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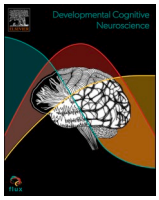

Anterior pituitary gland volume mediates associations between adrenarche and changes in transdiagnostic symptoms in youth

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ABSTRACT

The pituitary gland (PG) plays a central role in the production and secretion of pubertal hormones, with documented links to the increase in mental health symptoms during adolescence. Although literature has largely focused on examining whole PG volume, recent findings have demonstrated associations among pubertal hormone levels, including dehydroepiandrosterone (DHEA), PG subregions, and mental health symptoms during adolescence. Despite the anterior PG's role in DHEA production, studies have not yet examined potential links with transdiagnostic symptomology (i.e., dysregulation) pertinent to long-term functioning. Therefore, the current study sought examine whether anterior PG volume mediates associations between DHEA levels and changes in dysregulation symptoms in an adolescent sample ($N = 114$, 9 –17 years, $M_{age} = 12.87$, $SD = 1.88$). Following manual tracing, structural equation modeling revealed that greater anterior, not posterior, PG volume mediated the association between greater DHEA levels and increasing dysregulation symptoms across time, controlling for baseline dysregulation symptom levels. Results also showed that greater DHEA levels related to decreasing symptoms across time, suggesting potential attenuation effects. Altogether, these results provide support for separating the anterior and posterior PG by demonstrating specificity in the role of the anterior PG in adrenarcheal processes that may confer risk for adolescent psychopathology.

1. Introduction

The pituitary gland (PG) has been highlighted as the nexus of neuroendocrine regulation and stress responsivity, given its primary role in hypothalamic-pituitary-adrenal (HPA) axis function. Clear links have been made between morphometric estimates of the PG and responses to stressful experiences, as well as mental health functioning during development. Although the majority of studies have focused on whole pituitary volumes (Ganella et al., 2015; Kaess et al., 2013; Murray et al., 2016; Whittle et al., 2012; Zipursky et al., 2011), emerging work has suggested that the anterior PG, in particular, is highly relevant to puberty-related responses to early life stress and mental health symptoms that occur within the adolescent window (Díaz-Arteche et al., 2021; Farrow et al., 2020; Picci et al., 2023a). That is, the PG consists of two separable lobes that have dissociable structural and functional features. The anterior PG is primarily involved in triggering a cascade of events leading to the production and release of a variety of hormones (Kaiser and Ho, 2016), including dehydroepiandrosterone (DHEA), which along with estradiol, testosterone, and progesterone, is one of several key hormones involved in regulating pubertal development and the focus of the current investigation. Indeed, with adrenarche, the anterior PG plays an increasing role in the influx of DHEA, with concomitant volumetric increases in whole PG volume during this early pubertal event (Murray et al., 2016). Conversely, the posterior PG is

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largely responsible for the storage and release of antidiuretic hormone (i.e., vasopressin) and oxytocin, which are produced by the hypothalamus (Leng et al., 2015). Thus, the anterior PG, in particular, is of interest because its morphology may offer insights into the puberty-related emergence of mental health symptoms. Importantly, far less is known about how adrenarche and its associated hormones are related to adolescent mental health (Byrne et al., 2017); though such studies could offer foundational knowledge about how even the earliest pubertal events (i.e., before the major physical changes associated with puberty) set the stage for adolescent mental health functioning. In other words, because adrenarche most often starts before gonadarche, earlier detection of neurally-mediated adrenarche-related alterations in symptomology could yield greater prediction of who is most vulnerable to developing mental health disorders in the long term.

Specific links between adrenarche (e.g., DHEA levels), anterior PG volume, and mental health symptoms in youth have yet to be properly documented, especially in longitudinal samples. Generally, existing work has largely focused on whole PG volumes. Although mixed (Díaz-Arteche et al., 2021; Farrow et al., 2020; Ganella et al., 2015), there are reports that larger whole PG volume is related to subclinical and clinical levels of mental health symptoms. For example, longitudinal work has shown that larger PG volume prospectively predicts increases in internalizing symptoms during the pubertal window (Zipursky et al., 2011). Similarly, larger PG volume was found to mediate associations between elevated depressive symptomology and earlier puberty onset (Whittle et al., 2012). This corroborates earlier studies showing that youth diagnosed with unipolar and bipolar depression had larger PG volume than controls (MacMaster et al., 2008). More recently, work has highlighted the contribution of early life stress in accelerating PG growth (Ganella et al., 2015; Kaess et al., 2018) or promoting larger PG volumes into adulthood (Klinger-König et al., 2023). That is, in a population-based study of adults ($N > 2800$), PG volumes were related to psychopathology symptoms, which were further amplified by early life stress (Klinger-König et al., 2023). Discrepancies in existing findings include that some of the accelerated growth findings are only evident in girls (Ganella et al., 2015; Kaess et al., 2018) and that in some cases, PG volume does not relate to symptomology levels (Ganella et al., 2015) nor early life stress (Schär et al., 2022).

Existing work has also characterized how pubertal hormone levels are related to PG volume during the pubertal transition, and how this may correspond with the emergence of psychopathology. In one study, salivary testosterone, DHEA, and DHEA-S predicted increases in PG volume across time, irrespective of age (Whittle et al., 2020). Notably, this pattern of growth attributable to hormones was stronger for girls than boys. PG volume has also been shown to mediate associations between higher DHEA/DHEA-S levels and anxiety symptoms in youth (Murray et al., 2016). In contrast, other work has shown that youth with elevated trauma-related anxiety symptoms exhibit lower DHEA levels, which in turn predict smaller anterior PG volumes specifically (Picci et al., 2023a). Although contrary to some developmental work, these findings corroborate other literature showing both neuroprotective effects of elevated DHEA and systematically lower levels of DHEA in those with internalizing disorders (Farooqi et al., 2018; Mocking et al., 2015). This prior work motivates a more targeted, longitudinal investigation of whether anterior PG volume specifically mediates associations between DHEA levels and symptomology across adolescence.

Although foundational, extant literature has overwhelmingly examined whole PG volume, with more limited study of whether and to what extent the anterior PG is a key arbiter in emergent symptomology in adolescence. Some studies have begun to examine the anterior and posterior pituitary lobes separately, which may help to disentangle some of the discrepant findings by enhancing overall sensitivity to detect effects. Given its specific role in stress responsivity and pubertal hormone output (Le Tissier et al., 2012; Martí and Armario, 1998), it may be the case that there are specific stress- and hormone-related patterns of variability evident in the anterior versus the posterior lobe of the PG. The sparse findings that are available suggest that there is utility in separating the anterior and posterior lobes, as lobe specific effects have been uncovered (Díaz-Arteche et al., 2021; Farrow et al., 2020; Picci et al., 2023a). That is, two prior studies emphasize the role that early life stress may have in propagating risk for enlarged anterior PG volumes specifically, although neither of these studies found prospective links with psychopathology, and they did not include pubertal hormones (Díaz-Arteche et al., 2021; Farrow et al., 2020). Taken together, the current literature suggests that the anterior pituitary, in particular, may be a viable target for understanding associations among pubertal hormones, a stress sensitive neural region, and emergent psychopathology. Therefore, the current study is among the first longitudinal investigations to examine how the morphometry of the anterior PG may mediate associations between adrenarcheal hormone levels and changes in symptomology during adolescence.

Given that previous research has not yet shown that DHEA levels and pituitary volume amplify risk for specific diagnostic categories, the current study employed a more transdiagnostic approach by examining dysregulation symptoms. We built off of previous work highlighting that dysregulation is a potent predictor of long-term psychopathology diagnoses and comorbidities (Althoff and Ametti, 2021), as well as changes in key neural networks (Picci et al., 2023b). Dysregulation is often defined as difficulties in regulating affect, behavior, and cognition (ABCs), with symptoms peaking during early adolescence (Deutz et al., 2018). As a symptom profile, it does not completely fit into either internalizing or externalizing categories, but instead, has features of both, making it an ideal assessment of transdiagnostic symptoms that tend to reliably cluster together. In the Child Behavior Checklist Dysregulation Profile (CBCL-DP) employed here, dysregulation consists of the anxiety/depression, attention problems, and aggression subscales. Thus, the current study examined the extent to which DHEA levels (adrenarche) were indirectly associated with changes in dysregulation symptomology during adolescence, via anterior PG volume. To determine specificity of the effects on changes in dysregulation symptoms per se, we also tested whether similar patterns are evident in changes in internalizing and externalizing symptoms, given that they are transdiagnostic predictors of psychopathology (Reef et al., 2011; Roza et al., 2003) and are more deeply characterized in the literature. Building upon previous literature, we predicted that enlarged anterior (but not posterior) PG would mediate the relationship between higher DHEA levels and increases in dysregulation symptoms across time.

2. Methods

A final sample of 114 healthy children and adolescents ages 9–17 years-old ($mean_{age}$= 12.87, SD = 1.88; 58 females) completed a structural MRI scan and a hormonal assay as part of the Developmental Chronnecto-Genomics study (DevCoG study; for more information about the parent study, see Stephen et al., 2021). Briefly, the DevCoG study was a multisite study of neurodevelopment across 3 study visits conducted annually, with an extensive battery of neuroimaging, neuropsychological assessments, and biological assays (e.g., genetics, epigenetics, hormones). The parent study was designed to comprehensively examine environmental and genetic factors affecting neurodevelopment across adolescence (9–17 years old) with multimodal imaging. Participants were recruited from the local communities through flyers, advertisements, and community engagement events. Individuals in the current substudy included 44 participants recruited at the Boys Town National Research Hospital site in Omaha and 70 participants from the Mind Research Network (MRN) in Albuquerque, NM, USA. Participants were invited back to participate annually for three years. Participants' symptomology levels were collected via caregiver report annually (see *Child Behavioral Checklist* section). In the present study, we examined structural MRI data and hormonal assays from the same time point and change in symptomology across two timepoints. Specifically, we examined change in symptomology from the

scan/hormone assay session to the participant's next visit approximately 1 year later. The initial sample included 153 participants with a T1-weighted image and a usable hormonal assay; 16 participants (14 %) were excluded due to excessive motion and/or artifacts in their structural MRI data. In addition, 23 participants were excluded for only having usable DHEA data at their last data time point, which would preclude them from having multiple time points of CBCL data to contribute to the outcome variable. A total of 106 participants had complete datasets for all predictor variables. Note that the final sample of 114 was overlapping with the sample previously reported on cross-sectionally in Picci et al., (2023a). Inclusion criteria included English as a primary language, age, and participant and parent willingness to assent/consent, respectively. Exclusion criteria determined via parent report were as follows: history of developmental delays and/or diagnosed psychiatric disorders, history of neurological disorders (e.g., epilepsy), history of concussion or head injury, pregnancy, prenatal exposure to drugs, use of medications known to affect brain function, and MRI contraindications (e.g., orthodontia, metallic foreign bodies). During the study, participants who disclosed any newly emerging severe diagnoses (e.g., autism, psychosis) were withdrawn, and their data was excluded. However, participants who disclosed new diagnoses of anxiety, depression, or ADHD remained in the study. Two participants reported receiving an ADHD diagnosis after enrollment. All parents and youth provided written consent or assent, respectively, prior to participating in the study. The appropriate institutional review boards for both study sites approved all study procedures.

2.1. Structural neuroimaging acquisition & processing

Participants underwent a structural T1-weighted MRI with either a Siemens 3 T Skyra scanner at the Boys Town National Research Hospital study site (N = 44) or a Siemens 3 T TIM Trio at the MRN site (N = 70). MR images at both data collection sites were acquired with a 32-channel head coil and an isotropic MPRAGE sequence with the following parameters: TR= 2400 ms; TE= 1.94 ms; flip angle= 8°; field of view= 256 mm; slice thickness= 1 mm; base resolution= 256; 192 slices; voxel size= 1 × 1 × 1 mm. The images of all participants were processed using FreeSurfer version 6 (http://surfer.nmr.mgh.harvard.edu) to extract total intracranial volume estimates. We followed the ENIGMA protocol for quality assurance, including performing visual checks on all images (http://enigma.usc.edu/protocols/imaging-protocols) and checking for motion artifacts.

Pituitary Tracing. Tracing methods for this study have been reported previously (see Picci et al., 2023a). Briefly, the anterior and posterior lobes of the pituitary gland were manually traced using the 3D Slicer software (v4.11, www.slicer.org; Fedorov et al., 2012). Prior work has demonstrated that the pituitary is optimally visualized in the coronal and sagittal planes of T1-weighted MR images (Díaz-Arteche et al., 2021; Farrow et al., 2020; Lorenzetti et al., 2009; Whittle et al., 2012). The pituitary was defined based upon previously published tracing techniques (Farrow et al., 2020). Several boundaries and structures were visually inspected by the tracers to determine the boundaries of the PG (Fig. 1, adapted from Picci et al., 2023a). That is, the diaphragm sellae and lateral ventricles were located superiorly, the sphenoid sinus was located inferiorly and bilaterally, and the internal carotid arteries were located bilaterally, all in the coronal view. Contrast differences in the sagittal view were used to determine the boundary between the anterior and posterior lobes of the PG, which appear darker and lighter, respectively (Fig. 1). Estimates for the anterior and posterior lobe volumes were computed by summing all the voxels selected by tracers across all slices. The full sample was split in half and traced by 2 pairs of trained tracers (i.e., LO-NP, GP-CC were paired tracers). Each tracer traced both the anterior and posterior lobes (for example tracing, see Fig. 2). Intraclass coefficients (ICCs) with absolute agreement were calculated for anterior and posterior traces, and were .96–.97 (LO-NP) and .93–.95 (GP-CC), respectively.

2.2. Child behavior checklist

During two of the study visits, a caregiver completed the Child Behavior Checklist (CBCL, (Achenbach et al., 2001)) to assess their child's dysregulation behaviors over the past 6 months. The dysregulation profile is a summed score of the attention, aggression, and anxious/depressed subscales (Holtmann et al., 2011). In addition, to

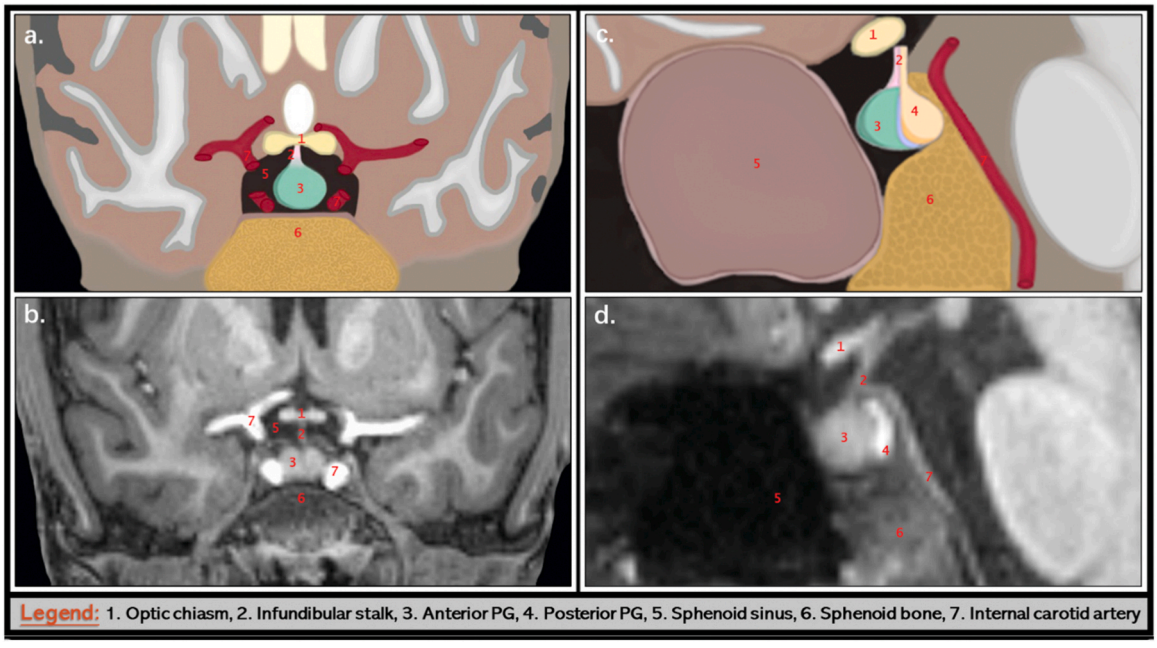

Fig. 1. Anatomical boundaries used to trace both lobes of the pituitary gland. (a) and (c) are coronal and sagittal schematic depictions of the T1-weighted slice images from a representative participant in (b) and (d). The red numbers denote the anterior and posterior lobes of the pituitary gland (PG), as well as the structures and anatomical boundaries surrounding them. Each of the numbered structures were used to manually trace the anterior and posterior PG. The legend (bottom of figure) provides the anatomical structures that correspond to each of the red numbers in a-d. Figure adapted with permission from Picci et al., (2023a).

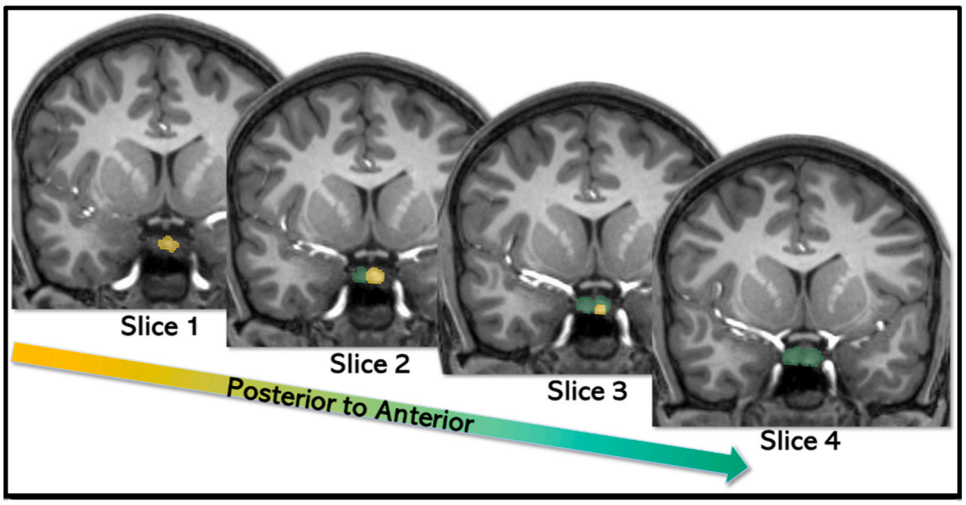

Fig. 2. Slice-by-slice example of a manually traced pituitary gland. A set of T1-weighted images in the coronal view from a representative participant is shown across multiple slices proceeding from posterior to anterior. The anterior pituitary gland (PG) is shown in teal/green and the posterior PG shown in yellow.

demonstrate the potential specificity of the effects in dysregulation, we examined the internalizing and externalizing composites to determine whether similar or divergent effects are evident in other commonly reported transdiagnostic symptom profiles. The internalizing composite consists of anxious/depressed, somatic complaints, and withdrawn subscales and the externalizing composite consists of rule-breaking behavior and aggressive behavior subscales. Scores from the participant's initial visit where they had both a usable T1-weighted structural scan and hormonal assays served as the baseline measure of dysregulation symptoms. Scores from the participant's next visit, approximately 1 year later, served as time point 2. Raw scores were used in our models, as both sex and age were controlled for in our models. A difference score was calculated for each individual to assess changes in dysregulation (as well as internalizing and externalizing) across time (i.e., Time 2 symptoms – Time 1 symptoms). Therefore, positive change scores indicate increasing dysregulation across time, whereas negative change scores indicate decreasing dysregulation symptoms.

2.3. Hormonal assays

At least 2.0 mL of whole unstimulated saliva was collected from each participant. Specifically, children were asked to passively drool into an Oragene DISCOVER (OGR-500; www.dnagenotek.com) collection tube until liquid saliva (not bubbles) exceeded the fill line indicated on the tube. Participants were instructed to refrain from consuming any food, liquids, or chewing gum for at least an hour before providing the saliva sample, and generally completed the study in the afternoon. Prior to the release of the protease inhibitors for long-term storage, a single-channel pipette was used to extract 0.5 mL from the collection tube, which was immediately transferred into a labeled micro-centrifuge tube and placed in a -20C freezer for storage. All samples were assayed together with duplicate testing using a commercially-available assay kit for salivary DHEA. The assay kit had a sensitivity of 5 pg/mL, with a range of 10.2–1000 pg/mL. The intra- and inter-assay coefficients of variation were 7.95 % and 10.17 %, respectively. The averages of duplicate tests were used for analyses in the present study. A natural log transform was applied to DHEA measurements to account for skewness of the raw data (before transform: skewness=3.32, kurtosis=13.34; after transform: skewness=0.36, kurtosis=-0.04).

2.4. Data analytic plan

We first ran descriptive statistics on all study variables of interest and demographics. Variables entered into subsequent models were examined for violations of normality (i.e., skewness and kurtosis) and were transformed according to their distribution type (e.g., positive versus negative skew). Next, we iteratively fit structural equation models to estimate 1) whether anterior and/or posterior PG volumes mediated associations between DHEA levels and changes in dysregulation symptoms across time (see Fig. 3 for model). We also ran models separately by sex to determine sex-specific patterns, given known sex differences in pubertal timing and mental health symptomology. Note that these sex-specific models were run as a multi-group analysis, as opposed to a single group analysis, whereby the same model is run simultaneously for each group. A model examining whether the effects were similar for changes in internalizing and externalizing behaviors, respectively, was also run.

Base models were fit to examine the effect of independent variables on the dependent variables. Next, covariates of no interest were introduced into the model, which included sex, age, study site, baseline levels of dysregulation symptoms, and total intracranial volume (ICV). Note that ICV was regressed only on anterior and posterior PG volumes. After introducing the covariates, models were fit to examine the mediating effect of anterior and posterior PG volume on the association between DHEA levels and symptomology levels (i.e., indirect effects of PG volume via DHEA on symptomology). All mediation models were bootstrapped with 1000 iterations with bias-corrected bootstrapping to test for significance of the indirect associations based upon the 95 % confidence intervals (MacKinnon et al., 2004). Unstandardized estimates of individual paths were examined for the directionality of relations with an *a priori* *p*-value significance threshold of $p < .05$. Finally, PG volume estimates (i.e., anterior and posterior lobe volumes) were permitted to freely correlate and all parameters were freely estimated. We ran models with and without missing data estimation using full-information maximum likelihood (FIML) and the same conclusions were reached. In order to reduce potential bias from data missing at random, we report results using FIML estimation. All models were tested in Mplus (v7.4).

We examined the goodness of fit for both models using standard criteria (Hu and Bentler, 1999). Specifically, we evaluated models for the root mean square error of approximation (RMSEA) < 0.06, standardized root mean square residual (SRMR) < 0.08, and comparative fit index (CFI) > 0.95. We also examined the χ^2 test of model fit, where a nonsignificant result indicates good model fit.

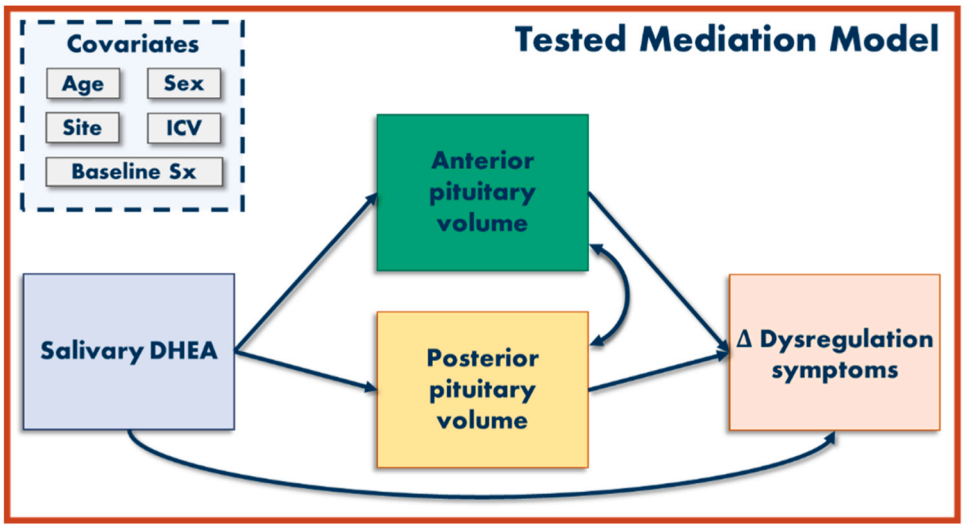

Fig. 3. Full structural equation model used in the current study. The mediation model tested whether anterior and/or posterior pituitary gland (PG) volume mediated the association between salivary DHEA levels and changes in dysregulation symptoms across two time points measured via the CBCL. Dysregulation symptom change scores were computed by subtracted time 1 scores from time 2 scores; larger values indicate increases in symptoms across time. All study variables were regressed on sex, age, study site, and baseline dysregulation symptoms. PG variables were regressed on ICV. ICV = intracranial volume, baseline Sx = baseline dysregulation symptoms, Δ Dysregulation symptoms = dysregulation change scores.

3. Results

3.1. Sample demographics

Descriptive statistics and demographic variables for the final sample (N = 114) are reported in Table 1. Correlations among study variables of interest are reported in Table S1. There were study site differences in ethnicity such that the MRN site included more Latinx/Hispanic participants compared to the Boys Town National Research Hospital (BTNRH) site (all $p < .05$, Table 1). In addition, there were site differences in anterior and posterior PG volumes, whereby the BTNRH site had significantly larger volumes for both segmentations (all $p < .05$, Table 1). There were no other site differences in participant distributions of age, sex, race, hormone levels, and symptomology. Crucially, study site was included in all models as a covariate to account for these initial differences.

3.2. Mediation model results

The mediation model examining the mediating role of anterior PG

Table 1
Demographics and study site comparisons.

Variable	Full Sample (n = 114)		Site 1 (BTNRH; n = 44)		Site 2 (MRN; n = 70)		Comparison	
	n	%	n	%	n	%	χ^2	*p*
Sex, female	58	51 %	26	59 %	32	46 %	1.93	.16
Race							6.03	.20
AI/AN	5	4 %	-	-	5	7 %		
Asian	1	1 %	1	2 %	-	-		
B/AA	5	4 %	3	7 %	2	3 %		
White	96	86 %	37	84 %	59	84 %		
More than one race	4	3 %	1	2 %	3	4 %		
Not reported	3	2 %	2	5 %	1	2 %		
Ethnicity							9.56	**< .05**
Latinx/Hispanic	25	22 %	3	7 %	22	31 %		
Not Latinx/Hispanic	89	78 %	41	93 %	48	69 %		
Not reported								
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	*t*	*p*
Age (years)	12.87 (1.88)	9 – 17	12.82 (1.61)	9 – 15	12.89 (2.05)	9 – 17	−0.20	.84
DHEA	53.09 (63.90)	5.15 – 417.99	44.26 (49.86)	5.15 – 302.48	58.63 (71.11)	6.58 – 417.99	−1.17	.24
Dysregulation symptoms	6.06 (6.07)	0 – 30	5.45 (5.41)	0 – 20	6.45 (6.45)	0 – 30	−0.83	.41
Internalizing symptoms	4.23 (4.33)	0 – 18	3.93 (3.78)	0 – 17	4.41 (4.65)	0 – 18	−0.57	.57
Externalizing symptoms	3.36 (3.98)	0 – 25	3.05 (3.45)	0 – 12	3.56 (4.29)	0 – 25	−0.65	.52
Δ Dysregulation	0.75 (5.02)	−12 – 21	0.52 (4.24)	−8 – 13	0.90 (5.49)	−12 – 21	−0.33	.74
Δ Internalizing	1.08 (4.58)	−9 – 17	0.67 (3.73)	−7 – 12	1.33 (5.05)	−9 – 17	−0.62	.54
Δ Externalizing	0.09 (3.08)	−8 – 12	−0.33 (2.12)	−5 – 5	0.35 (3.54)	−8 – 12	−0.95	.34
Anterior pituitary volume	404.04 (155.87)	87 – 851	442.66 (158.96)	158 – 844	379.76 (149.98)	87 – 851	2.13	**< .05**
Posterior pituitary volume	87.57 (35.84)	29 – 215	112.28 (33.88)	65 – 215	72.04 (27.47)	29 – 166	6.95	**< .001**

Note. AI/AN = American Indian/Alaska Native, B/AA = Black, African American. Brain measures are reported in volume mm^3. Age is reported in years, at the time of the MRI scan. DHEA is reported in picograms per milliliter (pg/mL). Dysregulation symptoms are all raw scores from the Child Behavior Checklist. Dysregulation change scores (Δ) were calculated as follows: T2 – T1 dysregulation symptoms; positive scores indicate increasing symptom severity across time. To evaluate potential study site effects, χ^2 analyses were conducted for binary variables. Significantly different *p*-values are bolded.

volume on the association between DHEA and changes in dysregulation symptoms had excellent fit [$\chi^2(2) = 1.34$, $p = .51$; RMSEA < 0.01; SRMR $= 0.01$; CFI $= 1.00$]. Table 2 reports all direct, indirect, and total effects and all path estimates are reported in Table S2. In terms of the mediation results, anterior PG volume mediated the association between DHEA and changes in dysregulation symptoms across time ($\beta = 0.10$, $b = 0.08$; 95 % CI[0.02, 0.19]; Fig. 4). There was a direct effect between DHEA levels and changes in dysregulation symptoms ($\beta = -0.31$, $b = -0.25$, $p = .02$). Participants with higher DHEA levels had larger anterior PG volumes ($\beta = 0.28$, $b = 0.51$, $p < .001$), which in turn predicted greater increases in dysregulation symptoms across time ($\beta = 0.35$, $b = 0.16$, $p = .03$). Note that this pattern of results remained the same with or without the inclusion of baseline dysregulation symptoms as a covariate.

Mediation effects were specific to the anterior PG such that the posterior PG did not mediate associations between DHEA levels and changes in dysregulation symptoms ($\beta = 0.005$, $b = 0.004$; 95 % CI [-0.01, 0.07]). There were no associations between DHEA levels and posterior PG volume ($\beta = -0.10$, $b = -0.04$, $p = .30$), nor were there associations between posterior PG and changes in dysregulation ($\beta = -0.05$, $b = -0.10$, $p = .72$).

Other notable effects in the model include sex-specific effects on the anterior ($\beta = 0.38$, $b = 1.23$, $p < .001$), but not the posterior PG ($\beta = -0.05$, $b = -0.03$, $p = .62$). Specifically, girls had significantly larger anterior PG compared to boys. In addition, there were no sex differences in DHEA levels ($\beta = 0.12$, b=-0.21, $p = .14$) nor changes in dysregulation ($\beta = -0.03$, $b = -0.04$, $p = .81$). Finally, age was associated with increasing DHEA ($\beta = 0.53$, $b = 0.24$, $p < .001$), anterior pituitary volume ($\beta = 0.40$, $b = 0.34$, $p < .001$), and posterior pituitary volume ($\beta = 0.28$, $b = 0.05$, $p = .002$), but not changes in dysregulation symptoms ($\beta = 0.08$, $b = 0.03$, $p = .61$).

The multi-group model examining within-sex effects had excellent fit [$\chi^2(4) = 3.71$, $p = .45$; RMSEA < 0.01; SRMR $= 0.03$; CFI $= 1.00$]. Table 3 reports all direct, indirect, and total effects and all path estimates are reported in Tables S3-S4. There were no significant mediating effects of anterior or posterior PG on the relationship between DHEA and changes in dysregulation in boys or girls. For boys only, there was a direct effect of DHEA on changes in dysregulation ($\beta = -0.44$, $b = -0.40$; 95 % CI[-0.72, −0.09]. Similar to the main model results, higher levels of DHEA related to decreasing dysregulation symptoms across time.

Finally, the model examining the mediating effect of anterior PG on the relationship between DHEA and changes in internalizing and externalizing symptoms had excellent model fit [$\chi^2(3) = 1.59$, $p = .66$; RMSEA < 0.01; SRMR $= 0.02$; CFI $= 1.00$], but there were no mediating effects of anterior PG volume on either symptom type. There were also no direct effects of DHEA or anterior PG volume on either internalizing or externalizing symptom changes. Table S5-S6 reports all direct, indirect, and total effects as well as path estimates.

Table 2
Direct, indirect, and total effect estimates for mediation model.

Indirect Effects		Estimates		95 % CIs	
Mediator	Outcome	β	*b*	Lower	Upper
Anterior pituitary	**Δ Dysregulation**	0.10	0.08	**0.02**	**0.19**
Posterior pituitary	Δ Dysregulation	0.005	0.004	−0.01	0.07

Direct Effects	Estimates		95 % CIs	
	β	*b*	Lower	Upper
DHEA → Δ Dysregulation	−0.31	−0.25	**−0.47**	**−0.03**

Total Effects	Estimates		95 % CIs	
	β	*b*	Lower	Upper
DHEA → Δ Dysregulation	−0.21	−0.17	−0.38	0.04

Note. Significant results are bolded based upon bootstrapped 95 % confidence intervals for indirect effects and $p < .05$ for direct effects.

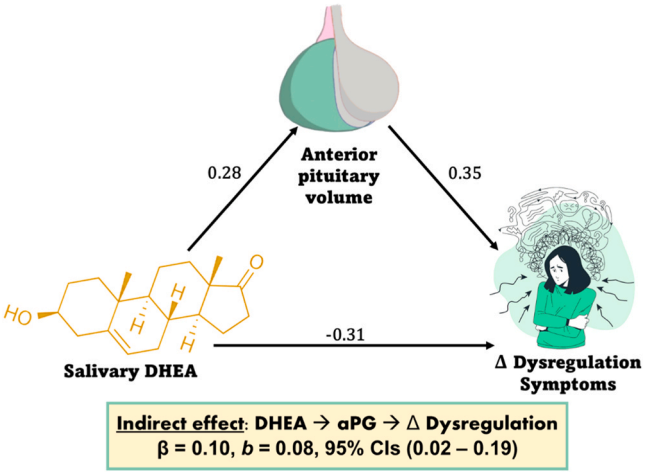

Fig. 4. Significant indirect effect of anterior pituitary volume on associations between DHEA and changes in dysregulation. Higher DHEA levels were related to larger anterior pituitary volume, which in turn predicted greater increases in dysregulation symptoms across time. There was also a direct relationship between DHEA and symptoms such that greater DHEA levels related to fewer symptoms. Standardized estimates are shown. Model fit was excellent.

4. Discussion

The current study is among the first to establish longitudinal associations between pubertal hormones, anterior PG volume, and changes in dysregulation symptomology during the pivotal adolescent period. Here, we report that greater anterior PG volume mediates the relationship between higher DHEA levels at baseline and increases in dysregulation symptomology across time. Crucially, these findings were only found in the anterior lobe of the PG, not the posterior lobe, suggesting specificity of effects in a region integral to HPA-axis functioning, which is consistent with extant literature (Farrow et al., 2020; Picci et al., 2023a). There were also no direct relationships between posterior PG volume and DHEA levels nor changes in dysregulation symptomology, further suggesting that the anterior PG is uniquely sensitive to pubertal hormones and is consequentially linked to mental health during the pubertal window. Although contrary to expectations, the direct relationship between greater DHEA and decreasing dysregulation symptomology adds to the literature showing neuroprotective effects of DHEA during development (Farooqi et al., 2018) and is consistent with systematically lower levels of DHEA in adults with internalizing disorders (Mocking et al., 2015). However, the applicability of the adult literature is in this context is not well understood, as DHEA levels are very different among adults and adolescents, and this could be associated with different relationships between DHEA and mental health symptoms at different developmental stages.

The mediation finding reported here is largely consistent with prior cross-sectional and longitudinal literature documenting associations among different metrics of puberty, PG volume, and symptoms during adolescence (Murray et al., 2016; Whittle et al., 2012; Zipursky et al., 2011). Specifically, previous work has shown a comparable mediation effect with whole PG volume, pubertal timing, and depressive symptoms across time (Whittle et al., 2012). The present study builds upon prior findings by documenting greater specificity of these effects in the anterior, but not the posterior, PG. These findings also corroborate and expand demonstrated associations between the influx of pubertal hormones during adolescence and larger whole PG volumes (Whittle et al., 2020; Wong et al., 2014) by providing further support for the specialized role that the anterior PG plays in pubertal processes and risk for psychopathology. Thus, findings reported here underscore the importance

Table 3
Indirect, direct, and total effect results for males and females from the multi-group mediation model.

Female					
Indirect Effects		Estimates		95 % CIs	
Mediator	Outcome	β	*b*	Lower	Upper
Anterior pituitary	Δ Dysregulation	0.18	0.13	−0.03	0.44
Posterior pituitary	Δ Dysregulation	0.03	0.02	−0.08	0.24
Direct Effects		Estimates		95 % CIs	
		β	*b*	Lower	Upper
DHEA → Δ Dysregulation		−0.14	−0.11	−0.49	0.27
Total Effects		Estimates		95 % CIs	
		β	*b*	Lower	Upper
DHEA → Δ Dysregulation		0.06	0.05	−0.26	0.35
Male					
Indirect Effects		Estimates		95 % CIs	
Mediator	Outcome	β	*b*	Lower	Upper
Anterior pituitary	Δ Dysregulation	0.05	0.04	−0.03	0.18
Posterior pituitary	Δ Dysregulation	−0.002	−0.002	−0.10	0.04
Direct Effects		Estimates		95 % CIs	
		β	*b*	Lower	Upper
DHEA → Δ Dysregulation		−0.44	−0.40	**−0.72**	**−0.09**
Total Effects		Estimates		95 % CIs	
		β	*b*	Lower	Upper
DHEA → Δ Dysregulation		−0.40	−0.37	−0.66	−0.07

Note. Significant results are bolded based upon bootstrapped 95 % confidence intervals for indirect effects and $p < .05$ for direct effects.

of examining the anterior and posterior PG lobes separately given their functionally distinct roles, particularly when studies are designed to look at puberty-related effects. One possible mechanism explaining the reported patterns could be that increased DHEA during adrenarche promotes enlargement of the PG, a proposed general indicator of HPA-axis activity, which may create amplified risk for mental health symptoms (Farrow et al., 2020; Ganella et al., 2015; Kaess et al., 2018; Whittle et al., 2012). Indeed, there is extensive support for links between patterns of HPA-axis reactivity and risk for psychopathology during adolescence (Colich et al., 2015; Kuhlman et al., 2018), but this work has primarily focused on salivary cortisol with limited links to either structural or functional brain measures. This interpretation needs further investigation with respect to how the timing, tempo, and hormonal changes across the pubertal window explain variability in HPA-axis functioning and anterior PG lobe growth in ways that either propagate or mitigate psychopathology symptoms. To disentangle how different HPA-related hormones influence these processes, more research focusing directly on the interplay between stress and adrenarcheal hormones (e.g., cortisol, DHEA, and their ratios at both basal and reactive levels; (Farooqi et al., 2018)) is needed, as this would garner greater understanding into how these complex processes influence puberty-related increases in mental health risk. Ideally, such studies would leverage longitudinal data, tracking dynamic changes in adrenarche indicators (i.e., hormonal and physical) and stress markers (e.g., cortisol levels, inflammatory markers), as well as concomitant changes in anterior PG morphology. Such an approach would contribute greater insight into how patterns of HPA-axis function and pubertal development propagate neuroendocrinological risk for psychopathology.

In line with more transdiagnostic approaches to characterizing developmental psychopathology (Choate et al., 2023), this study is among the first to show anterior PG-mediated pubertal hormone effects in a symptom profile (i.e., dysregulation) that maps onto transdiagnostic symptoms. To date, extant work has provided much needed insight into associations between overall PG volume and diagnosed psychopathology (e.g., PTSD: Thomas and De Bellis, 2004; depression/bipolar: MacMaster et al., 2008; MacMaster and Kusumakar, 2004; OCD: Atmaca et al., 2009; MacMaster et al., 2006). However, these findings are quite mixed, with some reporting larger or smaller PG volumes, even within the same diagnostic category (e.g., depression; Kessing et al., 2011). Moreover, others have not found associations between diagnostic status and PG volume (Chen et al., 2004; Lorenzetti et al., 2009; Sassi et al., 2001; Schär et al., 2022), which is likely due to a constellation of methodological differences (Anastassiadis et al., 2019), including heterogeneity or sub-phenotypes within one diagnostic category and/or comorbidities. Taken together, the divergence in findings may indicate that binary diagnostic categories are not necessarily as informative as more dimensional approaches aimed at capturing neurobiological variability related to common features shared across disorders affecting similar neural circuitry (Cuthbert, 2014; Cuthbert and Insel, 2013). Indeed, there is utility in examining transdiagnostic factors during development, as mental health disorders may not yet be evident or meet diagnostic criteria. Taking this approach has yielded crucial insights into a range of specific transdiagnostic behaviors that portend psychopathology over the short- and long-term (Klein et al., 2022; McLaughlin et al., 2014; Weissman et al., 2020). Dysregulation, in particular, has been shown to be highly predictive of more severe, unremitting psychopathology that encompasses both internalizing and externalizing features (Althoff and Ametti, 2021). In fact, dysregulation symptoms have been proposed as a generalized at-risk phenotype for pronounced risk of psychopathology and persistently poorer outcomes in adulthood, distinct from youth who evince either internalizing or externalizing symptom profiles (Blok et al., 2022; Oerlemans et al., 2020). It is notable that the mediation effects reported here were only detected for dysregulation, and not internalizing or externalizing symptom changes. This suggests that there may be some specificity with respect to how different facets of the HPA-axis and pubertal development propagate increases in specific transdiagnostic features. The lack of effects in internalizing symptoms is in contrast to other findings showing PG-mediated puberty- and DHEA-related increases in specific sets of internalizing symptoms (depression, social anxiety) during development (Murray et al., 2016; Whittle et al., 2012). This discrepancy in findings could be a function of prior work relying on whole PG volumes, differences in which pubertal factors were examined (e.g., perceived pubertal status vs. hormone

levels), and symptom assessment. Moreover, this study is among the first to examine a transdiagnostic symptom profile that also incorporates externalizing symptoms in this context, but more work is needed to continue to untangle how particular transdiagnostic symptomologies (e.g., irritability, rumination, emotional awareness) can be explained by different pubertal hormones that convey changes in PG morphology.

Notably, the finding that greater DHEA levels predicted longitudinal decreases in dysregulation symptomology was unexpected, but consistent with existing literature documenting buffering effects of elevated DHEA against long-term mental health symptoms in adults (Mocking et al., 2015). In addition, baseline levels of DHEA did not correspond with baseline levels of dysregulation, suggesting that these associations were best captured with a developmental approach in this sample. It is not intuitive that greater hormonal levels would relate to decreasing symptoms, as there is longstanding evidence that pubertal development is a risk factor for psychopathology. It may be the case that, given the known sex differences in pubertal onsets, boys are likely in an earlier window of adrenarche than girls. However, work documenting links between puberty and psychopathology has overwhelmingly been focused on gonadarche, and not necessarily adrenarcheal processes per se (Byrne et al., 2017; Pfeifer and Allen, 2021). Therefore, there is still much to uncover with respect to how DHEA levels during the pubertal window, and adrenarcheal processes more broadly, relate to mental health symptoms. Importantly, existing work distinguishes acute and basal DHEA levels, particularly in response to stressors, with documented increases in DHEA in adolescents following an acute stressor (Marceau et al., 2012; Shirtcliff et al., 2007). Conversely, systematically low levels of DHEA in adolescents with internalizing or externalizing symptoms compared to controls have also been documented (Kamin and Kertes, 2017). This suggests that attenuated DHEA levels may correspond with altered HPA-axis physiology in the context of chronic stressors (Jiang et al., 2017), which may be attributable to cortisol and DHEA demonstrating opposing actions in terms of stress-responsivity, with DHEA exhibiting anti-glucocorticoid properties (Pinto et al., 2015). This interpretation should be taken with caution, as this partially stems from cellular and adult work, and reactivity-based research rather than basal levels, which requires extensive follow-up in studies with developmental samples.

The addition of the PG as a mediator adds to this literature by lending insight to a potential pubertal mechanism that is distinguishable from other potential processes (e.g., stress-related symptomology), although this should be more thoroughly interrogated in future work. In other words, the "inconsistent mediation" observed here may be indicative of separable pathways and processes with conditional effects of the anterior PG as mediator, such that the inclusion of the mediator helps to explain or reveal a pubertal process at play. Indeed, it is not implausible or uncommon to have an "inconsistent mediation" effect whereby the direct and indirect effects carry different signs (MacKinnon et al., 2000). To disentangle this further, research specifically probing the involvement of acute and chronic stress as well as pubertal processes in PG growth and the emergence of mental health symptoms is necessary. To this end, studies with tighter and lower age ranges closer to the average onset of adrenarche may be even better suited to assess the role of adrenarche in initiating mental health symptom timing and onset, which could be crucial for delineating patterns of unremitting or persistent dysregulation that have been reported in behavioral studies (Althoff et al., 2010). Moreover, exploration of the unique effects of DHEA/DHEA-s, the ratio of DHEA to cortisol, in concert with characterization of physical changes associated with adrenarche would further disentangle the intersection of stress- and puberty-related hormonal cascades that contribute to PG growth and adolescent-specific upticks in psychopathology.

Although the present investigation contributes to a small but growing literature on pubertal hormone effects on PG size and mental health, this study is not without limitations. Specifically, changes in DHEA were not tracked longitudinally in the current study, which could provide crucial information on correspondence between DHEA levels, PG volume, and mental health symptomology. This would allow for more causal interpretations as well as discovery of potential feedback loops between hormone levels and mental health symptoms in youth. In this vein, it will be critical for future work to address how DHEA/DHEA-S levels correspond with physical indicators of adrenarche to understand if more comprehensive measures of adrenarche can explain variability in mental health symptomology and corresponding neural development during adolescence. Moreover, despite a strong emphasis on gonadarche in the literature, it would be valuable for subsequent studies to also examine the impact of other sex hormones (e.g., estradiol, progesterone, testosterone) that the anterior pituitary stimulates production of in primary sex organs; these efforts will be essential as the field continues to flesh out the involvement of other pubertal processes and axes (i.e., the HPG axis rather than the HPA axis) in risk for mental health symptoms during puberty. In addition, participants in this study did not have clinical levels of psychopathology upon enrollment and exhibited subclinical symptom levels. Thus, future work should seek to replicate and extend these effects in higher-risk samples. However, we argue that there is a need to characterize the full spectrum of symptomology, especially in developmental samples, where subclinical or preclinical symptoms could set the stage for diagnostic levels of psychopathology in the long term. Finally, although DHEA levels were assessed at roughly the same time of day in our participants, time of day was not assessed in the current sample; future work should use this as a covariate. It should be noted, however, that DHEA does not typically have an initial awakening "burst" response as other hormones do (e.g., cortisol), and tends to be more stable day-to-day compared to cortisol in adolescent and adult samples (Hucklebridge et al., 2005; Oskis et al., 2012).

Taken together, the present study provides a novel contribution to a body of literature documenting the role of pubertal hormones and the PG in developmental psychopathology. Using structural equation modeling, we report that with higher DHEA levels, specific mediating effects of the anterior, but not the posterior, PG volume confer risk for increasing dysregulation symptoms across time. This adds important nuance to the existing literature, which has largely focused on estimating whole PG volumes without consideration of the distinct functional roles of the anterior and posterior lobes. Moreover, this work underscores the utility of examining transdiagnostic factors, such as dysregulation, which carry known predictive ability for long-term psychopathology. Identifying how rising levels of DHEA influence an apex neural region within the HPA-axis and changing symptomology is a crucial step in characterizing what role adrenarche plays in adolescent mental health functioning.

CRediT authorship contribution statement

Yu-Ping Wang: Writing – review & editing, Resources, Methodology, Investigation, Funding acquisition, Conceptualization. **Erica L Steiner:** Writing – review & editing. **Grace C Ende:** Writing – review & editing, Data curation. **Anna T Coutant:** Writing – review & editing, Data curation. **Danielle L Rice:** Writing – review & editing, Data curation. **Hannah J Okelberry:** Writing – review & editing, Project administration, Data curation. **Lauren R Ott:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Chloe C Casagrande:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Tony W Wilson:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Nathan M Petro:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Vince D Calhoun:** Writing – review & editing, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Giorgia Picci:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis. **Julia M Stephen:** Writing – review & editing, Resources, Project administration, Investigation,

Funding acquisition, 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. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2025.101507.

Data availability

Data will be made available on request.

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