Motor Abnormalities, Depression Risk, and Clinical Course in Adolescence Supplemental Information

Clinical Assessments.

KSADS –Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL; ABCD short name: abcd_ksad01). The Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL) is a semi-structured parent-child interview designed to assess present and lifetime psychopathology[1]. K-SADS-PL measures affective and psychotic impairments on both diagnosis-specific and global levels and is highly reliable and wellvalidated. This measure has been previously validated and found to be reliable (test-retest reliability kappa=.86) [2].

In the current study, the K-SADS-PL a total count of symptoms that were endorsed with clinically relevant severity (current or in the past), resulting in a possible score of 0 to 35, were included as a continuous measure of depression symptoms [3]. A categorical variable was also created to reflect the presence of the automated depression spectrum diagnoses and included major depressive disorder (MDD), MDD not otherwise specified (NOS), and dysthymia, which were generated by questions endorsed by the child, but not clinically assessed. As these automated diagnoses are not clinically validated, they only appear in the supplement for transparency. These diagnoses should be interpreted with caution and treated as preliminary, exploratory evidence.

The Child Behavior Checklist (CBCL; ABCD short name: abcd_cbcl01). The Child Behavior Checklist (CBCL) is a 113-item questionnaire that measures behavioral and affective

problems (e.g., conduct problems, attention problems, anxiety/depression) among children from 6 to 18 years of age [4, 5]. The checklist is completed by the child's parent or caregiver, who are asked to describe their child as they are now or over the past 6-months. The scores are measured using a three-point Likert scale (0 = absent, 1 = occurs sometimes, 2 = occurs often). For the current analyses, the single item (item 62) "Poorly coordinated or clumsy" was used as a validated measure of motor issues [6]. For this item, the participants responded on a three-point scale (0 = not true, 1 = somewhat true, 2 = often true); this item has high inter-rater reliability (.85), test-restest (r=.56) [4, 7].

ABCD Family History Assessment (ABCD short name: fhxp). The Family History Assessment Module Screener (FHAM-S; Rice et al., 1995) screens for the presence/absence of psychopathological symptoms in first- and second-degree biological relatives. This scale has been previously validated and found to be reliable in terms of depression (test-retest kappa=.76) [8]. In the current study, we leveraged the modified version of the FHAMS-S that was utilized by Lees et al. (2020). We looked at first-degree relatives with MDD and first-degree relatives who "experienced visions of others spying/plotting or similar problems". Participants were categorized as either having or not having a first-degree relative with a diagnosis based on their endorsement of the items that ask for the presence of parents or siblings with depression. This information was then used to group individuals into MDD or no family history. In addition to these group statuses, a total number of first-degree relatives endorsed as having either depression were used as a proximal measure of genetic loading of risk.

ABCD Developmental History Questionnaire (ABCD short name: dhx01). The ABCD Developmental History Questionnaire was used to measure motor delay [9, 10]. Specifically, the parents/caregivers were asked "At approximately what age (number of months)

was he/she FIRST able to do each of the following: rollover, sit without assistance, walk without assistance" and "Would you say his/her motor development (i.e., sitting, crawling, walking) was earlier, average, or later than most children?" The participants were given 5 options to answer these questions: (1) much earlier, (2) somewhat earlier, (3) about average, (4) somewhat later, and (5) much later. The responses were later reclassified into no motor delay (responses 1-3) or endorsement of a motor delay (responses 4 or 5).

Statistical Approach and Models

Logistic regressions analyses assessed the relationship of Depression diagnoses (y/n), to each motor symptom accounting for stimulant use in separate models. In continuous analyses, motor variables were used to predict depression symptoms and familial risk loading in separate models accounting for stimulant use. All motor abnormalities were then entered into a single model simultaneously to examine unique contribution of each motor symptom to predicting depression diagnoses and vulnerabilities for depression in separate models of specificity. Finally, to examine the utility of motor symptoms to predict future depression diagnoses, depression diagnoses were classified using a discriminant function analyses accounting for baseline stimulant use and all motor variables (dyscoordination, motor agitation, and motor slowing) in a single model. To examine the utility of motor symptoms to predict future depression symptoms, a step-wise linear regression predicted symptoms endorsed at follow-up accounting for baseline depression symptoms endorsed and stimulant use in the first step and motor symptom variables in the second step.

Correction for multiple comparisons were set within each definition of depression (depression diagnoses, depression symptoms, family history of depression, familial loading of depression risk) which were related to four distinct motor symptoms. Using this logic, clinical

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comparisons were considered significant if they passed Bonferroni correction for 4 model comparisons (p<.0125). It is notable, however, that if a more stringent 16 test correction were used (p<.003); this would only impact the interpretation of 2 findings. These findings include the family history of depression relating to motor delays (p=.018) and motor slowing (p=.01). This may signal some caution in interpreting these findings, however the significance relationship among of these variables to familial loading of depression may add some confidence that this relationship merits further investigation in future research.

Supplemental Table S1

Income	Whole Sample	MDD Diagnoses	No MDD Diagnoses	$\chi^2(11, 11786)=94.55, p<.001$			$\chi^{2}(17, 11800)=142.28, p<.001$
Less than \$5,000	3.5%	6.80%	3.3%		4%	3.30%	
\$5,000-11,999	3.5%	7%	3.4%		3.80%	3.40%	
\$12,000-15,999	2.3%	3.8%	2.2%		2.80%	2.10%	
\$16,000-24,999	4.4%	7.3%	4.2%		4.90%	4.10%	
\$25,000-34,999	5.5%	7.3%	5.4%		6.90%	4.80%	
\$35,000-49,999	7.9%	9.6%	7.8%		9.30%	7.20%	
\$50,000-74,999	12.6%	11.6%	12.7%		14.70%	11.70%	
\$75,000-99,999	13.2%	9.0%	13.5%		13.30%	13.20%	
\$100,000-199,999	28.0%	22.0%	28.3%		26.10%	28 80%	
\$200,000+	10.6%	6.1%	10.8%		7 10%	12 10%	
Unknown	8.5%	9.4%	8.5%		7.10%	7 10%	
Race				$\chi^2(17, 11787) = 54.13, p < .001$	/.10/0	/.10/0	$\chi^{2}(17, 11787) = 54.13, p < .001$
American Indian	0.5%	0.2%	0.5%		< 0.1%	0.5%	
Asian Indian	0.5%	< 0.1%	0.6%		0.4%	0.7%	
African American	15.1%	20.5%	14.8%		13.3%	15.9%	
Chinese	0.9%	0.3%	0.9%		0.4%	1.1.%	
Filipino/a	0.7%	0.3%	0.7%		0.5%	0.8%	
Japanese	0.2%	0.7%	0.3%		0.1%	0.3%	
Korean	0.4%	0.7%	0.4%		0.2%	0.5%	
Multiracial	5.3%	6.8%	5.3%		6.8%	4.7%	
Native Hawaiian	< 0.1%	< 0.1%	<0.1%		<0.1%	< 0.1%	
Other Asian	0.4%	0.2%	0.4%		0.1%	0.5%	
Other Race	5.3%	7.2%	5.2%		4.9%	5.5%	
Pacific Islander	0.1%	0.5%	0.1%		0.1%	0.1%	
Samoan	<0.1%	< 0.1%	<0.1%		0.1%	<0.1%	
Vietnamese	0.2%	< 0.1%	0.2%		0.1%	0.2%	
White	68.8%	60.6%	69.2%		71.9%	67.4%	
Unknown	1.6%	1.9%	0.9%		0.8%	1.9%	

Results with KSADs Depression Diagnoses

Depression Diagnoses and Psychomotor Agitation. A higher percentage of the youth with a depression diagnosis (3.2%) endorsed Psychomotor agitation symptoms compared to individuals not diagnosed with depression (1.4%), OR= 2.34, B=0.54, SE=.18, p=.001, sensitivity=3.3%, specificity=98.6%, Supplemental Table S2.

Depression Diagnoses and Psychomotor Retardation. Individuals with and without depression did not differ (0.3%) on the endorsement of Psychomotor retardation, B=.004, SE=.176, OR=1.81, p=.99, sensitivity=.3%, specificity=99.96%, Table 2.

Depression Diagnoses and Developmental Motor Milestones Delays. More youth diagnosed with depression (13.79%) exhibited developmental motor delays than youth without depression (8.55%), $\chi^2(1,10619)=18.56$, p<.001, OR=1.71, sensitivity=12.14%, specificity=91.40%, Table 2.

Depression Diagnoses and Dyscoordination. Youth with depression were more likely to endorse dyscoordination (35.5%) than those without depression (18.4%, OR=2.43, B=0.60, SE=.064, p<.001, sensitivity=35.3%, specificity=81.6%, PPV=9.1%, and NPV=96.02%, Table 2.

Motor Abnormalities Relative Contribution to Depression Diagnoses. In a multiple logistic regression that included all 4 motor abnormalities, there was a high overall model fit, demonstrating that motor abnormalities overall are related to the presence of a depression diagnosis, $\chi^2(5,11786)=134.22$, $r^2=.03$, p<.001. Three of the four motor variables uniquely related to a depression diagnosis – Psychomotor agitation (B=0.53, *SE*=0.19, *p*=.004, *OR*=1.67, 1.16-2.40 95% C.I.), developmental motor delays (B=0.49, *SEM*=0.13, *p*<.001, *OR*=1.79, 1.58-2.03 95% C.I.) and dyscoordination (B=0.58, *SEM*=0.07, *p*<.001, *OR*=1.63, 1.37-1.94 95% C.I.)

with the exception of Psychomotor retardation (B=0.44, SEM=0.54, p=.41, OR=0.65, 0.22-1.89
95% C.I.).

Depression Diagnoses at One-Year Follow-Up. In a logistic regression, predicting depression diagnoses at follow-up, the first step included baseline diagnoses of depression and stimulant uses, and the second step included baseline motor abnormalities (motor agitation, motor retardation, and dyscoordination). The overall model was significant, F(5, 6448)=54.93, $r^2=.025$, p<.001, all variables significantly contributed to the model, and the change between steps was significant (χ^2 -change(4, 6448)=31.24, p<.001). In the first step, baseline depression symptoms significantly contributed to the model ($\beta=.57$, p<.001), but stimulant medication use at baseline did not (p=.41). In the second step, three of the four motor abnormalities uniquely predicted follow-up depression diagnosis (Psychomotor agitation: $\beta=1.19$, p<.001, OR=4.45; dyscoordination: $\beta=0.25$, p=.007; OR=1.52), but not Psychomotor retardation ($\beta=0.38$, p=.43, OR=2.75). The test characteristics of motor abnormalities in predicting a future depression diagnosis include Psychomotor agitation: sensitivity=6.1%, specificity=99.0%; Psychomotor retardation: sensitivity=25.1%, specificity=82.0%, Supplemental Table S3.

	Major Depression Diagnosis					
	Whole Sample	Yes	No	Group Comparison		
	n=11,870	n=605	n=11,265	Statistics		
Age (Months) -M(StD)	118.95 (7.46)	119.73 (7.20)	118.9 (7.47)	<i>t</i> (11859)=2.65, <i>p</i> =.008		
Sex (% Female)	67.75%	42.10%	48.20%	χ^2 (11801)=8.30, <i>p</i> =.004		
Psychomotor Agitation	1.50%	3.20%	1.40%	$\chi^{2}(2, 11800)=24.66, p<.001$		
Psychomotor Retardation	0.30%	0.30%	0.30%	$\chi^2(2, 11800)=3.34, p=.18$		
Developmental Motor Delays	8.80%	13.79%	8.55%	$\chi^{2}(1, 11654) = 18.84, p < .001$		
Dyscoordination	19.40%	35.50%	18.50%	$\chi^{2}(2, 11800)=135.11, p<.001$		

Supplemental Table S2. Demographic and Motor Sign Distribution by Diagnoses

Supplemental Table S3. Test Characteristics of Motor Abnormalities for Detecting Depression Diagnoses

	Depression Diagnoses at Baseline				Depression Diagnoses at Follow-Up					
Motor Abnormalities	Sensitivity	Specificity	PPV	NPV	OR	Sensitivity	Specificity	PPV	NPV	OR
Psychomotor Agitation	3.25%	98.59%	10.73%	95.12%	2.34	6.07%	98.97%	25.00%	94.90%	4.45
Psychomotor Retardation	0.34%	99.69%	5.41%	95.04%	1.81	1.16%	99.85%	30.77%	94.69%	2.75
Developmental Motor Delays	12.14%	91.40%	7.75%	94.59%	1.71	10.17%	91.05%	6.07%	94.69%	1.15
Dyscoordination	35.32%	81.59%	9.12%	96.02%	2.43	25.07%	81.96%	7.31%	95.07%	1.52

Supplemental Figure S1. Effect Size of Motor Abnormalities by Current Depression and Depression Vulnerability Measures



Psychomotor Agitation- Red, Psychomotor Retardation -Purple, Developmental Motor Delays – Yellow, Dyscoordination Symptoms -Green ; Effect Sizes above were transformed into calculated in raw, not model-corrected data; Odds Ratios (see Table 2) and standard error were transformed to Cohen's d using the Michaela package in R; Error bars reflect the standard error; Effect sizes were converted to common values using the R Michaela package [11] and visualized with the metaviz package [12]. Damme et al.

Supplement

Results with Individuals on Antipsychotics Included and no Stimulant Use Covariates Statistical Approach and Models

For many of the analyses Chi-Square compared clinical categorizations (e.g., Depression diagnoses (y/n), First Degree Relative (y/n)) and motor symptom categories (e.g., Motor Delays (y/n), CBCL not coordinated (y/n), Psychomotor Slowing (y/n), Psychomotor Agitation (y/n)). Student's T-tests were used to compare the continuous clinical outcome variables (e.g., Total Current Depression Symptoms Endorsed, Total Number of First-Degree relatives with Depression) across motor symptom categories. Finally, in separate multilevel mixed models, sensorimotor network connectivity (cortico-cerebellar, coritco-striatum, cortico-thalamic) were compared to depression measures (Depression diagnoses (y/n), Total Depression Symptoms, First Degree Relative (y/n), Total First Degree Relatives with Depression) with scanner type, maximum framewise displacement, sex, race, and age at scan as subject level covariates, and subjects were nested within families and site.

Depression Diagnosis.

Motor Milestones (any motor, speaking) Delay Categorization (early/typical, later) Related to KSADS Diagnosis (Major Depression Disorder, None). Groups were significantly different in terms of motor delays, $\chi^2(2)=27.72$, p>.001; Odds Ratio (OR)=1.75. 14.2% of the MDD group (OR= 1.776) reported motor delays, which was significantly more than 8.5% of the non-psychiatric illness controls.

Current Symptoms of Dyscoordination not coordinated on (CBCL; yes, no) were compared across KSADS Diagnosis groups (Major Depression Disorder, None) in a Chi-Square. Groups were significantly different in terms of endorsing not coordinated on CBCL $\chi^2(2)=155.87$, p<.001, such that more individuals who were diagnosed with MDD (34%; OR= 2.52) endorsed not being coordinated compared to non-psychiatrically diagnosed controls (18%).

Current Symptoms of Psychomotor Slowing (KSADS; yes, no) were compared across KSADS Diagnosis groups (Major Depression Disorder, None). Groups were significantly different when grouped by the endorsement of current psychomotor retardation, $\chi^2(2, 11722)=12.70$, p=.002, such that 4% of the individuals diagnosed with MDD (OR=1.10) endorsed psychomotor slowing, this was significantly greater than 2% of the non-psychiatrically diagnosed controls.

Current Symptoms of Psychomotor Agitation (KSADS; yes, no) were compared Across KSADS Diagnosis groups (Major Depression Disorder, None). Groups were significantly different in terms of endorsing psychomotor agitation, $\chi^2(2, 11722)=12.70$, p=.002, such that a higher percentage of the group with an MDD diagnosis (3.5%; OR=2.49) endorsed psychomotor agitation compared to non-psychiatrically diagnosed controls (1.4%; OR=1.47).

Current Depression Symptoms.

Motor Milestones (any motor) Delay Categorization (early/typical, later) in an analysis of variance were related to Symptoms Totals for Major Depression Disorder (KSADS). In the KSADs Symptoms, Depression symptoms totals were significantly higher in the motor delayed group t(11722)=6.77, p<.001, M=1.26, StD=3.35, compared to individuals with no motor delays, M=0.72, StD=2.39.

Current Symptoms of Dyscoordination (not coordinated on CBCL; yes, no) were related to Current Symptom Totals for Major Depression Disorder (KSADS) in a t-test. Individuals who endorsed being less coordinated had more KSADS depression symptoms t(11864)=17.16, p<.001, M=1.56, StD=3.52, compared to coordinated individuals, M=0.58, StD=2.10.

Current Symptoms of Psychomotor Slowing (KSADS; yes, no) were compared to Totals for Major Depression Disorder (KSADS) using a t-test. Individuals who endorsed being psychomotor slowing endorsed more KSADS depression symptoms t(11864)=4.25 p<.001, M=2.51, StD=4.39, compared to those without motor slowing, M=0.76, StD=2.49.

Current Symptoms Total for Major Depression Disorder (KSADS) was related to Current Psychomotor Agitation (yes, no) using a t-test. Individuals who endorsed psychomotor agitation endorsed more KSADS depression symptoms, t(11860)=4.69, p<.001, M=1.63, StD=3.89, compared to those who did not endorse motor symptoms, M=0.76, StD=2.46.

Family History of Depression.

Family History of Psychiatric Illness (Yes/No) Related to Motor Milestones (any motor) Delay Categorization (early/typical, later). There was a significant impact of family history in first degree relatives, $\chi^2(1,11733)=7.15$, p=.008. Individuals with no family history of depression only included 8.5% individuals with motor delays; in contrast, individuals who had a family history of depression 14.2% endorsed motor delays (OR=1.78).

Current Symptoms of Dyscoordination not coordinated on (CBCL; yes, no) were related to Family History of Psychiatric Illness (Major Depression Disorder, No Depression History). There was a significant impact of family history on endorsing not coordinated, $\chi^2(1,11874)$ = 59.59, p<.001. For individuals with no family history of depression, 17.5% reported being not coordinated. Among individuals with a family history of depression, 23.7% reported current dyscoordination symptoms (OR=1.45).

Current Symptoms of Psychomotor Slowing (KSADS; yes, no) were compared across Family History of Psychiatric Illness (yes, no). There was a significant difference in endorsing current motor slowing based on family history of psychiatric illness, $\chi^2(1,11870)=7.48$, p=.006.

Current Symptoms of Psychomotor Agitation (KSADS; yes, no) were compared to Family History of Depression (yes, no). There was a significant difference in endorsing current motor agitation based on a family history of psychiatric illness, $\chi^2(1,11870) = 11.41$, p=.001. Individuals with no family history of depression only included 1.28% individuals with motor agitation; in contrast, individuals who had a family history of depression 2.12% endorsed motor agitation (OR=1.66).

Familial Risk Loading - Total Number of Family Members with History of Depression.

Motor Milestones (any motor, speaking) Delay Categorization (early/typical, later) Related to Total Number of Family Members with Depression in a t-tests. There was a difference in motor delays related to the number of relatives with a depression diagnosis, t(11730)=2.93, p<.001. Individuals with delayed motor had more first-degree relatives with depression (M=0.47, StD=.759) than individuals who did not experience delays (M=0.40, StD=.727).

Current Symptoms of Dyscoordination not coordinated on (CBCL; yes, no) were related to Total Number of Family Members with Depression. There was a difference in coordination related to the number of relatives with a depression diagnosis, t(11730)=8.50, p<.001. Individuals who endorsed current dyscoordination symptoms had more first-degree relatives with depression (M=0.52, StD=.845) than those who were coordinated (M=0.38, StD=.699).

Current Symptoms of Psychomotor Slowing (KSADS; yes, no) were compared to Total Number of Family Members with Depression. There was no difference in psychomotor slowing related to the number of relatives with a depression diagnosis, t(11730)=2.00, p=.04. Individuals who endorsed psychomotor slowing had more first-degree relatives with depression (M=0.65, StD=.73) than individuals who did not experience psychomotor slowing (M=0.41, StD=.72).

Current Symptoms of Psychomotor Agitation (KSADS; yes, no) were compared Total Number of Family Members with Depression. There was a difference in psychomotor agitation related to the number of relatives with a depression diagnosis, t(11730)=3.91, p<.001. Individuals who endorsed psychomotor agitation had more first-degree relatives with depression (M=0.62, StD=.87) than individuals who did not experience psychomotor agitation (M=0.40, StD=.72).

Familial Risk as a Categorical Vulnerability Factor

Prevalence of Motor Abnormalities Among Adolescents with Familial Risk for

Depression. Logistic regressions analyses assessed the relationship of clinical categorizations (e.g., Depression diagnoses (y/n), First Degree Relative (y/n)) to each motor symptom accounting for stimulant use.

Psychomotor Agitation. More individuals with a family history of depression (2.0%) endorsed psychomotor agitation (OR=1.58) compared to individuals with no family history of depression only included (1.3%), B=0.31, SE=0.11, p=.004.

Psychomotor Retardation. More individuals with a family history of depression reported psychomotor retardation (0.5%; OR=2.41) compared to 0.2% of individuals with no family history of depression, B=0.59, *SE*=0.35, *p*=.013.

Developmental Motor Milestones Delays. More individuals with a family history of depression (8.4%) endorsed developmental delays in achieving motor milestones compared to individuals with no family history of depression (2.6%), $\chi^2(1, 11662)=5.62$, p=.018.

Dyscoordination. More individuals with a family history of depression, 23.3% reported current dyscoordination symptoms (OR=1.44) compared to individuals with no family history of depression, 17.5%, B=0.24, *SE*=0.04, p<.001.

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Supplement

Motor Abnormalities Specificity Sensitivity to Depression Vulnerability - Familial Risk for Depression. In logistic regression, there was a high overall model fit demonstrating that motor abnormalities overall are related to the presence of a first degree relative with a depression diagnosis, $\chi^2(5, 11795)=143.04$, p<.001. Traditional measures of motor abnormalities, including psychomotor agitation (B=0.22, *SE*=0.12, *p*=.062) and retardation (B=0.48, *SE*=0.25, *p*=.056), were not related to the presence of the familial risk when accounting for the variance related to other motor abnormalities. Developmental motor delays (B=0.15, *SE*=0.07, *p*=.036) and dyscoordination (B=0.23, *SE*=0.04, *p*<.001) were uniquely related to the presence of familial risk for depression.

Discriminant Function Analyses of Depression Diagnoses at One-Year Follow-Up.

In examining the appropriateness of the model, there was low intercorrelation between the items of interest (r's<.3). The Wilks' lambda for each predictor was significant, Λ =0.98, χ 2=47.42, df=4, p's<.001, indicating that overall, the predictors differentiated among those with depression diagnoses and non-depressed individuals. The unstandardized canonical discriminant function evaluated at a group mean showed that this function was positive in the depression group (M=.46) and negative in the non-depressed group (M=-.026). The discriminant function correctly classified 94% (93.9% depression, 99% non-depressed) of the individuals in our sample in both the original data and the leave-one-out cross-validation approach, Figure 2. The test characteristics of motor abnormalities in predicting a future depression diagnosis include psychomotor agitation: sensitivity=6.1%, specificity=99.0%, PPV=25.0%, and NPV=94.9%; psychomotor retardation: sensitivity=1.2%, specificity=99.9%, PPV=30.8%, and NPV=94.7%; dyscoordination: sensitivity=25.1%, specificity=82.0%, PPV=7.3%, and NPV=95.1%, Table 2.

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Social Anxiety Total Symptoms to Motor Signs

Motor Abnormalities Relative Association with Social Anxiety Symptoms. A general linear model with simultaneously entered predictors of all motor abnormalities were related to depression symptoms accounting for the variance related to stimulant medication use, F(5,11646)=13.29, $r^2=.04$, p<.001. Traditional motor variables were related to number of social anxiety symptoms endorsed - psychomotor agitation (B=1.584, 1.04-2.13 95% C.I., t=5.72, SE=0.28, p<.001) and psychomotor retardation (B=1.65, 0.74-2.57 95% C.I., t=3.56, SE=0.47, p<.001). Social anxiety disorder is not related to developmental motor delays (B=0.07, -0.28-0.43 95% C.I., t=0.40, SE=0.18, p=.69) and dyscoordination (B=-0.008, -0.24-0.22 95% C.I., t=-0.07, SE=0.115, p=.94).

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