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DHEA and response to antidepressant treatment: A Mendelian Randomization analysis

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ABSTRACT

Treatment response is hard to predict and detailed mechanisms unknown. Lower levels of the dehydroepiandrosterone sulphate (DHEA(S)) – a precursor to testosterone and estrogen – have been associated to depression and to response to antidepressant treatment. Previous studies however may have been ridden by confounding and reverse causation. The aim of this study is to evaluate whether higher levels of DHEA(S) are causally linked to response to antidepressants using mendelian randomization (MR). We performed a Two-sample MR analysis using data the largest publicly available GWAS of DHEA(S) levels (n = 14,846) using eight common genetic variants associated to DHEA(S) (seven single nucleotide polymorphisms and one variant rs2497306) and the largest GWAS of antidepressant response (n = 5218) using various MR methods (IVW, MR Egger, Weighted mean, weighted mode, MR-PRESSO) and single SNP analysis. We further investigated for pleiotropy conducting a look up on PhenoScanner and GWAS Catalog. Results show no evidence for DHEA(S) gene risk score from any of MR methods, however, we found a significant association on individual variant analysis for rs11761538, rs17277546, and rs2497306. There was some evidence for heterogeneity and pleiotropy. This is the first paper to show some evidence for a causal association of genetically-predicted DHEA and improvement of depressive symptoms. The effect is not a simple linear effect, and we were unable to dissect whether the effect was direct effect of DHEA(S), mediated by DHEA(S) or on the pathway is not yet clear. Further studies using more refined instrumental variables will help clarify this association.

1. Introduction

Depression is a disease that has several central and systemic consequences such as mood swings, reward system dysfunction, anxiety symptoms, sleep, and appetite disturbances, in addition to being associated with suicide and increased risk of mortality. Depression is one of the greatest leading causes of disability worldwide and it is estimated that by 2030 depression will become the main cause of disease burden regardless of sex, ethnicity, or age (WHO, 2012). The complete understanding of depression etiology, however, remains unclear.

DHEA is a male sex hormone produced by the adrenal gland and found in both sexes. It displays a central role in the production of testosterone and estrogen as a precursor. The exact function of DHEA and/or DHEA(S) is unknown, but it helps control heart rate, blood pressure and it is involved in the development of male sexual characteristics at puberty and regulation of menstrual cycle (MedlinePlus). Depression is twice as likely to occur in women than in men. Depression occurs twice in as many women as men. It is thus possible that one of the reasons why depression develops in some individuals is due to a disturbance in DHEA and/or DHEA(S) levels.

Evidence from randomized control trials, longitudinal, experimental, and cross-sectional studies suggest a role for dehydroepiandrosterone (DHEA) and-or its sulfated form (DHEA(S)) in depression but data remain conflicting. The association between depressive symptoms and DHEA and/or DHEA(S) levels were found to be positive (Assies et al., 2004; Heuser et al., 1998), negative (Barrett-Connor et al., 1999; Goodyer et al., 1996; Michael et al., 2000; Morsink et al., 2007; Souza-Teodoro et al., 2016), or absent (Hsiao 2006; Osran et al., 1993;

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Young et al., 2002), with possible differences depending on sex (Souza-Teodoro et al., 2022). The largest study up to date shows that DHEA (S) is indeed inversely associated with depression in both cross-sectional and longitudinal analysis, regardless of sex (Souza-Teodoro et al., 2016).

Despite associations of DHEA and response to antidepressants, evidence is weak. The relationship between these hormones and response to monoaminergic antidepressants thus remains inconclusive. Most of the studies show that antidepressant treatment from different classes diminishes DHEA and/or DHEA(S) levels (Souza-Teodoro et al., 2022). However, other studies have found no association (Hough et al., 2017), or effect dependent on antidepressant class (Deuschle et al., 2004). Deuschle et al. found that DHEA(S) is only modulated by the tricyclic amitriptyline but not by the selective serotonin reuptake inhibitor (SSRI) paroxetine (Deuschle et al., 2004). The direction of effect is also controversial regarding DHEA and/or DHEA(S) levels and response to monoaminergic antidepressants. While Paslakis et al. (2010) showed that remitted patients had decreased DHEA(S) levels, Hough et al. (2017) showed the opposite.

Despite the evidence above, drawing causal inferences on the role of DHEA and/or DHEA(S) in antidepressant response is complex due to reverse causation, confounding and other biases (Smith and Ebrahim, 2003). The aim of this study was to evaluate whether increased levels of DHEA(S) is causally linked to response to monoaminergic antidepressant treatment by performing a Mendelian Randomization analysis.

2. Methods

2.1. Two-sample Mendelian Randomization

We used a Two-sample Mendelian Randomization design (Pierce and Burgess, 2013), in which the genetic variants associated to exposure (circulating levels of DHEA(S)) was acquainted from a previously published genome wide association study (GWAS, Zhai et al., 2011). These genetic variants were used as instrumental variables (IVs), which intermediates the development of a certain phenotype (Bennett, 2010; Davies et al., 2018). We applied regression coefficients and standard errors from the genotype-exposure variable relationship to the genotype and outcome (depression) data from the second database (PGC/UkBiobank), which comprises an interchangeable ethnic population. The two-sample approach allows the exploration between an exposure and an outcome in the absence of both traits evaluated in interchangeable populations (Lawlor, 2016). According to Mendelian Randomization (MR) principle, the effect on observed outcome occurs exclusively through participation of the risk factor itself. Thus, the causality estimates of an exposure factor (X) on a given outcome of interest (Y) mediated from one or more genetic variants (Z) is performed with no influence by confounding variables (U) (Fig. 1) (Imbens and Angrist, 1994; Leeuw et al., 2021; Teumer, 2018).

2.2. Exposure data

Eight genetic variants associated to DHEA(S) were previously identified in a genome-wide association study including 14,846 individuals of European ancestry (Zhai et al., 2011). Five of these variants were found in a discovery meta-analysis and 3 were found following a conditional analysis (Table S1). Of these, seven were single nucleotide polymorphisms (rs11761528, rs17277546, rs2185570, rs2637125, rs7181230, rs740160) and one multi-allelic variant (rs2497306). Serum samples for DHEA(S) measurement were obtained in the morning, regardless of fasting or not, and evaluated by immunoassay or liquid chromatography with mass spectrometry.

2.3. Outcome data

We used the largest GWAS of antidepressant response currently available (Pain et al., 2022). Their meta-analysis analyzed 13 cohorts, 10 of European ancestry and 3 East Asian ancestry (excluded from the analysis as per MR assumption that populations between datasets should be interchangeable). In total, 5218 patients diagnosed with depression were assessed for depressive symptoms before and after beginning antidepressant treatment. No standardization or differentiation related to treatment duration (minimum of at least 4 weeks and maximum of 12 weeks), drug class nor study design was available. The quantitative measure of Percentage Improvement was calculated as 100*(baseline score – final score)/baseline score. Thus, a higher Percentage Improvement implies a better treatment response, and a negative Percentage Improvement implies the patient's symptom score worsened during treatment. Percentage Improvement was standardized into a Z-score within each cohort (Pain et al., 2022).

2.4. Statistical analysis

Within the Mendelian Randomization framework, we used Wald ratio coefficients to calculate the causative effect of an exposure on an outcome from a single IV. Variants were flipped if necessary, so that all effect alleles on the exposure dataset corresponded to lower levels of DHEA(S). To evaluate the combined effect of all identified IVs, we used the inverse variance weighted (IVW) method as the main method, thus presenting the weighted average of IVs causal effects. For robustness and sensitivity of the analysis, we also conducted maximum likelihood analysis, leave-one-out, MR egger, weighted median and mode, and heterogeneity tests. Additional pleiotropy investigation was performed

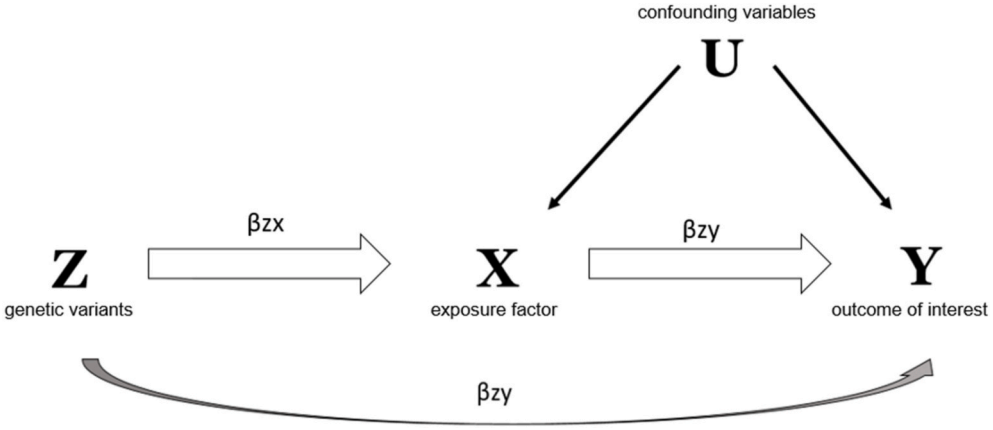

Fig. 1. - Representation of the estimated effect (β, open arrows) of the genetic variant (Z) under the exposure factor X, and the phenomenon of interest (Y). The confounding variable (U, closed arrow) does not affect the X and Y variables.

using MR-pleiotropy test, Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO), and a look up on PhenoScanner and GWAS catalog (Staley et al., 2016). Data analysis was evaluated using software R version 4.3.1 (2023-06-16) - "Beagle Scouts", and "TwoSampleMR" R package (source: https://mrcieu.github.io/TwoSampleMR). This package combines three components: management, harmonization, and statistics to evaluate likely causal effects between exposure and outcome datasets, and sensitivity analysis. Statistical significance was considered as results with p-value ≤ 0.05.

3. Results

The current study aimed at evaluating whether genetically-predicted DHEA(S) levels were likely causal to antidepressant response through Two-Sample MR approach. Eight single nucleotide variants (SNVs) associated to DHEA(S) levels previously identified (Zhai et al., 2011) in the exposure dataset were extracted from the outcome dataset. During harmonization process (Table S2), rs6738028 was removed due to being palindromic. Thus, seven variants were taken forward to the next step. Results from global MR estimates incorporating all seven variants did not find significant effects of genetically-predicted DHEA on antidepressant response (Table 1).

We then conducted individual variants MR analysis on improvement in depressive symptoms. Results from individual IVs corresponding to single variant showed a significant association for rs11761528, rs17277546 and rs2497306 between genetically-predicted DHEA(S) levels and improvement in depressive symptoms (Table 2 and Fig. 2). It is of note that the only multi-allelic variant (rs2497306) was inversely associated to improvement in depressive symptoms suggesting that a simple linear causal effect is unlikely to be at play.

We performed several sensitivity analyses. We first investigated heterogeneity using Cochran's Q test (Table 3). Results showed significant heterogeneity in IVW and MR Egger, analysis indicating that either the modelling assumptions have been violated, or that some of the genetic variants violate the IV assumption — e.g., by exerting a direct effect on the outcome not through the exposure. Horizontal pleiotropy occurs when the variant has an effect on disease outside of its effect on the exposure in Mendelian randomization. Horizontal pleiotropy was investigated using different methods. Firstly, the horizontal pleiotropy test result from the Mendelian Randomization package was not significant when testing the Egger intercept (Table 3). We then used MR-PRESSO - a test to identify horizontal pleiotropic outlier in multi-instrument summary-level MR testing. MR-PRESSO indicated significant horizontal pleiotropy (Global Test 31.47, $p = 0.017$), and identified SNVs (rs11761528, RSSobs = 0.0157, $p = 0.008$; rs740160 RSSobs = 0.016, $p = 0.048$) as outliers. Because horizontal pleiotropy was found and outliers detected, MR-PRESSO performed a distortion test to test the difference in the causal estimates before and after outlier removal. MR-PRESSO did detect a significant distortion (Distortion Coefficient = 3924, $p = 0.019$). Taking together, the variants rs17277546 or the rs2497306 seem to have a likely causal association with antidepressant response that is not explained by horizontal pleiotropy.

Finally, with the three SNVs (rs17277546, rs11761528, rs2497306) - and close proxies ($r^2_{EUR} > 0.8$) - that were significantly associated with monoaminergic antidepressant response, we further conducted a lookup in PhenoScanner (Kamat et al., 2019) and the GWAS catalog. It showed that these SNVs had previously been associated with one or more traits at genome-wide significance (Table S3). The SNV rs17277546 within the locus mapping to the *TRIM4/CYP3A43* gene was previously associated at genome-wide significance level ($P < 5 \times 10^{-8}$) to height, and other DHEA metabolites such as estrogen, androsterone, and testosterone; rs11761528 within the locus mapping *ZKSCAN5,* had been previously associated with height, adiposity, and metabolic pathways; and rs2497306 mapping to gene *EXOC6* had been previously associated with immune, obesity and type 2 diabetes. Therefore, these results suggest that the MR association with all variants may be affected by pleiotropy.

A further sensitivity analysis was performed using the leave-one-out approach (Table 4) which did not show an association when removing any of the SNVs. This analysis suggests that the association was not driven by a particular SNV.

Table 1
– Global MR Estimates for genetically predicted-DHEA(S) levels on depression using different methods.

Method selection	Beta[a] ± SE	p-value
MR Egger	0.733 ± 0.460	0.172
Weighted median	0.345 ± 0.204	0.091
IVW	0.138 ± 0.242	0.568
Weighted mode	0.509 ± 0.23	0.067

a – log changes in serum DHEA(S) μmol/L on depressive symptoms; se – standard error; IVW – inverse variance weighted.

Table 2
Individual Wald ratio and combined MR estimates for genetically predicted-DHEA(S) levels on depression.

SNV	Beta[a] ± SE	p-value
rs11761528	**0.639 ± 0.228**	**0.005**
rs17277546	**0.929 ± 0.458**	**0.042**
rs2185570	−0.188 ± 0.508	0.711
rs2637125	0.333 ± 0.318	0.294
rs2497306	**−0.997 ± 0.505**	**0.048**
rs7181230	−0.258 ± 0.428	0.547
rs740160	−0.609 ± 0.317	0.054

a – log changes in serum DHEA(S) μmol/L on depressive symptoms; se – standard error; IVW – inverse variance weighted.

4. Discussion

The association between DHEA and/or DHEA(S) and depression has been investigated in the literature, with controversial results particularly related to antidepressant response. To the best of our knowledge, this is the first study to show some evidence for a causal effect of genetically-predicted DHEA(S) level in monoaminergic antidepressant response. Results from individual IVs showed that each of the SNVs rs17277546 and rs11761528, rs2497306 unit change in DHEA(S) levels led to 1% of improvement of depression symptoms per copy of the risk allele. Pleiotropy was detected for all variants on the same or different pathways as DHEA(S). Thus, whether a direct effect of DHEA(S), mediated by DHEA(S) or on the pathway of DHEA(S) exist in response to antidepressant treatment is not yet clear.

SNV rs17277546 located near gene include TRIM4/CYP3A4 a member of the tripartite motif TRIM, CYP3A4 belongs to cytochrome P450 enzymes, this region also encompasses many other genes related to the cytochrome P450 group of enzymes. The exact method by which such mechanism leads to decrease in DHEAS levels is not yet clear but could be related to the increased metabolism of such molecules in the body and thus it is a possible candidate for DHEAS. Genetic differences in cytochrome P450 have been previously associated to antidepressant response (Hodgson et al., 2014). We suggest a fine mapping in this region may be helpful to explain associations.

SNV rs11761528 located within *ZKSCAN5* and encodes a zinc finger protein of the Kruppel family. In Zhai et al. (2011), rs11761528 was responsible for the strongest effect on DHEA(S) levels, accounting for approximately 1% of variation. Based on data shown in the current study, it is suggested that even small variations related to DHEA(S) levels may be of relevance for depression. In fact, remitted patients showed that lower levels of DHEA(S) are associated with recurrence (Mocking et al., 2015). Whether this suggests DHEA(S) as a causal trait of susceptibility of depression development is yet to be explored. Since MR-PRESSO detected potential horizontal pleiotropy, and identified this

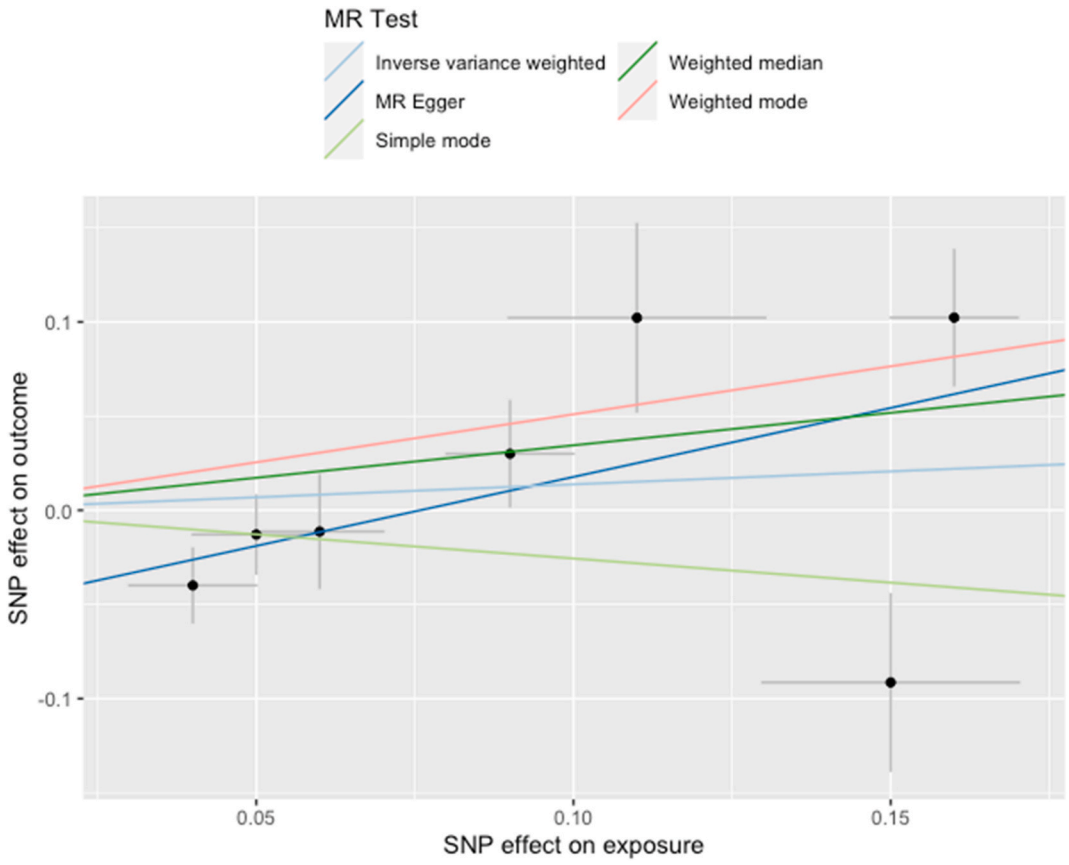

Fig. 2. – Individual SNVs plot of MR estimates of genetically-predicted-DHEA(S) and antidepressant response.

Table 3
– MR sensitivity analysis (heterogeneity and pleiotropy) of DHEA(S) levels on depression.

	Method			p-value
Heterogeneity		**Q**	**Q_df**	
	MR Egger	14.00	5	0.015
	IVW	20.08	6	0.002
Pleiotropy				
		Beta	**SE**	
	Egger intercept	−0.055	0.037	0.200

Table 4
– Leave-one-out MR estimates for DHEA(S) levels on depression.

SNVs	Beta[a] ± SE	p-value
rs11761528	−0.011 ± 0.259	0.655
rs17277546	0.066 ± 0.254	0.794
rs2185570	0.161 ± 0.271	0.551
rs2497306	0.221 ± 0.234	0.344
rs2637125	0.097 ± 0.289	0.736
Rs7181230	0.179 ± 0.272	0.508
rs740160	0.296 ± 0.238	0.213
Leave-one-out (all SNVs)	0.138 ± 0.242	0.568

a – log changes in serum DHEA(S) μmol/L on depressive symptoms; se – standard error.

SNV as an outlier, it is possible however that the association of this SNV with antidepressant response may be due to horizontal pleiotropy, which would invalidate one of the MR assumptions.

To date, there is barely any direct biological effect, if any, of *ZKSCAN5 or TRIM4/CYP3A4* modulating DHEA and/or DHEA(S) levels. SNVs within this gene such as rs10278040, rs34670419 were found to modulate both DHEA(S) and cortisol/DHEA(S) ratio (Wood et al., 2013; Pott et al., 2019; Golovchenko et al., 2022). Other authors have explored a possible role of an interplay between DHEA and/or DHEA(S) and cortisol effects (Butcher et al., 2005; Young et al., 2002). In a group of untreated depressed patients without, the isolated levels of cortisol and DHEA did not represent an association with depression while the ratio cortisol/DHEA was significantly increased in depressed patients (Young et al., 2002). Depressed patients with different treatments have demonstrated a greater ratio cortisol/DHEA than remitted or healthy patients (Michael et al., 2000).

Gene *HHEX*, in which rs2497306 is located, has been associated with type 2 diabetes. This gene encodes a transcript factor involved in pancreas development through Wnt signalling (Bort et al., 2004; Hunter et al., 2007). Also, GWAS studies showed that mutations in *HHEX* are associated to islet cells function by maintaining differentiated phenotype of the δ cell, paracrine regulation of β-cell activity and insulin-secretory defects (Perry and Frayling, 2008; Zhang et al., 2014). The relationship between diabetes and depression is complex and they represent a bidirectional risk factor for each other. Shared pathways between these two conditions include low birth weight, adverse events in childhood, lifestyle, and obesity (Sartorius, 2018). Also, insulin usage reduces DHEA and DHEA(S) through increased metabolic clearance, while DHEA administration increases insulin sensitivity (Nestler et al., 1994; Bates et al., 1995; Lavallee et al., 1997). Therefore, mutations in *HHEX* may indeed account for pleiotropic effects regarding diabetes-depression. Although our direct tests for pleiotropy were marginally significant, tests for robustness accounting pleiotropy showed a significant association with weighted median, and marginally significant results in the same direction with weighted mode and MR Egger. Using multiple MR methods allows the strengths and weaknesses of each one to complement results interpretation, once each method differs in patterns of violation assumptions (Hemani et al., 2018; Burgess

et al., 2020; Lee, 2020). Also, it was shown that IVW met statistical significance for heterogeneity, which indicates that multiple genetic variations may be leading to depression, emphasizing the plurality of causes and symptoms related to the disorder.

SNV rs2637125, located in the gene *SULT2A1*, failed to show a significant association. This gene codes the enzyme sulfotransferase 2A1 (SULT2A1, E.C. 2.8.2.2), which promotes a sulfation of DHEA to DHEA (S) (Rainey et al., 2002). This polymorphism has been demonstrated to decrease DHEA(S) levels without altering the ratio DHEA/DHEA(S) (Haring et al., 2012). Therefore, although the circulating levels of DHEA (S) are diminished by this mutation, levels of the active form of the hormone (DHEA) may be unaffected. Gene *BMF*, which encodes Bcl-2-modifying factor protein, also has limited known biological influence on DHEA and/or DHEA(S) levels apart from its association with ageing processes and regulator of apoptosis (Zhai et al., 2011; Puthalakath et al., 2001).

Our study has both strengths and limitations. By using the largest GWAS of representative cohorts comprising information from DHEA(S) and antidepressant response, this study showed for the first time some causal association between DHEA(S) and response to antidepressant. On the other hand, our study would benefit from large sample sizes as it is unlikely that a simple linear causal effect is at play here. More variants from the exposure dataset will increase the power to detect true associations. The increase in power will also enlighten the role of pleiotropy.

In conclusion, we have found some evidence of a causal association between higher DHEA(S) and beneficial antidepressant response. Further studies on larger sample sizes for both exposure and outcome are necessary to validate our findings.

CRediT authorship contribution statement

LAC research supervision, resources, conceptualization, and methodology. LHSGA was responsible for resources and supervision. LHST was responsible for the formal analysis, investigation, and writing the original draft. All authors reviewed and edited final drafts.

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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2024.02.049.

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