predictive of suicidal behavior. More research is needed to investigate optimal cut-off values, confounding factors and the potential usefulness of the DST in clinical practice in terms of personalized medicine.

1. Introduction

Suicide attempts and completion are among the most serious calamities in psychiatry. Such suicidal behaviors influence not only the well-being of patients, but their broader network of family, friends, acquaintances and possibly also their clinicians or potential witnesses to the attempt. Suicidal behavior remains hard to predict, even though many risk factors are known, due to its heterogeneity, complexity and the relatively low prevalence of suicide completion (Kessler et al., 2020). Although major depressive disorder is the most common diagnosis among patients committing suicide, suicidal behavior occurs across a wide variety of psychiatric diagnoses including substance use, psychotic, anxiety, personality-, eating-, and trauma-related disorders (Bachmann, 2018). At present, phenotype and clinical history of presenting with suicidal thoughts or behaviors are used for identification of those at highest risk, but there still is a critical need for healthcare providers to further evaluate at-risk individuals. Biomarkers provide a potential measure of the functioning of underlying biological pathways, which may be used to identify patients at high risk for suicide. The dexamethasone suppression test (DST) is such a biomarker for hypothalamic-pituitary-adrenal axis (HPA-axis) dysfunction, and it has been studied in relation to suicidality (Alacreu-Crespo et al., 2020). Like suicidal behavior, HPA-axis dysregulation is considered a trans-diagnostic phenomenon as it co-occurs with many mental (and physical) health disorders, such as mood disorders, anxiety disorders, PTSD, schizophrenia, chronic fatigue syndrome, fibromyalgia, anorexia nervosa (Zänkert

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et al., 2019), and substance use and dependence (Hulme et al., 2023). Knowledge on how the DST is related to suicidal behaviors (i.e. attempted or completed suicide) may improve the ability to predict such behaviors, and thereby further our attempts towards personalized medicine.

The DST is conducted by providing a subject with a 1 mg tablet of the synthetic glucocorticoid dexamethasone, usually around 11 pm, and then inspecting the HPA-axis response the day after, based on the measurement of cortisol values in blood at fixed time points. The typical response to dexamethasone is a suppression (i.e. decrease) of the blood cortisol levels due to binding on the glucocorticoid receptor reducing the production of corticotropin-releasing hormone (CRH) in the hypothalamus and adrenocorticotropic hormone (ACTH) in the pituitary. Non-suppression of cortisol levels is therefore considered an indication of dysregulation of the HPA axis negative feedback loop. The DST is currently used as a screener for Cushing's syndrome (Fleseriu et al., 2021) and has been investigated as a potential biomarker for melancholic depression since Carroll et al. (1981) proposed that a cortisol value of 5 mg/dl or higher during the DST indicated non-suppression. An advantage of this type of HPA-axis measurement is that reactivity to a challenge is measured, therefore there is an active intervention rather than passive cortisol measurement which may be much more influenced by confounders, such as stressors, daily fluctuations, and life style. Furthermore, the pharmacological challenge can be standardized so that each subject receives the same amount, which may not hold true for a psychological challenge test, such as the Trier Social Stress Test.

Mechanisms by which the HPA-axis can become dysregulated is chronic, early life, or severe stress. Reviews of childhood maltreatment and life events suggest that exposure to those stressors may lead to a hyporeactive HPA-axis (Leroux et al., 2023; Young et al., 2021). Another example of a more acute factor that is associated with HPA-reactivity is sleep: the link between inadequate sleep and decreased HPA-axis reactivity appears to be bidirectional with low quality sleep both being caused by HPA-axis dysregulation and creating more dysregulation as well (van Dalfsen & Markus, 2018). In addition to environmental causes, HPA-axis reactivity may be partly explained by genetic or epigenetic factors and their interaction with psychosocial stressors, for example childhood maltreatment or trauma (Zänkert et al., 2019). Many types of psychopathology have mainly been related to hypoactive HPA-axis responses, for example psychotic disorders, somatic and pain-related disorders, and anxiety disorders (Zänkert et al., 2019). However, a meta-analysis by Zorn et al. (2017) has shown that depressive and anxiety disorders were associated with HPA-axis hyporeactivity in females, while these disorders were related with hyperreactivity in males. Studies on PTSD and burnout have shown mixed effects, with both hyporeactive and hyperreactive HPA-axis responses in patients (Handwerger, 2009; Zänkert et al., 2019). Chronic or severe stress, particularly early in life, sleep and (epi-)genetic vulnerabilities may thus lead to decreased HPA-axis reactivity causing both decreased resilience to stress and psychopathology. In turn, psychopathology may lead to HPA-axis dysregulation and much remains unclear about these potential bidirectional influences.

Multiple meta-analyses have investigated biomarkers for suicidal behavior and some have included data on the DST as potential biomarker. For example, Mann et al. (2006) reported on nine prospective studies on the DST in relation to suicide completion with an overall odds ratio (OR) of 4.65. That is, patients with dexamethasone non-suppression were estimated to commit suicide 4.65 times more often than dexamethasone suppressors. In contrast, Chang et al. (2016) described four prospective studies on suicide attempts, and found no evidence of a significant association with DST status. Using eight studies on suicide completion, Chang et al. found an overall OR of 1.49, which with a correction for possible publication bias became non-significant (OR = 1.45, 95 % CI [0.78–2.68]). Another meta-analysis looked into the positive predictive value of nine studies on DST status and suicide completion and found that 10.2 % (5.5–18.2) of DST non-suppressing patients later committed suicide (Carter et al., 2017). One older meta-analysis focused solely on the DST in relation to suicidal behavior (Lester, 1992). The findings indicate that suicide attempts prior to the DST are not associated with DST non-suppression status ($k = 19$, $\varphi = -0.01$), but non-suppression was associated with completed suicide ($k = 9$, $\varphi = 0.19$). There were too few prospective suicide attempt studies to conclude whether there was an association on that outcome.

Previous meta-analyses have some important limitations, that warrant a new synthesis of the available literature. First, most of those meta-analyses focused on a broader range of biomarkers for suicidal behaviors, not just the DST, and based on our systematic search seem to have missed some relevant studies which may have influenced the overall conclusions. Second, data from less reliable sources, such as conference abstracts and cover letters (e.g. Boza et al., 1988; Nielsen and Bostwick, 2004), were sometimes included. In such communications, study limitations may remain unclear, as it is often unknown whether the data were gathered systematically, for example when only reporting on suicide completion in a part of the sample. Results may be affected by selective reporting bias. Therefore, previous meta-analyses may have overestimated the effect of DST suppression status on suicide outcomes. Third, although the DST is less often investigated in relation to psychiatric outcomes nowadays than a few decades ago, new studies are still being conducted and provide new evidence on this topic (2021). A new synthesis of findings, focused on the DST and its association with suicidal behavior, may provide a less biased and more thoroughly informed conclusion. In addition to providing state of the art academic knowledge on associations between HPA-axis reactivity and suicidal behavior, the findings may inform suicide risk assessment and prevention efforts, and therefore is highly relevant to clinical practice as well. The current study synthesizes findings on the DST in relation to suicide attempts and completion. Furthermore, potential moderators of this association are inspected, such as the difference in effect size between retrospective and prospective studies and between studies with patient samples with mood disorders only versus studies that included other types of psychopathology as well. Study quality and potential publication bias are investigated.

2. Method

2.1. Search strategy and selection

To find studies on associations between the DST and suicidal behavior, trained librarians conducted a systematic search in several databases: Embase, MEDLINE, Web of science, Cochrane CENTRAL, PsycINFO, CINAHL and Google scholar. The search was updated last on August 17, 2023 and included terms related to suicidal behavior (e.g. suicid*) in combination with terms related to the DST (e.g. dexamethasone, cortisol*); an overview of the full search terms is provided in the Supplementary Material, available online. In addition, reference lists of the meta-analyses discussed in the introduction were reviewed. Studies were eligible for selection if they met the following criteria: (a) English reported peer-reviewed research, (b) human subjects, (c) included a DST intervention (or DST/CRH) with plasma measurements from blood, (d) reported on suicide attempts or completion versus the absence of such behaviors. Studies were excluded if they (e) reported on a case report or case series or (f) included patients with medical issues that influenced DST measurements, for example Cushing's syndrome (Carroll et al., 1981). We did not exclude any studies based on their publication date for two reasons. First, the DST was a popular topic of research in the 1980's. Exclusion of studies before e.g. 2000 might deprive the meta-analysis of valuable information and would decrease its power. Second, and more importantly, we did not expect the association of DST non-suppression with suicidal behavior to change meaningfully over time; that is we do not assume there to be any time period bias. Full-text study eligibility was inspected in the order: (a), (b), (f), (c), (e) and (d). Two researchers independently selected all titles and abstracts with

substantial agreement, $\kappa = 0.79$, $p < .001$; (Landis and Koch, 1977). Full texts were also selected independently by two researchers. Disagreements were solved by discussion or if necessary agreement of a third researcher. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) and an overview of the search and selection process is provided in the PRISMA flow diagram in Fig. 1.

2.2. Data collection

Data coding was conducted with an a priori developed protocol for effect size, study, sample and assessment data. All studies were coded by two independent researchers. The initial agreement over 190 effect size cells was 96.3 %. In case of disagreement, the article was consulted again and discussed until consensus was reached. Effect sizes were coded based on two by two tables of DST suppressor status (non-suppressor or suppressor), by outcome status (suicide attempt or completion versus no attempt or completion) or continuously as mean and standard deviation of the cortisol level for a suicide attempt versus no suicide attempt group or a suicide completion versus no completion group. Furthermore, one effect size was based on a χ^2-test and one on an independent samples *t*-test. Authors were contacted if there was not enough information to compute an effect size. We contacted the authors of 20 studies to request effect size data; for 11 studies an author responded, with 2 authors being able to provide effect size data. One more study of a contacted author we were unable to reach could be included based on a subset of data in the article.

In eligible studies, multiple options for extracting an effect size were

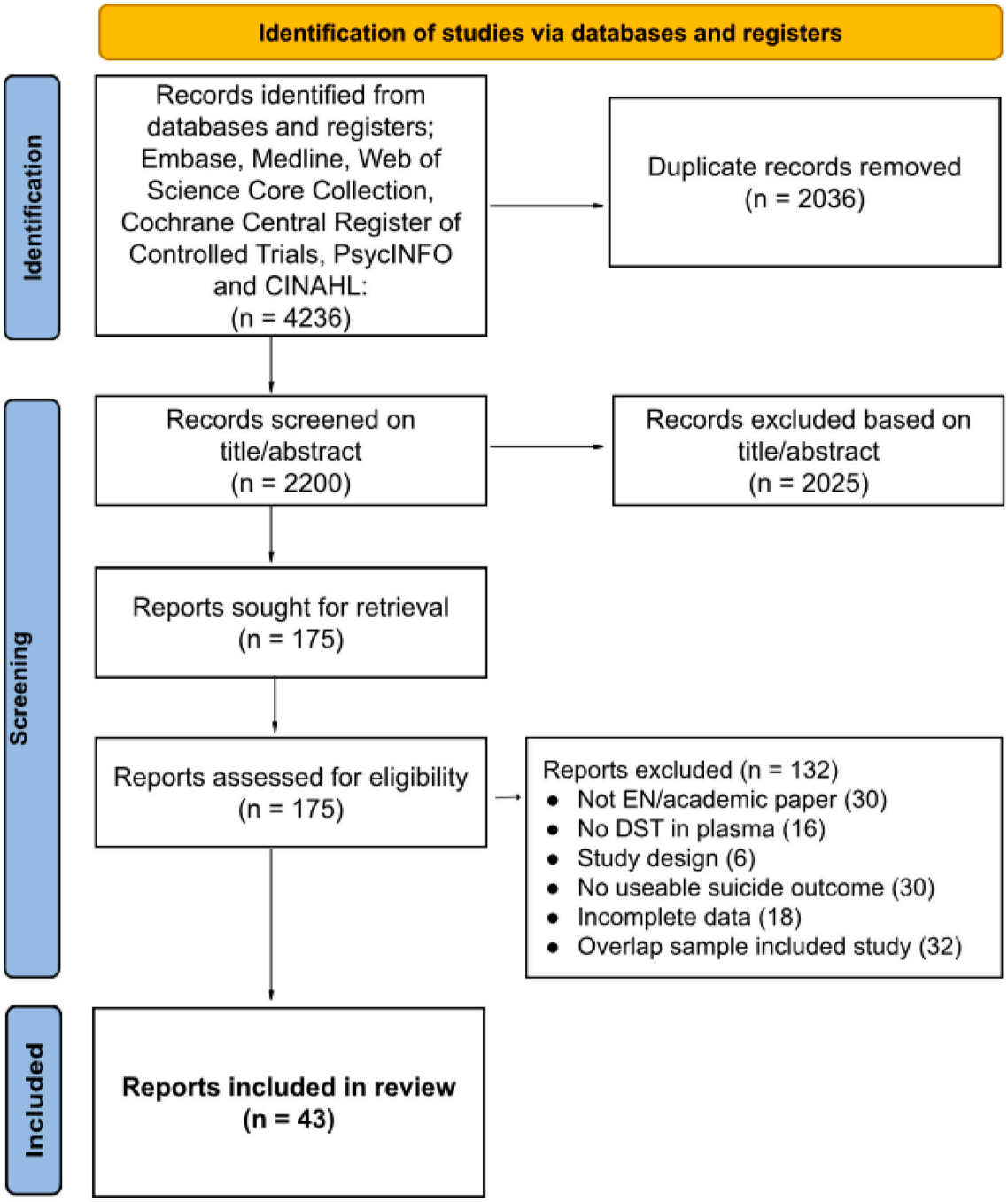

Fig. 1. PRISMA flow diagram illustrating study identification, inclusion and exclusion.

sometimes present, therefore the following rules, established a priori, were used in cases of multiplicity. For studies that reported on both suicide attempts and completion, data for both outcomes were extracted separately. For studies with multiple measurements of one type of outcome, prospective data were preferred over retrospective data and recent retrospective data were preferred over lifetime retrospective data. For example, suicide attempts in the last year were preferred as outcome over lifetime attempts. In clinical prospective studies, post-treatment DST measurements were preferred over pre-treatment measurements, to prevent interference by intervention. In line with Carroll's guidelines (1981) the following decisions were made in terms of DST data: (1) for studies reporting multiple cut-off points for DST suppression status, a cut-off of 5 mg/dl (or 138 nmol/l) was preferred over other cut-offs and over mean cortisol values, (2) a measurement one day after the dexamethasone was preferred over data several days after dexamethasone, (3) for studies that measured and reported DST suppression at multiple time points on a single day, non-suppression status on any of the time points was preferred over data using a single time point, (4) if no overall non-suppression data were reported, the time point with the highest amount of cortisol non-suppression was selected. In a similar way, the time point with the highest amounts of cortisol was preferred for continuous cortisol value data over other time points.

In addition to effect size data, information on the following study characteristics and potential moderators was collected: study – year, location, study design (prospective or retrospective; i.e. DST before or after suicidal behavior); patients - sample size, primary psychiatric disorders, percentage inpatients, sex and age; DST intervention - DST type, dexamethasone dose, time of administration, time of cortisol measurement analyzed, time between administration and outcome, non-suppression cutoff; control - type of control group, type of comparison; suicide outcome - average follow-up time or maximum time between TS/admission and DST. Study quality was assessed with the Newcastle – Ottawa Quality Assessment Scale for non-randomized, case-control and cohort, studies (Wells et al., 2012); assessments were conducted by the first author.

2.3. Statistical approach

The meta-analysis was conducted using Comprehensive Meta-Analysis Version 3. Effect sizes were expressed as odds ratios (ORs); ORs of up to 1.5 were considered small and 5 or above as large (Chen et al., 2010). Effect sizes were analyzed using the random effects model, assuming heterogeneity across studies (Lipsey and Wilson Lipsey and Wilson, 2001). Q and I^2 statistics were inspected to examine heterogeneity between studies. When Q is significant, this indicates considerable variance between effect size outcomes across studies. I^2 represents the amount of heterogeneity, where values of 25 %, 50 % and 75 % indicate low, moderate and high heterogeneity, respectively (Higgins et al., 2003). When heterogeneity was present ($I^2 \leq 50$ %), moderator analyses were conducted and a mixed model was used. The random effects model combined the studies per subgroup and a fixed effects model combined the subgroup effects as subgroups were assumed to be exhaustive. We assumed a common among-study variance component and pooled within-group estimates of tau^2. For continuous moderators, we used meta-regression based on z-scores and maximum likelihood with log OR outcomes. Publication bias was tested for with trim-and-fill analysis and Egger's regression analysis. Duval and Tweedie's (2000) trim-and-fill analysis estimates the amount of missing studies due to publication bias and a corrected effect size. Egger's regression tests whether the intercept statistically differs from 0, indicating publication bias (Egger et al., 1997).

3. Results

3.1. Study characteristics

We included 43 studies, reporting on 41 different samples for a total of 48 effect sizes; study characteristics are presented in Table 1. Study samples originated mostly from the US ($k = 17$) and Europe ($k = 22$); 2 studies originated from Asia and none from either South-America, Oceania, or Africa. Most studies were published before the year 2000 ($k = 24$). Suicide attempt data were available on 3733 subjects with 1022 events. In the suicide attempt studies, 37.3 % of participants were male and the average age was 42.8 ($SD = 16.6$). Suicide completion data were available on 1626 subjects with 102 events. In the suicide completion studies, 34.7 % was male and the average age was 44.3 ($SD = 18.5$). There was only one adolescent sample, all other studies reported on adult samples. Most studies included in patients with depressive or mood disorders as primary diagnosis, with some also including patients with psychotic, alcohol abuse, adjustment, eating, and personality disorders. The DST was usually conducted at the start of inpatient admission, with a dose of 1 mg (1.5 mg for DEX/CRH; $k = 4$) and a cut-off for suppression versus non-suppression of 5 mg/dl. Studies often reported DST non-suppression and suppression based on multiple measurements; dexamethasone administration was usually at 23:00 and the time between administration and measurement ranged from 3 to 25 h. One study compared patients to healthy controls, another sample compared patients to controls with and without disorders (adolescents with suicidal poisoning versus adolescents with accidental poisoning), but all other studies compared suicidal patients to non-suicidal patients, often originating from the same source population. Fourteen studies reported prospective data, i.e. with the DST measurement before the suicidal behavior, with follow-up times ranging from a half year to eighteen years. Seventeen studies reported retrospective data, of which 17 reported on the lifetime history of suicide attempts and 14 reported on recent suicide attempts (two days to a year before the DST measurement).

3.2. DST and attempted suicide

The random effects model meta-analysis on attempted suicide studies ($k = 37$) resulted in an odds ratio of 1.16 (95 % CI [0.88, 1.53], $p = .298$); the forest plot is presented in Fig. 2. This indicates that the odds of a suicide attempt did not differ between DST suppressors and non-supressors. The test of heterogeneity indicated significant between-study variance, $Q(36) = 78.30$, $p < .001$. The variance caused by effect differences between studies, rather than chance ($I^2 = 54$ %), was moderate. Therefore, subgroup analyses were conducted to investigate the potential effect of moderators.

Duval and Tweedie's trim-and-fill funnel plot showed that the studies in this meta-analysis were not distributed symmetrically around the mean effect size. Five imputed points were filled on the left side of the funnel plot, indicating possible evidence of publication bias. After adding these imputed points, the adjusted odds ratio for DST on attempted suicide was 1.00 (95 % CI [0.74, 1.33]). Egger's test of the intercept indicated potential publication bias as well (intercept 1.14, 95 % CI [0.16, 2.14], $t(35) = 2.35$, one-tailed $p = .012$).

3.3. DST and completed suicide

The random effects model meta-analysis on completed suicide studies ($k = 11$) resulted in an odds ratio of 2.10 (95 % CI [1.37, 3.23], $p < .001$); the forest plot is presented in Fig. 3. This indicates that the odds of completed suicide of those with dexamethasone non-suppression of cortisol are over 2 times higher than for those with suppression. It corresponds to a number needed to screen (NNS) of 17. It shows a small to moderate positive association of dexamethasone non-suppression with suicide completion. The test of heterogeneity indicated no significant

Table 1
Summary of Studies on the Dexamethasone Suppression Test and Suicidal Behavior.

Study	Patient sample					DST Intervention					Control		Outcome				
study, year location	*N*	DSM disorders	% in-patient	% male	age (*M* ± *SD*)	test type	dose (mg)	max. Hours	time point	CU (mg)	type	comparison	years FU	DBE	*N* events	% violent	Q
Agren and Niklasson, 1986 Sweden	151	mood	100	43.71	41.24 ± 12.64	DST	1	20.5	all	N/A	unhealthy	attempt history vs not	N/A	N/A	51	NR	9
Arató et al., 1986 Hungary	353	mood	100	16	NR	DST	1	17	all	5	unhealthy	attempt history vs not	N/A	N/A	163	NR	6
Ayuso-Gutiérrez et al., 1987 - Spain	117	mood	100	16.24	56.34 ± 13.79	DST	1	25	all	N/A	unhealthy	attempt vs not before admission	N/A	7	24	NR	8
Banki et al., 1984 Hungary	111	mix (mood, psychotic and substance use)	100	0	42.00 ± 11.00	DST	1	17	all	5	unhealthy	attempt vs not before admission	N/A	7	39	42	5
Beck-Friis et al., 1985 Sweden	32	depressive	100	43.75	43.00 ± 10.75	DST	1	24	all	7.25	unhealthy	attempt history vs not	N/A	N/A	10	30	6
Berger et al., 1984 Germany	93	mix (mood, psychotic and substance use)	100	NR	NR ± NR	DST	1	24	all	5	unhealthy	attempt vs not before admission	N/A	2	11	NR	8
Black et al., 2002 US	423	mood	100	36.64	42.96 ± 16.72	DST	1	17	all	5	unhealthy	attempt vs not (FU) & suicide vs not (FU)	3.5	N/A	21 & 11	NR	8
Brown et al., 1986 US	57	depressive	100	33.33	61.09 ± 12.64	DST	1	17	all	5	unhealthy	attempt vs not before admission	N/A	28	10	15	6
Brunner et al., 2002 Germany	15	mood	100	36.84	38.00 ± 13.08	DEX/CRH	1.5	17.25	all	N/A	unhealthy	attempt history vs not	N/A	23	8	33	5
Chaudhury et al., 1989 India	34	depressive	100	100	34.70 ± 7.00	DST	1	24	all	5	unhealthy	attempt history vs not	N/A	N/A	5	NR	8
Coryell and Schlesser, 2001 US	78	mix (mood, psychotic and substance use)	NR	33.33	35.95 ± 14.26	DST	1	17	all	5	unhealthy	suicide vs not (FU)	10.5	N/A	8	NR	8
Coryell et al., 2006 US	334	mood	55	29.34	41.47 ± 15.47	DST	1	NR	1	5	unhealthy	suicide vs not (FU)	18	N/A	13	NR	8
Coryell et al., 2008 US	54	mix (mood or psychotic)	100	66	39.60 ± 15.20	DST	1	NR	all	5	unhealthy	suicide vs not (FU)	17	N/A	4	NR	8
De Leo et al., 1986 Italy	77 & 37	mix (depressive or adjustment)	81 & 100	27.27 & 21.62	34.48 ± 15.65 & 33.81 ± 13.11	DST	1	17	1	5.00	unhealthy	attempt vs not before admission & suicide vs not (FU)	N/A & 1	3 & N/A	37 & 2	3	7
Duval et al., 2001 France	71	depressive	100	39.44	44.20 ± 9.27	DST	1	23	all	4.71	unhealthy	attempt history vs not	N/A	N/A	40	13	7
Fink et al., 1987 US	37	mix (mood or psychotic)	100	32.55	49.30 ± 21.70	DST	1	24	all	5.50	unhealthy	attempt vs not (FU)	0.5	N/A	2	NR	5
Fountoulakis et al., 2008 Greece	50	depressive	NR	30.00	41.00 ± 11.40	DST	1	24	all	5.00	unhealthy	attempt vs not before admission	N/A	30	5	0	7
Gmitrowicz and Kołodziej-Meciejewska, 2002 Poland	114	mix (adolescents with suicidal poisoning)	100	29.76	18.04 ± 1.63	DST	1	9	1	5.00	mix (accidental poisoning)	attempt vs not before admission	N/A	7	84	0	6
Hennings, Ising, Uhr, Holsboer and Lucae, 2021Germany	568	mood	100	48.20	47.20 ± 13.40	DEX/CRH	1.5	17.25	all	N/A	unhealthy	attempt vs not before admission	N/A	7	62	11	8
Hubain et al., 1986 Belgium	65	mood	100	41.53	48.77 ± 12.19	DST	1	16.5	1	N/A	unhealthy	attempt history vs not	N/A	N/A	17	NR	7

(*continued on next page*)

Table 1 (*continued*)

Study	Patient sample					DST Intervention					Control		Outcome				
study, year location	*N*	DSM disorders	% in-patient	% male	age (*M* ± *SD*)	test type	dose (mg)	max. Hours	time point	CU (mg)	type	comparison	years FU	DBE	*N* events	% violent	Q
Ismail et al., 1998 UK	60	schizophrenia	100	81.25	37.50 ± 10.00	DST	1	18	1	5.00	unhealthy	attempt history vs not	N/A	N/A	27	NR	8
Jokinen et al., 2007 Sweden	382	mood	100	32.98	52.00 ± 16.40	DST	1	24	all	5.00	unhealthy	suicide vs not (FU)	18	N/A	36	NR	8
Jones et al., 1994 US	22	schizophrenia	100	68.67	31.60 ± 7.37	DST	1	17	1	N/A	unhealthy	attempt history vs not	N/A	N/A	13	NR	7
Krishnan et al., 1984 US	24	borderline personality	100	NR	28.15 ± NR	DST	1	24	all	NR	unhealthy	attempt history vs not	N/A	N/A	13	NR	7
Kunugi et al., 2004 Japan	20	mood	100	35.00	58.00 ± 15.00	DEX/CRH	1.5	17.25	all	N/A	unhealthy	attempt history vs not	N/A	N/A	7	NR	7
Lopez-Ibor Jr and Saiz-Ruiz, 1985 Spain	42	mood	100	29	47.70 ± 14.30	DST	2	24	all	5.00	unhealthy	attempt history vs not	N/A	N/A	21	NR	7
Menke et al., 2021 Germany	150	depressive	100	53	45.86 ± 14.67	DST	1.5	3	1	N/A	unhealthy	attempt history vs not	N/A	N/A	48	NR	7
Modestin and Ruef, 1987 & Modestin and Bangerter, 1999 Switzerland	51	depressive	100	35	48.14 ± 17.74	DST	1	24	all	5.00	unhealthy	attempt vs not before admission & suicide vs not (FU)	N/A & 12.0	14 & N/A	21 & 7	NR & 57	7 & 8
Norman et al., 1990 US	53 & 66	depressive	100	44	43.88 ± 14.65	DST	1 or 2	23	all	5.00	unhealthy	attempt history vs not & suicide vs not (FU)	N/A & 6.5	N/A	25 & 13	31	8
Pickar et al., 1986 US	24	schizophrenia	100	50	28.00 ± 2.83	DST	1	24	all	5.00	unhealthy	attempt history vs not	N/A	N/A	12	NR	8
Pitchot et al., 2003 Belgium	40	depressive	100	100	41.20 ± 12.90	DST	1	17	1	5.00	unhealthy	attempt history vs not	N/A	N/A	20	NR	7
Płocka-Lewandowska et al., 2001 - Poland	32	schizophrenia	100	66	29.00 ± NR	DST	1	24	all	5.00	unhealthy	suicide vs not (FU)	8.5	N/A	5	NR	7
Roy et al., 1986 & Roy et al., 1987 US	27 & 51	mood	100 & 75	15 & 24	43.22 ± 11.96 & 42.98 ± 13.98	DST	1	24	all	5.00	unhealthy	attempt history vs not & suicide vs not (FU)	N/A & 1.0	N/A	19 & 4	16 & NR	7 & 7
Roy, 1992 US	43	mood	82	18	44.20 ± 14.00	DST	1	24	1	N/A	unhealthy	attempt vs not (FU)	5.0	N/A	8	NR	7
Schmidtke et al., 1989 Germany	126	mood	100	23	45.49 ± 13.64	DST	1	17	all	5.00	unhealthy	attempt vs not before admission	N/A	7	44	45	7
Secunda et al., 1986 US	78	mood	100	53	47.11 ± 5.91	DST	1	10	all	5.00	unhealthy	attempt vs not before admission	N/A	356	25	NR	8
Sher et al., 2013 US	17	depressive	0	71	40.40 ± 13.20	DEX/CRH	1	17	all	N/A	unhealthy	attempt history vs not	N/A	N/A	4	NR	7
Targum et al., 1983 US	49	depressive	100	22	43.93 ± 50.56	DST	1	24	all	5.00	unhealthy	attempt vs not (FU) & suicide vs not (FU)	0.5	N/A	5 & 1	NR	7
Westrin et al., 2003 Sweden	219	mix (mood, anxiety, substance abuse, eating or personality)	100	39	36.16 ± 16.23	DST	1	17	all	5.00	healthy (hospital employees)	attempt before admission vs neither	N/A	7	52	21	6
Yerevanian et al., 2004 US	101	depressive	0	45	41.49 ± 13.84	DST	1	17	1	5.00	unhealthy	attempt vs not & suicide vs not (FU)	2.1	N/A	14 & 3	NR	8
Zimmerman et al., 1986 US	187	depressive	100	29	40.00 ± 16.40	DST	1	17	all	5.00	unhealthy	attempt versus not during index episode	N/A	NR	50	NR	6

Abbreviations, CU = cut-off; DBE = days between event and test; DEX/CRH = combined dexamethasone suppression and corticotrope releasing hormone test; DSM = diagnostic and statistical manual of mental disorders; DST = dexamethasone suppression test; FU = follow-up; N/A = not applicable; NR = not reported; Q = study quality rating.

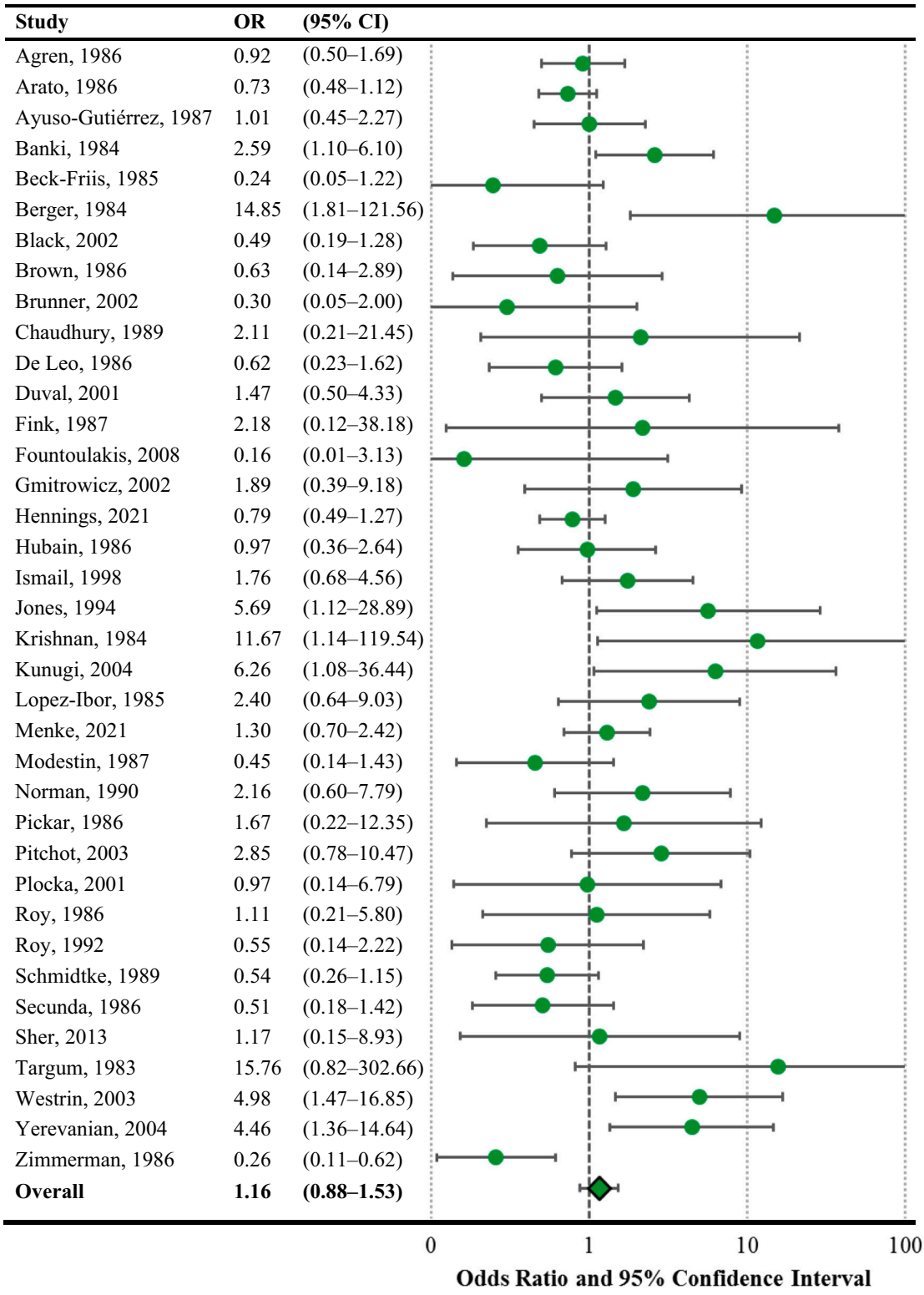

Fig. 2. Forest plot showing Associations Between the Dexamethasone Suppression Test and Suicide Attempts.

between-study variance, $Q(10) = 5.56$, $p = .851$. Relatedly, the variance caused by effect differences between studies was no different than would be expected from sampling error ($I^2 = 0$ %; Higgins et al., 2003).

Duval and Tweedie's trim-and-fill funnel plot showed that the studies in this meta-analysis were not distributed symmetrically around the mean effect size. Five imputed points were filled in the left bottom of the funnel plot, indicating possible evidence of publication bias. After adding these imputed points, the adjusted odds ratio for DST on completed suicide was still positive 1.75 (95 % CI [1.18, 2.62], $p < .001$). Egger's test of the intercept indicated potential publication bias as well (intercept 1.11, 95 % CI [0.32, 1.90], $t(9) = 3.18$, one-tailed $p = .006$).

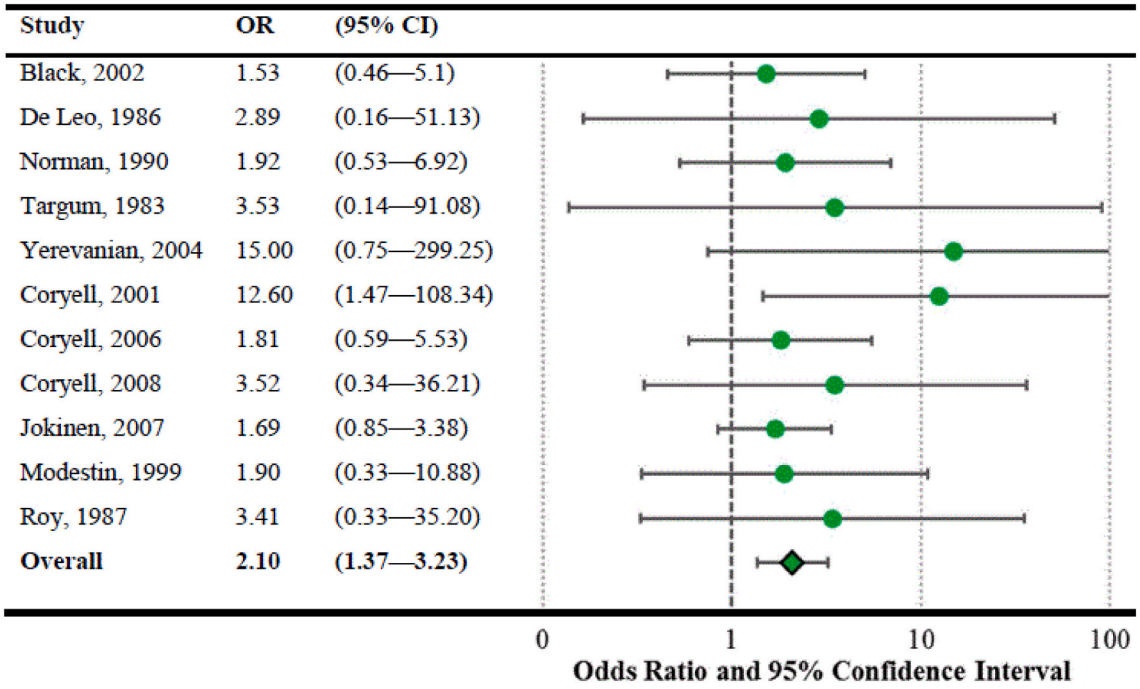

Fig. 3. Forest Plot showing Associations Between the Dexamethasone Suppression Test and Suicide Completion.

3.4. Moderator analyses

Subgroup and meta-regression analyses were conducted to investigate moderators that might explain heterogeneity between the suicide attempt studies; results are presented in Table 2. We found a moderating effect of patient sample DSM diagnoses on suicide attempts. Specifically, no predictive effect of DST on suicide attempts was found in studies based on mood or depressive patient samples. However, in samples including patients that suffer from other disorders (e.g. schizophrenia, personality disorders, substance use), the DST was associated with suicide attempts (OR = 2.34, 95 % CI [1.39–3.93]; the effect size was moderate. This corresponds to a NNS of 5. We found no indication that other study characteristics regarding the publication, patient sample, DST intervention, or suicide outcome moderated the effect of DST on suicide attempts.

3.5. Sensitivity analyses

We conducted two more subgroup analyses *post-hoc*, to further examine how DST non-suppression was related to suicide attempts depending on the type of patient sample. First, we separated depressive disorder and mood disorder samples to test any evidence for an association of DST non-suppression with suicide attempts in either of the separate groups; we did not find this to be the case (depressive disorders: $k = 13$, OR = 1.06, 95 % CI [0.67–1.67], $p = .808$; mood disorders: $k = 13$, OR = 0.82, 95 % CI [0.56–1.18], $p = .286$). We were unable to further specify the mixed patient group based on diagnosis, because there were too little studies for meaningful analyses (e.g. for schizophrenia, $k = 4$). Second, we removed the two studies with a healthy control group from the mixed patient samples and reran the analysis. We still found a moderate effect of DST non-suppression on suicide attempts in the mixed patient sample after removal of the studies with healthy controls (mixed disorders: $k = 9$, OR = 2.15, 95 % CI [1.20–3.86], $p = .286$).

Table 2
Overview of subgroup and meta-regression analyses results for suicide attempts outcome.

Subgroup Analyses

Moderator	Subgroup	*k*	OR	95 % CI	*Q*	*p*
Design	Prospective	6	1.30	0.58–2.93	3.31	0.19
	Retrospective – recent	14	0.86	0.56–1.33		
	Retrospective – historic	17	1.49	0.98–2.26		
Published	Before 2000	24	1.05	0.74–1.49	0.96	0.33
	After 2000	13	1.41	0.87–2.28		
DSM	Depressive or other mood disorders	26	0.91	0.68–1.20	**9.90**	**0.002**
	Other disorder	**11**	**2.34**	**1.39–3.93**		
DST dose	1 mg	30	1.13	0.82–1.55	0.25	0.62
	Other (1.5 or 2.0 mg)	7	1.35	0.71–2.56		
Time point	Multiple	28	1.04	0.75–1.43	1.61	0.21
	Single	9	1.54	0.91–2.61		

Meta-Regression

Variable	*k*	*b*	95 % CI	*Z*	*p*
Year published	37	0.01	−0.02–0.03	0.58	0.57
Percentage inpatients	36	−0.01	−0.02–0.01	−1.06	0.29
Percentage male	35	0.01	−0.00–0.02	1.40	0.16
Mean age	35	−0.02	−0.06–0.01	−1.21	0.23
Hours from DST to analysis	37	0.01	−0.05–0.07	0.37	0.71
Days from event to DST (retrospective recent studies only)	13	−0.00	−0.01–0.00	−1.03	0.30
Follow-up time in years (prospective studies only)	6	−0.28	−0.63–0.07	−1.55	0.12
Percentage violent events	13	0.00	−0.03–0.03	0.19	0.85
Study quality	37	0.07	−0.23–0.37	0.43	0.66

Abbreviations, CI = confidence interval; DSM = diagnostic and statistical manual of mental disorders; DST = dexamethasone suppression test; *k* = number of studies; OR = odds ratio; *Q* = Q for difference between subgroups; *Z* = *Z* for regression weight significance test.

4. Discussion

4.1. Interpretation

The results of this meta-analysis support the hypothesis that DST non-suppression, that is HPA-axis hyporeactivity, is predictive of completed suicide. For suicide attempts, there was considerable heterogeneity between studies. We found no evidence for an overall association of DST non-suppression with suicide attempts and no evidence for an association in patients with mood disorders with regards to suicide attempts. However, in study samples including patients with psychopathology other than mood disorders, the DST was associated with suicide attempts. None of the other moderators investigated in this meta-analysis further explained the heterogeneity. Earlier meta-analyses on the relationship between the DST and suicide completion by Lester (1992) and Mann et al. (2006) found an effect as well, but their effects were larger and based on less studies (both $k = 9$). Our findings contrast Chang et al.'s (2016) conclusion that the DST did not predict suicide completion. Their pooled odds ratio based on eight studies was higher than one as well (OR = 1.45, 95 % CI [0.78–2.68]), and in the same direction as our found effect. However, taking into account the large between-study variance and correction for publication bias led to their conclusion that there was no evidence for an effect. The effect size we found (OR = 2.10, 95 % CI [1.37, 3.23]) may be explained by the inclusion of more studies ($k = 11$), which granted us more power to find an effect; thereby illustrating the importance of conducting updates to underpowered meta-analyses. For suicide attempts, our results align with earlier meta-analyses (Chang et al., 2016; Lester, 1992), but points to potential specificity of associations in a subgroup of patient samples.

The discrepancy of findings among suicide attempters and suicide completers might be explained by several factors such as the potential lethality of the used method, the choice of a physically violent method, or the level of suicidal intent (e.g. Levi-Belz e.a., 2016). Since suicide attempters might include a relatively large group of individuals with non-violent attempts or attempts with a low likelihood of being lethal, studies using attempts as an outcome might therefore introduce more heterogeneity. It might be that the DST is a particular marker of violent attempts. Since most research focused on patients with major depressive disorder, it has been hypothesized that DST suppression may be indicative of depressive symptom severity or at least to some extend may covary with symptoms (Hellebuyck et al., 1988). However, DST suppression in response to a low dexamethasone dose (0.5 mg) was not associated with depression symptoms in both a general population sample (Direk et al., 2016), and a mixed patient and population sample (Vreeburg et al., 2009). One explanation for these findings may be that the measure of depression symptoms is too broad, and more specifically melancholic symptom severity should be researched. Other potential clinical features of violent attempts might be externalizing symptom severity or aggression. Aggression is often thought of as behavior aimed at others, but studies have shown that there is considerable overlap in aggression aimed at others and self (in the form of suicidal behavior or non-suicidal self injury) within individuals, which is termed *dual harm* (Shafti et al., 2021). It is tempting to speculate that DST non-suppression may be related to aggression, as we found a predictive effect for suicide attempts in patient samples that also included individuals with primarily substance abuse, psychotic and personality disorders because of the more aggressive or violent nature of attempts in these samples. There is a considerable literature of evidence relating HPA-axis dysfunction to externalizing and aggressive behavior (Hartman et al., 2013; Walker et al., 2018; Waltes et al., 2016) as well as to other disorders, such as psychotic disorders (Zänkert et al., 2019). Unfortunately, many of the studies in this meta-analysis did not report the violent versus non-violent events. For example, only 4 of the 11 samples with patients other than mood disorders reported on the percentage of violent events. In the overall meta-regression for the suicide attempts outcome, there was no evidence of studies with a higher percentage of violent events having larger effect sizes. However, there could be an association on a patient level that is not established by such an analysis and on a meta-analysis level it may be masked by missing data.

It could also be the case that DST-suppressors and non-suppressors may have differed in other biopsychosocial factors than merely (internalizing, externalizing or psychotic) symptom severity, for example in epigenetic vulnerability, familial history of suicide, personal history of trauma or abuse, sleep quality, or a low SES. For example, Staner et al. (2003) found that the cluster of patients with the most severe sleep disturbances measured by EEG abnormalities also had the highest post-dexamethasone cortisol values. Therefore, one of the ways in which HPA-axis dysfunction may lead to suicidal completion and more violent suicide attempts is through sleep disturbances and exhaustion or emotional dysregulation resulting from those; given that emotion dysregulation is related to both sleep disturbances and aggression (Shi et al., 2023). Another potential mechanism in which non-suppression of cortisol may lead to more aggressive suicidal attempts is by influencing testosterone regulation of the hypothalamic-pituitary-gonadal (HPG) axis. Non-suppression of cortisol, may then also be linked to non-suppression of testosterone, and higher post-dexamethasone testosterone levels have been related to more aggression (Sher et al., 2021). Furthermore, a way through which HPA-axis dysfunction may lead to more suicidal behavior is through the suppression of the immune system, which may lead to more inflammation, pain, and pain hypersensitivity as has been suggested in the etiology of chronic fatigue syndrome (Zhang and Wang, 2024). The suicide attempts may in that case be an attempt to not only escape from mental pain (Hennings, Ising, Uhr, Holsboer and Lucae, 2021) and exhaustion, but also physical pain.

Some methodological limitations of the included studies could also explain the heterogeneity found with regard to the suicide attempt outcome. That is, although most studies on the suicide attempt outcome included all attempts, regardless of severity, there were some that only included 'serious' attempts, for example defined as attempts that resulted in a need for specialized medical treatment. The definition and interpretation of what constitutes a 'serious' attempt likely leads to at least some heterogeneity between studies (Levi-Belz et al., 2016). Most of the included studies excluded patients because of medical reasons in line with Carroll et al. (1981), but hardly any of the studies controlled for other confounders or compared effects by sex or age. Washout periods before dexamethasone administration also differed per study. More research is necessary to determine factors that influence or confound DST results. For example, studies on suppression of a low dexamethasone dose have found associations with sex, low income, exercise, instrumental disability, smoking status (Direk et al., 2016) psychoactive medication use (Vreeburg et al., 2009) and the menstrual cycle (Altemus et al., 1997). However, replication of such studies, and with the standard 1 mg DST, is still lacking. More specifically, the finding that DST non-suppression was only related to suicide attempts in mixed patient samples, might be partially explained by some of the smaller study samples (e.g. studies with 22 to 37 patients) providing an overestimation of the effect size. However, the analysis weighs on sample size and that subgroup also included two large studies (with 114 and 219 patients). We lacked the power to conduct subgroup analyses based on the type of control samples to explain heterogeneity in the findings, since only two of the control samples included non-patient general population controls.

4.2. Limitations of current study

One of the limitations of the current study is that it may have been affected by publication bias. However, the effect of DST non-suppression in predicting suicide completion remained, even taking into account potentially missing values. Another potential reason for funnel plot asymmetry could be poor methodological quality leading to exaggerated effects in smaller studies. Furthermore, we know that there are some studies that collected relevant data, for which no effect size could be

calculated. We were not able to get in touch with all authors, and some authors replied that data were no longer available. There were also studies that measured cortisol in saliva and those studies were not taken into account in this review, because we aimed to get a more homogeneous sample and there is no known cut-off for non-suppression in saliva (Alacreu-Crespo et al., 2020; Fries et al., 2013; Hubers et al., 2014). Furthermore, in saliva the measurement represents only free cortisol while blood serum measurements represent both bound and free cortisol. Finally, there were some missing data for the moderator analyses, which decreased our ability to explain heterogeneity between studies.

4.3. Clinical implications

Suicide is one of the leading causes of death worldwide. Predicting suicide attempts and suicide completion in individuals remains a difficult task, and might be even more challenging in specific high-risk subgroups such as mental healthcare patients. Although it is reasonable to assume that genetic and biological differences exist in suicidality, most clinicians should still rely on clinical phenotype alone. Suicide is associated with many factors across clinical, life events, family history, and sociodemographic domains (Kessler et al., 2020). Developing risk profiles on the basis of both demographic and clinical features, as well as biomarkers might increase the clinical ability to prioritize patients for monitoring, hospitalization, specific treatments or even for timing of treatment discharge or termination. Furthermore, the DST is an easy to conduct, minimally invasive, procedure, making it a feasible option for screening efforts. The predictive ability of DST for suicide completion is again highlighted in this meta-analysis. Although the association is only small to moderate, every prevented suicide counts. More research is needed to establish if the DST can be a useful biomarker for future suicide in clinical practice. We propose that the DST should be studied as a part of a comprehensive and multi-stage suicide risk assessment (see Kessler et al., 2020).

4.4. Future research

Further research is needed to study to what extend DST non-suppression is indicative of trait and state risk for suicide. Non-suppression may to some extend reflect a trait risk or lifetime suicidal vulnerability, for example it may be indicative of familial or genetic risk or of a history of trauma, which may affect the consistency of findings within patients over time. More evidence however seems to point at DST non-suppression being indicative of a state risk, as the few studies that have reported on multiple DST measurements in the same psychiatric patients suggest that at least some of the patients change suppressor status over time, for example from beginning to end of treatment (e.g. Fink et al., 1987; Yerevanian et al., 1983). Knowledge on to what extend DST non-suppression reflects trait and state risk for suicide, may inform when and how often to apply this measurement (i.e. at the start and/or end of treatment) and may provide more clarity on to interpret the results. At present, it also remains unknown whether the DST can add suicide risk information to data that are already gathered by clinicians (e.g. clinical information from a standard psychiatric intake or standardized instruments). In addition, further research on the cut-off value of DST is warranted. The study by Jokinen et al. (2007) included in this paper is an example of a study that did investigate different cut-off values in relation to suicide completion. In their sample, a cut-off at 3.3 microgram/dl for males and 7.5 microgram/dl for females optimized the prediction of completed suicides, which differs considerably, by sex, from the 5 microgram/dl cut-off used in the majority of studies in depressed patients (Carroll et al., 1981). Similarly, studies could compare the effect of low dose (e.g. 0.25 or 0.5 mg) in comparison to the standard 1 mg dose, or could compare the effectiveness of simple DST versus the combined DST and CRH stimulation test (DEX/CRH), which may be more sensitive to HPA-axis dysfunction but is also more intrusive and therefore less practical to implement (Heuser et al., 1994). Furthermore, more research is needed in different psychiatric patient populations, especially those at high risk of suicide completion, such as individuals with bipolar or psychotic disorders, substance use and personality disorders (Arsenault-Lapierre et al., 2004; Yeh et al., 2019). In a review on DST in patients with PTSD for example, evidence was found for hyper-suppression of cortisol instead of non-suppression (Handwerger, 2009) and it is unclear whether patients at risk for suicide completion might be harder to detect in such samples. In addition, an older meta-analysis on the DST as a predictor of treatment outcome in depression found that DST non-suppression at the start of treatment predicted poorer effectiveness of placebo and persisting non-suppression, measured at the start and end of treatment, predicted increased risk of relapse and other poor outcomes, such as rehospitalization (Ribeiro et al., 1993). Research should further investigate the potentially broad clinical use of the DST in informing not only risk of suicide completion, but also personalized choice of treatment type and duration.

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CRediT authorship contribution statement

Pascalle Spaan: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tessa Verrijp:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Philip J.S. Michielsen:** Writing – review & editing, Investigation. **Tom K. Birkenhager:** Writing – review & editing. **Witte J.G. Hoogendijk:** Writing – review & editing. **Sabine J. Roza:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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