Oxytocin Receptor Gene DNA Methylation: A Biomarker of Treatment Response in Obsessive-Compulsive Disorder?

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\section*{Keywords}
OXTR · OCD · Cognitive-behavioral therapy · Obsessions · Epigenetics

\section*{Abstract}

\textbf{Introduction:} Obsessive-compulsive disorder (OCD) is associated with high chronicity and treatment resistance, indicating the need for early therapy response markers enabling fast and personalized treatment adaptations. Although epigenetic mechanisms such as DNA methylation of the oxytocin receptor (OXTR) gene have previously been linked to OCD pathogenesis, epigenetic markers as predictors of treatment success have not yet been investigated in OCD.

\textbf{Objective:} For the first time, this therapy-epigenetic study aimed to investigate the role of OXTR methylation as a treatment response marker in OCD.

\textbf{Methods:} In total, 113 inpatients with OCD (57 females) were compared to 113 age- and sex-matched healthy controls. Patients were investigated over a 10-week course of standardized, OCD-specific cognitive-behavioral psychotherapy. Clinical response was measured using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) at baseline, before in vivo exposure, and after therapy. OXTR exon III methylation was analyzed via direct sequencing of sodium bisulfite-treated DNA extracted from blood cells.

\textbf{Results:} Relative OXTR hypermethylation was observed in OCD patients compared to healthy controls. In OCD, higher baseline OXTR methylation was found to predict impaired treatment response at both categorical (responders vs. non-responders) and dimensional (relative Y-BOCS reduction) levels, whereas lower baseline methylation was related to treatment response and greater symptom improvements. Analysis of Y-BOCS subdimensions revealed that the association between OXTR hypermethylation with impaired treatment response applied especially to symptoms related to obsessions, but not compulsions.

\textbf{Conclusions:} OXTR hypermethylation may constitute a predictive marker of impaired treatment response in OCD and thus carries great potential for future personalized treatment efforts in OCD.

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Introduction

Obsessive-compulsive disorder (OCD) is a highly burdensome, often chronic mental disorder with a lifetime prevalence of 1–3% [1, 2]. The etiology of OCD is multifactorial, entailing complex interactions between environmental and genetic factors with a heritability of 27–65% [3]. For the treatment of OCD, besides pharmacological options, cognitive-behavioral therapy entailing exposure and response prevention exercises has been established as first-line, evidence-based psychotherapeutic treatment. Approximately 50% of patients treated for OCD respond well to standard-of-care treatment; however, the remaining half are considered partial responders or nonresponders [4]. Consequently, there is an urgent need to identify predictive treatment response markers that could potentially guide clinical decision making towards more personalized and thus more efficacious therapeutic interventions.

Epigenetic mechanisms, prominently DNA methylation, have been crucially implicated at the crossroads between genetic and environmental factors by critically influencing gene regulation and mediating adaptation to environmental factors [4–6]. While some previous studies (n = 9–65) have reported epigenetic alterations associated with OCD [7–12], no study has so far evaluated DNA methylation patterns as predictors of therapy outcome in this phenotype.

A promising candidate in the pathogenesis of OCD is the oxytocin system [13]. In rats, oxytocin injection into the central nucleus of the amygdala has been shown to induce hypergrooming, assumed to reflect OCD-related behavior [14]. Accordingly, elevated plasma and cerebrospinal fluid oxytocin levels were found in OCD [15, 16]. On an epigenetic level, increased OXTR exon III methylation was discerned in OCD patients compared to healthy controls [12].

Thus, in the present study, OXTR exon III methylation was investigated using (i) a case-control design as well as for the first time a longitudinal approach enabling the evaluation of (ii) the potential of OXTR methylation as a predictor of the clinical response to standardized cognitive-behavioral therapy in OCD, and (iii) the temporal dynamics in OXTR methylation as a potential mechanism conveying treatment response. Given the aforementioned body of literature, we expected OXTR methylation (i) to be increased in patients with OCD relative to healthy controls, (ii) to predict impaired treatment response, and (iii) to decrease along with treatment response if considered a state marker, or to remain stable if considered a trait marker in OCD.

Materials and Methods

Samples and Treatment

In total, 113 Caucasian patients with OCD (mean age ± SD: 34.31 ± 11.57 years; 57 females) were recruited at the Psychosomatic Hospital Windach, Germany, between 2014 and 2017. OCD diagnosis was ascertained based on a structured clinical interview according to DSM-IV criteria (SCID-I) by experienced psychiatrists and/or clinical psychologists. Patients underwent an 8- to 10-week semi-standardized cognitive-behavioral therapy comprising psychoeducation, exposure and response prevention/management (phase I), and intensive in vivo exposure ("flooding") (phase II). Eighty-four patients additionally received psychiatric medication at baseline (see online suppl. Material, for all online suppl. material, see www.karger.com/doi/10.1159/000509910); cf. [17].

Healthy controls (n = 113; age: 33.63 ± 10.12 years; 57 females) of Caucasian background without a history of mental disorder matched for age and sex to the patient group were recruited at the Department of Psychiatry, University of Würzburg, Germany, within the Collaborative Research Center SFB-TRR58 between 2013 and 2016 [18, 19].

Inclusion/exclusion criteria and sample characteristics are detailed in the online supplementary Material.

In patients, OCD severity was assessed via the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) at baseline (T0) and after treatment phases I (T1) and II (T2; for details see online suppl. Material), with items 1–5 reflecting symptoms related to obsessions and items 6–10 symptoms related to compulsions [20].

Genetic and Epigenetic Analyses

Genotyping for OXTR rs53576 as well as OXTR exon III DNA methylation analyses were performed according to published protocols (cf. [21, 22]; see online suppl. Material).

Statistical Analyses

Between-group differences in dimensional variables were tested by means of independent-sample t tests or univariate ANCOVA, and differences in dimensional variables by means of correlation analyses. Binary logistic regression was applied for categorical, linear regression for dimensional treatment response analyses (see online suppl. Material). The significance level was set at p < 0.05. For secondary analyses (single CpG sites), Benjamini-Hochberg correction for multiple testing was applied.

Results

Sample Descriptives

For methylation levels (average, single CpGs) at T0, T1, and T2 see Table 1. In patients, OXTR T0 methylation did not correlate with total Y-BOCS scores (r = 0.060, p = 0.531) or obsessive (r = 0.004, p = 0.970) and compulsive (r = 0.095, p = 0.317) subscales at T0. See online supplementary Material for further descriptive statistics and confounder analysis.
Case-Control Differences in Baseline OXTR Methylation

At baseline, average OXTR methylation was significantly higher in OCD patients than controls ($p < 0.001$), which also held true for CpGs 1, 2, 4, 8, 11, and 12 (all $p < 0.001$). For CpGs 3, 5–7, and 9, no differences (all $p \geq 0.132$) or lower methylation at CpG10 ($p < 0.001$) were observed.

### Table 1. OXTR exon III methylation levels in the total sample of healthy controls and patients with obsessive-compulsive disorder

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th></th>
<th>Patients</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
<td>T0</td>
<td>T1</td>
<td>T2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>SE</td>
<td>M</td>
<td>SE</td>
<td>M</td>
<td>SE</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>0.091</td>
<td>0.007</td>
<td>0.131</td>
<td>0.006</td>
<td>0.131</td>
<td>0.006</td>
</tr>
<tr>
<td>CpG1</td>
<td>0.028</td>
<td>0.007</td>
<td>0.102</td>
<td>0.005</td>
<td>0.095</td>
<td>0.004</td>
</tr>
<tr>
<td>CpG2</td>
<td>0.008</td>
<td>0.005</td>
<td>0.077</td>
<td>0.004</td>
<td>0.074</td>
<td>0.004</td>
</tr>
<tr>
<td>CpG3</td>
<td>0.097</td>
<td>0.013</td>
<td>0.120</td>
<td>0.006</td>
<td>0.121</td>
<td>0.007</td>
</tr>
<tr>
<td>CpG4</td>
<td>0.008</td>
<td>0.003</td>
<td>0.095</td>
<td>0.005</td>
<td>0.097</td>
<td>0.005</td>
</tr>
<tr>
<td>CpG5</td>
<td>0.129</td>
<td>0.013</td>
<td>0.147</td>
<td>0.008</td>
<td>0.148</td>
<td>0.007</td>
</tr>
<tr>
<td>CpG6</td>
<td>0.171</td>
<td>0.015</td>
<td>0.189</td>
<td>0.008</td>
<td>0.192</td>
<td>0.009</td>
</tr>
<tr>
<td>CpG7</td>
<td>0.142</td>
<td>0.012</td>
<td>0.165</td>
<td>0.007</td>
<td>0.165</td>
<td>0.007</td>
</tr>
<tr>
<td>CpG8</td>
<td>0.020</td>
<td>0.006</td>
<td>0.107</td>
<td>0.005</td>
<td>0.103</td>
<td>0.006</td>
</tr>
<tr>
<td>CpG9</td>
<td>0.130</td>
<td>0.013</td>
<td>0.151</td>
<td>0.006</td>
<td>0.150</td>
<td>0.007</td>
</tr>
<tr>
<td>CpG10</td>
<td>0.301</td>
<td>0.019</td>
<td>0.208</td>
<td>0.008</td>
<td>0.214</td>
<td>0.008</td>
</tr>
<tr>
<td>CpG11</td>
<td>0.009</td>
<td>0.003</td>
<td>0.076</td>
<td>0.004</td>
<td>0.076</td>
<td>0.004</td>
</tr>
<tr>
<td>CpG12</td>
<td>0.044</td>
<td>0.009</td>
<td>0.137</td>
<td>0.007</td>
<td>0.134</td>
<td>0.007</td>
</tr>
</tbody>
</table>

M, mean; SE, standard error of the mean; T0: baseline, T1: after treatment phase I, T2: after treatment (for details, see Methods section). For statistics see Results section.

### Table 2. Prediction of responder status after therapy (T2) by OXTR exon III methylation at baseline (T0) in patients with obsessive-compulsive disorder

<table>
<thead>
<tr>
<th>Methylation</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>$p$</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>–0.135</td>
<td>0.057</td>
<td>5.500</td>
<td>1</td>
<td><strong>0.019</strong></td>
<td>0.874 (0.781–0.978)</td>
</tr>
<tr>
<td>CpG1</td>
<td>–0.142</td>
<td>0.060</td>
<td>5.565</td>
<td>1</td>
<td><strong>0.018</strong></td>
<td>0.867 (0.771–0.976)</td>
</tr>
<tr>
<td>CpG2</td>
<td>–0.151</td>
<td>0.068</td>
<td>4.931</td>
<td>1</td>
<td><strong>0.026</strong></td>
<td>0.860 (0.752–0.982)</td>
</tr>
<tr>
<td>CpG3</td>
<td>–0.082</td>
<td>0.048</td>
<td>2.917</td>
<td>1</td>
<td>0.088</td>
<td>0.921 (0.838–1.012)</td>
</tr>
<tr>
<td>CpG4</td>
<td>–0.100</td>
<td>0.063</td>
<td>2.548</td>
<td>1</td>
<td>0.110</td>
<td>0.904 (0.800–1.023)</td>
</tr>
<tr>
<td>CpG5</td>
<td>–0.076</td>
<td>0.040</td>
<td>3.565</td>
<td>1</td>
<td>0.059</td>
<td>0.927 (0.857–1.003)</td>
</tr>
<tr>
<td>CpG6</td>
<td>–0.097</td>
<td>0.042</td>
<td>5.249</td>
<td>1</td>
<td><strong>0.022</strong></td>
<td>0.908 (0.835–0.986)</td>
</tr>
<tr>
<td>CpG7</td>
<td>–0.120</td>
<td>0.048</td>
<td>6.128</td>
<td>1</td>
<td><strong>0.013</strong></td>
<td>0.887 (0.807–0.975)</td>
</tr>
<tr>
<td>CpG8</td>
<td>–0.137</td>
<td>0.062</td>
<td>4.902</td>
<td>1</td>
<td><strong>0.027</strong></td>
<td>0.872 (0.773–0.984)</td>
</tr>
<tr>
<td>CpG9</td>
<td>–0.106</td>
<td>0.049</td>
<td>4.634</td>
<td>1</td>
<td><strong>0.031</strong></td>
<td>0.900 (0.817–0.991)</td>
</tr>
<tr>
<td>CpG10</td>
<td>–0.084</td>
<td>0.039</td>
<td>4.539</td>
<td>1</td>
<td><strong>0.033</strong></td>
<td>0.919 (0.851–0.993)</td>
</tr>
<tr>
<td>CpG11</td>
<td>–0.149</td>
<td>0.070</td>
<td>4.476</td>
<td>1</td>
<td><strong>0.034</strong></td>
<td>0.862 (0.751–0.989)</td>
</tr>
<tr>
<td>CpG12</td>
<td>–0.143</td>
<td>0.053</td>
<td>7.290</td>
<td>1</td>
<td><strong>0.007</strong></td>
<td>0.867 (0.782–0.962)</td>
</tr>
</tbody>
</table>

Responder status defined by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score ≤12 at T0 (indicating “wellness” as defined by symptom remission, good quality of life, and a high level of adaptive functioning; cf. Farris et al. [39]). Analyses were corrected for age, Y-BOCS sum at baseline, and illness duration. $p$ values significant at Benjamini-Hochberg corrected significance level of $p < 0.038$ are in bold. B, unstandardized beta; SE, standard error of the mean; df, degrees of freedom; OR, odds ratio; 95% CI, 95% confidence interval.
OXTR Methylation and Treatment Response Prediction

Categorical Analysis

Average OXTR methylation and methylation at single CpG sites 1, 2, and 6–12 at T0 significantly predicted categorical treatment response (total Y-BOCS ≤12; see online suppl. Material) at T2 (for statistics, see Table 2). For each unit (%) increase in methylation, the odds of being classified as a responder decreased, i.e., relative OXTR hypermethylation was related to treatment nonresponse, whereas hypomethylation was linked to treatment response.

Dimensional Analysis

Total Y-BOCS Score. Average OXTR methylation at T0 significantly predicted changes in total Y-BOCS score from T0 to T1 (β = 0.221, t = 2.10, p = 0.039) (Fig. 1), with lower T0 methylation levels associated with greater Y-BOCS reductions. For single CpGs, methylation at CpG1 (β = 0.224, t = 2.25, p = 0.028), CpG2 (β = 0.250, t = 4.41, p = 0.019), CpG10 (β = 0.224, t = 2.10, p = 0.039), CpG11 (β = 0.268, t = 2.61, p = 0.011), CpG12 (β = 0.224, t = 2.20, p = 0.031), but not CpGs 3–9 (all p ≥ 0.07), was related to changes in total Y-BOCS scores from T0 to T1 on a suggestive significance level following Benjamini-Hochberg correction.

For T0–T2 changes, only methylation at CpG12 was nominally related to differences in Y-BOCS total score (β = 0.223, t = 2.18, p = 0.032), with lower T0 methylation linked to greater Y-BOCS reduction, whereas average T0 methylation and methylation at all other CpGs failed to reach statistical significance (all p ≥ 0.10) related to changes in Y-BOCS scores (Fig. 1).

Y-BOCS Subscale “Obsessions”. Average OXTR methylation at T0 (β = 0.297, t = 2.78, p = 0.007) (Fig. 1) as well as methylation at CpG1 (β = 0.283, t = 2.78, p = 0.007), CpG2 (β = 0.336, t = 3.21, p = 0.002), CpG3 (β = 0.239, t = 2.25, p = 0.028), CpG4 (β = 0.265, t = 2.46, p = 0.016), CpG5 (β = 0.241, p = 0.030), CpG6 (β = 0.265, t = 2.44, p = 0.017), CpG7 (β = 0.268, t = 2.42, p = 0.018), CpG8 (β = 0.255, t = 2.35, p = 0.021), CpG9 (β = 0.268, t = 2.46, p = 0.017), CpG10 (β = 0.277, t = 2.54, p = 0.013), CpG11 (β = 0.342, t = 3.29, p = 0.002), and CpG12 (β = 0.298, t = 2.89, p = 0.005) were predictive of T0–T1 changes in the

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Fig. 1. Prediction of dimensional treatment response by OXTR exon III methylation at baseline (T0). Y-BOCS, Yale-Brown Obsessive Compulsive Scale; T0, baseline; T1, after treatment phase I; T2, after treatment (for details, see Methods section).

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DOI: 10.1159/000509910
Y-BOCS “obsessions” subscale, all withstanding Benjamini-Hochberg correction for multiple testing. Again, lower T0 OXTR methylation was related to greater reductions in Y-BOCS “obsessions” scores.

Average T0 methylation significantly predicted changes in the Y-BOCS “obsessions” subscale (β = 0.235, t = 2.14, p = 0.035) from T0 to T2 (Fig. 1), with lower T0 methylation accompanying greater reductions in the Y-BOCS “obsessions” scale. With respect to single CpGs, although not withstanding Benjamini-Hochberg correction, methylation at CpG1 (β = 0.247, t = 2.34, p = 0.022), CpG7 (β = 0.250, t = 2.20, p = 0.031), CpG8 (β = 0.233, t = 2.10, p = 0.039), and CpG12 (β = 0.289, t = 2.75, p = 0.008) but not CpGs 2–6 and 9–11 (all p ≥ 0.052) was suggestively related to T0–T2 changes in Y-BOCS “obsessions” scores.

Y-BOCS Subscale “Compulsions.” Neither average T0 methylation (Fig. 1) nor single CpG methylation was significantly related to changes in the Y-BOCS “compulsions” subscale for T0–T1 (all p ≥ 0.165) or T0–T2 (all p ≥ 0.236) comparisons.

OXTR Methylation and Treatment Response Mechanism

Comparing average methylation levels and methylation at single CpGs over time (T0, T1, T2) between responders (Y-BOCS ≤12 at T2) and nonresponders (Y-BOCS >12 at T2) revealed no significant changes in OXTR methylation over the course of treatment in interaction with responder status (all p ≥ 0.311) or independently of group (all p ≥ 0.090).

Dimensional symptom changes (Δ%) were also unrelated to simultaneous changes in methylation levels (average, single CpGs; %) for T0–T1 and T0–T2 comparisons (all p ≥ 0.280).

Discussion

OXTR exon III hypomethylation at baseline was for the first time observed to be associated with posttreatment symptom improvement both categorically and dimensionally in OCD patients, and thus might serve as a potential early biomarker predictive of treatment response, while relative hypermethylation at baseline—possibly constituting a trait marker of OCD as evidenced by the presently observed case-control differences—predicted treatment nonresponse. This pilot finding thus replicates and extends a previous observation of increased OXTR exon III methylation in OCD [12]. While increased methylation of the promoter/exon I gene region has been shown to entail silenced gene transcription, hypermethylation of the gene body has been linked to enhanced transcription [23]. Accordingly, the presently observed increased OXTR exon III methylation—and thus presumably heightened oxytocinergic transmission—conferring impaired treatment response is furthermore in accordance with elevated plasma as well as cerebrospinal fluid oxytocin levels in OCD patients [15, 16] and with oxytocin inducing OCD-like behavior in the rodent model [14]. Along these lines, oxytocin administration—which although proposed as a treatment adjunct in other mental disorders [23–26]—has been shown to be ineffective in treating OCD [27, 28]. A detrimental role of increased oxytocin in OCD pathogenesis and treatment response could be interpreted in the context of oxytocin having been linked to volitional and emotional ambivalence [29], and an observed strong ambivalence regarding apparently opposing interpersonal styles of prosocial attitudes and latent aggression in OCD [30]. Furthermore, analysis of OCD symptom subdimensions revealed that the presently observed predictive value of increased OXTR exon III methylation regarding impaired dimensional treatment response applied in particular to symptoms related to obsessions, but not compulsions. This finding could be interpreted in light of patients with predominant obsessions displaying worse memory deficits than those with cleanliness/washing compulsions [31] and the proposition of oxytocin as an “amnesic” neuropeptide. Indeed, oxytocin appears to attenuate memory consolidation and retrieval [32–35], suggesting that increased oxytocin could thereby perpetuate obsessive thoughts and thus impair treatment response via memory deficits. Interestingly, the predictive quality of relative OXTR hypermethylation was particularly apparent for impaired dimensional treatment response during the early stages of treatment (i.e., following phase I), which is in line with oxytocin administration having been shown to increase fear responding in the early stages of extinction learning [36, 37] and to even impair response to exposure therapy [38]. Therefore, assuming higher oxytocinergic transmission as a consequence of increased OXTR methylation, the link to impaired treatment response particularly in the early stages of exposure-based therapy may partially be due to the effects of increased anxiety resulting in less confidence in the therapeutic alliance and treatment efficacy, and, ultimately, impaired consolidation effects in the long term [35, 38]. Thus, epigenetically conferred, increased oxytocin transmission might constitute one of several biologi-
cal factors contributing to a hampered treatment response in OCD, particularly during early stages of treatment and in conjunction with predominantly obsessive symptoms. Future studies are thus warranted to investigate whether blockade of the oxytocin receptor with a blood-brain barrier-penetrating oxytocin receptor antagonist might constitute an effective treatment adjunct towards alleviating OCD symptoms.

When analyzing the temporal dynamics of OXTR methylation in the course of treatment, no relationship between OXTR methylation changes and categorical treatment response or dimensional symptom changes was observed, thus not supporting the notion of OXTR methylation to be involved in treatment response mechanisms. Instead, differential OXTR methylation may constitute a predictive marker facilitating – or hindering – treatment success.

Despite the strengths of the present study, e.g., comprising the largest sample size so far in the field of OCD epigenetics, a case-control approach, high clinical and demographic homogeneity, strict inclusion and exclusion criteria minimizing the risk of confounding factors, and a longitudinal epigenetic approach, our findings ought to be interpreted in light of some limitations as detailed in the online supplementary Material.

**Conclusion**

The present data corroborate and extend a previous study implicating increased OXTR exon III methylation in OCD [12] by for the first time suggesting relative OXTR exon III hypermethylation as (i) a trait marker of OCD and (ii) a predictive marker of impaired therapy response in OCD, particularly related to obsessive symptoms. The present results thus carry genuine potential to translate into clinical routine by informing indicated preventive measures in at-risk individuals and personalized treatments in OCD in order to determine the most accurate treatment for the individual patient and to enable early treatment modification or augmentation based on epigenetic information.

**Acknowledgments**

We gratefully acknowledge the skillful technical assistance by C. Gagel, P. Veratti, U. Wering, U. Götzinger-Berger, B. Günter, and S. Meixensberger. K.D. and M.A.S. are members of the Anxiety Disorders Research Network (ADRN), European College of Neuropsychopharmacology (ECNP).

**Statement of Ethics**

This study was approved by the Ethics Committee of the University of Würzburg, Germany (votes 07/08, 79/12, 128/14) and conducted in agreement with the Helsinki Declaration. All participants gave written informed consent prior to participation.

**Conflict of Interest Statement**

K.D. is a member of the Janssen Pharmaceuticals, Inc. Steering Committee Neurosciences. All other authors have no conflicts of interest to declare.

**Funding Sources**

Funding of this study was provided by the EQUIP Medical Scientist Program of the Medical Faculty of the University of Freiburg, Germany (to M.A.S.), and the German Research Foundation (DFG) – project No. 44541416 – SFB-TRR 58, subprojects C02 and Z02 (to K.D.); neither of the funding agencies had a role in the study design or in the collection, analysis, and interpretation of the data, in the writing of the report, or in the decision to submit the paper for publication.

**Author Contributions**

K.D., M.Z., and G.B. designed the study. L.F., L.P., R.K., W.H., and M.M. coordinated or performed patient recruitment and ascertainment of psychometric data as well as blood samples. M.Z. and G.B. supervised sample recruitment. E.R. and M.G.G. contributed to data curation. C.T. and L.K. performed genotyping and DNA methylation analyses. M.A.S. managed the database and performed the statistical analyses. M.H. was instrumental in the intellectual discussion. M.A.S. and K.D. managed the literature searches and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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