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Salivary secretory immunoglobulin A as a potential biomarker of psychosocial stress response during the first stages of life: A systematic review

Águeda Castro-Quintas [a,b,c], Helena Palma-Gudiel [b,d], Nerea San Martín-González [a,b,c], Javier R. Caso [b,e], Juan C. Leza [b,e], Lourdes Fañanás [a,b,c,*]

[a] Department of Evolutionary Biology, Ecology and Environmental Sciences, University of Barcelona, Spain
[b] Network Centre for Biomedical Research in Mental Health (CIBER of Mental Health, CIBERSAM), Institute of Health Carlos III, Spain
[c] Institute of Biomedicine of the University of Barcelona (IBUB), Barcelona, Spain
[d] Department of Epidemiology, University of Florida, United States
[e] Department of Pharmacology and Toxicology, Faculty of Medicine, Complutense University of Madrid, Imas12. IUIN, Madrid, Spain

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ABSTRACT

Mucosal secretory immunoglobulin A (s-IgA) has been recognized as a key component of human first line defense against infection. However, its reactivity to psychosocial stressors is poorly understood. This systematic review aimed to explore whether s-IgA levels changed after psychosocial stress in subjects under the age of 18. Fifteen articles were included. s-IgA basal levels are increased in children older than 9 years old exposed to stress. Furthermore, s-IgA seems to follow a circadian rhythm, which is altered under stress conditions. Finally, the collective evidence suggests that salivary s-IgA rapidly increases under acute stress after puberty. Overall, our review indicates that s-IgA could be considered a potential psychosocial stress biomarker of interest for pediatric and child-juvenile psychiatric population. Further studies are needed to validate the role of s-IgA circadian rhythm and basal levels as psychosocial stress biomarkers and disentangle the role of age and type of stressor.

1. Introduction

The ability to efficiently detect and respond to potential threats is essential for survival. The brain coordinates the stress response to keep the balance in physiological processes and maintain homeostasis after any perturbation. Activation of the sympathetic nervous system (SNS) and the hypothalamus–pituitary–adrenal (HPA) axis under psychological challenges causes respectively epinephrine (adrenal medulla) and cortisol (adrenal cortex) release into the bloodstream (Carrasco & Van de Kar, 2003; Godoy et al., 2018), and a rapid physiological adaptation to maintain vigilance and to regulate energy expenditure, such as glucose storage (Sapolsky et al., 2000; Selye, 1936). Along with those two systems, acute stress also activates the innate immune system as a countermeasure to the potential exposure to pathogens in a "fight or flight" scenario.

From an evolutionary perspective, life-threatening situations can lead to injury. Consequently, the sentinel immune system (innate) activates in response to any situation that is encoded as threatening, regardless of its type (pathogen, non-pathogen or other damaging signals, including chemical, physical or psychological stress), first recognizing the threatening signal and releasing multiple inflammatory proteins and oxido/nitrosative mediators into the bloodstream and mucosal surfaces (Miller & Raison, 2016; Segerstrom & Miller, 2004). This response orchestrates a network of regulatory pathways that prevents over activation of the immune system, which could be deleterious (Rook, 2013). Improved sanitation of urban environments has critically reduced the infectious challenges that were primary sources of mortality across most of human evolution (Miller & Raison, 2016). However, according to literature, social daily situations that are experienced as stressful can induce the activation of the stress response and the immune system in the absence of infectious agents, increasing the individual's susceptibility to chronic inflammatory diseases (Herr et al., 2018; Segerstrom & Miller, 2004). Moreover, factors such as stressful events, urban setting, and the exposure to some infections have been considered

* Corresponding author.
E-mail address: lfananas@ub.edu (L. Fañanás).

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as risk factors for developing mental disorders including schizophrenia spectrum disorders (Arango et al., 2021).

The immune system provides defense from pathogens via a vast network of cells and tissues, performing a complex and orchestrated attack once the intruder is detected. The immune response has two major components: the innate and the adaptive immune systems. Innate immunity is the first line of defense, it remains active in the span of minutes to hours after infection; and after recognizing signature molecules of pathogens through pattern-recognition receptors (Kumar et al., 2009), it gives rise to the release of cytokines, small proteins important in cell signaling, and the activation of the complement system, a regulated network of proteins involved in a sequential cascade of enzymatic reactions resulting in the opsonization of the pathogen (Sarma & Ward, 2010; Segerstrom & Miller, 2004). Meanwhile adaptive immunity is directly activated by pathogens and may last for a few weeks, months or even for a person's entire life. Particularly, the adaptive immunity response is specific and involves specialized immune cells, such as lymphocytes, and immunoglobulins (Ig), Y-shaped proteins that bind to an antigen preventing disease development. There are five different types of immunoglobulins (Igs) (IgA, IgD, IgE, IgG, and IgM), which differ in their biological features, structure, target specificity and distribution.

A particular form of IgA, secretory-IgA (s-IgA), is found in mucosal secretions of gastrointestinal tract and in other secretions, including saliva and breast milk, acting as a first line barrier against invading pathogens (Carpenter, 2020). The s-IgA is constituted by two IgA molecules and a secretory component. This component is added to the dimeric IgA when it is carried across the epithelium before mucosal lumen release. The s-IgA prevents the passage of microorganisms into the circulatory system (Bosch et al., 2002) and plays a key-role in the maintenance of oral health, among others (Gutierrez-Corrales et al., 2017). Although at birth no salivary s-IgA can be detected, infants' s-IgA is already present at one week of age. (Haworth & Dilling, 1966). In the first year of life, s-IgA reaches 30% of adult levels (Fagerås et al., 2011), and these levels continue to increase until 20 years old (Jafarzadeh et al., 2010).

Furthermore, s-IgA is under strong neuroendocrine control (Fig. 1). Specifically, the autonomic nerves innervating the salivary glands robustly influence s-IgA production, thus, sympathetic nervous system activation enhances preformed-IgA release by plasma B cells and its epithelial translocation (Teeuw et al., 2004). This mechanism may explain why some environmental challenges perceived as acute stressors (e.g., academic exams, public speech or standardized stressful laboratory conditions such as an arithmetic task or a simulated job interview) could increase salivary s-IgA within minutes after its initiation (Ohira, 2004; Takatsuji et al., 2008; Trueba et al., 2012) and with a rapid decrease during recovery (Campisi et al., 2012; Tsujita & Morimoto, 1999). In fact, s-IgA is released following circadian rhythms, with a peak in the morning just after waking up (Nader et al., 2010), followed by a sharp decline the next four hours and reaching the lowest value just before bedtime (Shirakawa et al., 2004), in a similar way to cortisol, suggesting a possible synchrony on both responses (Hucklebridge et al., 1998).

However, under prolonged or chronic psychological stress (e.g.,

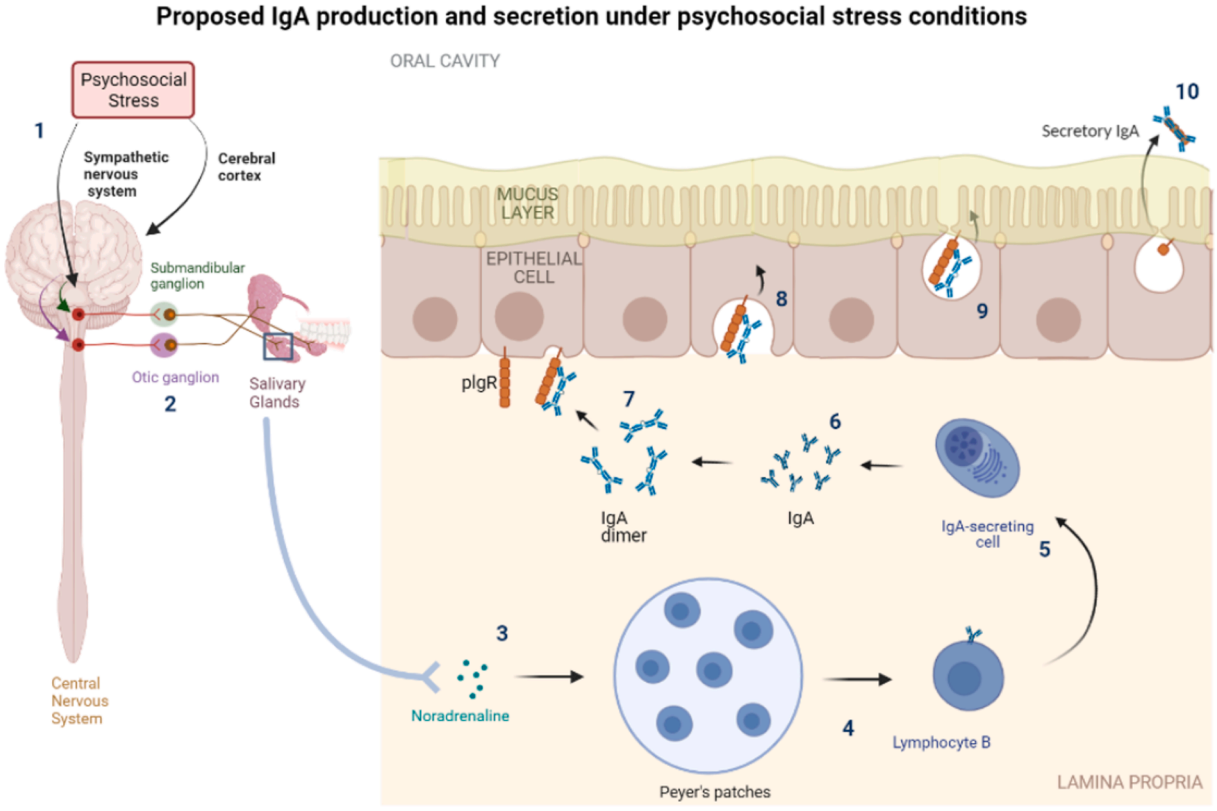

Fig. 1. Proposed IgA production and secretion under psychosocial stress conditions. (1) Psychosocial stress activates sympathetic nervous system. (2) Then, preganglionic nerves of the thoracic segment of the spinal cord are activated, which synapse with postganglionic nervous in both submandibular and otic ganglions. (3) Consequently, neurotransmitter norepinephrine in salivary glands that (4) started salivary immune response in Peyer's patches, aggregated lymphoid nodules, by activating unspecific lymphocyte B. (5) Along with signals elicited by specific proteins binding, IgA-secreting cells formation is induced. (6) As soon as monomeric IgA are released in the lamina propria, (7) they are joined in pairs by the J chain to form dimeric IgA (8) which is captured by the polymeric immunoglobulin receptor (pIgR). (9) The dimeric IgA-pIgR complex is internalized and transported by transcytosis to the oral cavity. (10) The former is then released as secretory component bound to dimeric IgA to yield secretory IgA (s-IgA). s-IgA secreted into the mucus layer prevents the direct adhesion to the epithelium of pathogenic agents. Created with BioRender.com

major adverse life events, poor care during childhood and maternal distress exposure during pregnancy) s-IgA response seems to be suppressed (Kang et al., 2018; Phillips et al., 2006; Vermeer et al., 2012), and this suppression in turn predicted higher susceptibility to different illnesses such as upper respiratory tract infections (Welch, 2018), or orthodontic pain and caries (da Silva Campos et al., 2010). Although previous studies have identified specific psychosocial stressors or challenges that are associated with changes in s-IgA concentration, especially in saliva, most of them have only examined adult populations, leaving unanswered questions regarding s-IgA dynamics under acute or chronic psychosocial stress during childhood and adolescence. Noticeably, child nervous system nor the immune system are fully developed at birth, but rather continue to mature in response to the postnatal environment. An increased vulnerability to immune system perturbations due to early exposure to stress spans prenatal life and infancy but also childhood and adolescence, periods characterized by the acquisition of immune memory. A two-way interaction between the brain and the immune system makes it possible for prenatal, childhood and adolescent psychosocial stressors to have a major and long lasting impact on both systems (McCrory et al., 2010) increasing susceptibility to several diseases, including mental disorders (O'Connor et al., 2014).

The fact that s-IgA quickly rises after acute stress exposure in saliva, an accessible and non-invasive sample (Engeland et al., 2019), together with its putative detectability throughout all lifespan, could make it a promising biomarker of acute and chronic psychosocial stress reactivity in young population. Therefore, the objective of the present systematic review is to examine the existing studies measuring mucosal secretory IgA levels after psychosocial stress exposure in infancy, childhood, and adolescence and to discuss its utility as a possible biomarker of altered psychosocial stress immunity response. Finally, we suggest future directions for this body of research.

2. Material and methods

2.1. Eligibility criteria

PRISMA guidelines for conducting and reporting systematic reviews were followed in the elaboration of the current systematic review (Page et al., 2021). The following inclusion criteria were considered: (1) human studies, (2) studies in infants and adolescents (under 18 years old), and (3) studies addressing the association between psychosocial stress and IgA response in mucosal tissues (saliva, tears, intestinal secretions or urine). Additionally, the following exclusion criteria were considered: (4) studies in which the stressor addressed was either *in vitro* or non-psychological in nature (i.e. physical exercise), and (5) studies in which the measured IgA was specific to a particular antigen. The search was limited to articles written in English. There was no limitation regarding publication time. With regard to the age of the participants, studies reporting mean age instead of age range were included whenever the mean age plus the standard deviation was lower than 18 years old, although we acknowledge that, some of the studies reviewed might include a minority of older subjects.

2.2. Search strategy

Research was conducted in the databases PubMed, PsycINFO and Web of Science on November 8th, 2022 using the Spanish Foundation for Science and Technology (FECYT in its Spanish acronym) interface. The search terms were the following: "immunoglobulin A or IgA", "trauma, adverse, stress or maltreatment" and "baby or toddler or infant or child* or adolescent or teen or young". All the citations found in each database were imported to EndNote X9 and de-duplicated.

2.3. Study selection

The titles, abstracts and full texts of all papers retrieved were independently screened by two authors for eligible articles. In case of disagreement, a consensus between the authors was reached. In some instances, a third author helped to take an agreement.

2.4. Data collection process and risk of bias assessment

Data was extracted by one author and later checked by a second author. Extracted data included first author, year of publication, the number of participants, the age and sex of the participants, the procedure for inducing stress, stress outcomes, psychiatric outcomes, timing of sample collection, the source tissue, the methodology employed for determining s-IgA concentration, other measures determined, and the main findings of each study (Table 1).

The risk of bias of all included studies was evaluated following the "Newcastle - Ottawa Scale" (NOS) for quality assessment of cohort studies and case-control studies (Wells et al., 2009). Adaptations of NOS were made considering the methodological design of the studies, in order to better assess the quality of the information that was relevant for this review. To that aim, 6 items were considered and evaluated from 0 to 2, where 2 is the best score. The items considered were: 1) the population sample size, 2 was given when the sample size was higher than 97, calculated considering unlimited population with a confidence level of 0.95 and an error of 0.10 (Marrugat & Vila, 2012); 1 was given when the sample size was between 69 and 97, calculated considering an infinite population with a confident level of 0.90 and an error of 0.10; 0 was given when the sample size was between 1 and 69; 2) quality of stress definition (2, stress induction or direct measures of participants stress; 1, standardized environmental stress measures; 0, non-standardized measure); 3) quality of sample collection (2, samples collected by professionals following adequate instructions; 1, self-collection following adequate instructions; 0, self-collection with no previous instructions) 4) Timing of sample collection (2, sample collection throughout the day and at least one at awakening and one before going to bed [s-IgA circadian rhythm] or in the evening [s-IgA reactivity to acute stress or basal levels]; 1, sample collection throughout the day [s-IgA circadian rhythm] or in the morning [s-IgA reactivity to acute stress or basal levels]; 0, the time was not indicated); 5) Adequate number of samples (2, at least two [s-IgA basal levels], three [s-IgA reactivity to acute stress] or four [s-IgA circadian rhythm] samples per day; 1, repeated measures across the study [s-IgA basal levels] or two [s-IgA reactivity to acute stress] or three [s-IgA circadian rhythm] samples per day; 0, one sample across the study [s-IgA basal levels] or one [s-IgA reactivity to acute stress] or two [s-IgA circadian rhythm] samples per day); 6) Control by covariates (2, control by sex, age and other variables related to the sampling;1, control by sex and age; 0, not controlling by covariates). An overall score was calculated for each study by summing the scores of each criterion and expressing it as a percentage, considering the total possible score. The studies with a total score lower than 50% were classified as low-quality, those between 50% and 74% as mid-quality and those equal or higher than 75% as good-quality. Although this risk of bias score evaluates different important methodological aspects, this measure should only be taken as a general approximation of the quality of each study.

3. Results

3.1. Study selection

The process followed for article selection is presented in Fig. 2. A total of 4746 articles were identified: 2362 in PubMed, 272 in PscyINFO and 2111 in Web of Science. After removing duplicates, we proceeded to a screening phase, reading 4366 titles and abstracts and 83 articles were selected for eligibility. A total of 15 articles were included in this review.

Table 1

Outline of papers reviewed (n = 15) including subjects information (number of subjects, ethnicity, sex and age); type of stress induced, and the protocol followed; psychological and psychiatric outcomes that could been measured; procedure, time and tissue of extracted sample for s-IgA determination; statistic approach and the reported s-IgA dara; main biological variables assessed apart from s-IgA and main s-IgA findings. The articles are sorted by alphabetical order and reference country information is also reported.

Authors (Year) Country	Sample Ethnicity	Age[a] Sex Research design	Stressors *Measures*	s-IgA measurement Procedure of sample collection[b, c]	Time of sample extraction (hours)	Statistic approach Reported s-IgA data[d]	Other measures: Biological and Psychological	Findings[e]
Abraham et al. (2021) Israel	47 children and their parents 100% Caucasian	3.37 ± 0.40 years 55.3% male Longitudinal	Parenting style *CIB* *Parent-infant synchrony* Fear eliciting task ("Mask")	Basal s-IgA Three salivary samples (*cotton swab*): 1. 10 min after arrival to infant's home 2. 20 min after the end of the masks assessment 3. 35 min after the end of the mask assessment	Between 16:00 and 19:00	Correlations *Raw data and AUCg calculations* s-IgA (ru/ml) = 3442.9 ± 279.9	Cortisol	• Reduced parental synchrony was associated with higher child s-IgA levels (p =.03). • Child's high levels of self-regulation were significantly associated with lower s-IgA levels (p =.001).
Byrne et al. (2017) USA	102 healthy children NA	9.50 ± 0.34 years 46% male Cross sectional	Parenting style *APQ*	Basal s-IgA One salivary sample (*passive drool*)	At waking	Linear regressions (Adjusted for flow rate) *Log transformations* s-IgA (μg/mL) = 4.79 ± 11.06	BMI CRP	• APQ poor monitoring and supervision by parents was associated with significantly higher levels of s-IgA in their children (p =.016). • Higher children's s-IgA levels were associated with a higher BMI(p =.005).
Ellberg et al. (2019) USA	51 toddlers/ mother dyads Caucasian 90.2%	At 1, 3 and 6 months (longitudinal) 53% males Longitudinal	Pre-postnatal maternal distress *EPDS* *PSS* *PANAS*	Basal s-IgA Three salivary samples (One sample/time point) (*cotton swab*): 1. 1 month 2. 3 months 3. 6 months	Around 16:00	ANCOVAS *Log transformations* s-IgA (μg/mL) 1 month = 170.87 ± 181.33 3 months = 51.24 ± 42.22 6 months = 41.40 ± 22.29	Breastfeeding Infant's length Infant's weight	• Higher maternal distress during the postnatal period was associated with reduced infant s-IgA (p =.03). • Maternal prenatal distress did not predict infant s-IgA changes across the assessments (p >.05).
Kang et al. (2020) Canada	1043 Children/ mother dyads NA	3.7 ± 1.1 (2–8) months 53.4% male Longitudinal	Pre-postnatal maternal distress *PSS* *CES-D scale*	Basal s-IgA One fecal sample	NA	Multiple linear and logistic regression models *Log transformation* Median s-IgA (μg/mg) = 6.1 (2.9–11.0)	Antibiotic exposure Breastfeeding Infant's length Infant's weight	• Maternal depressive symptoms in prenatal period and in both pre and postnatal periods were significantly associated with reduced infants' fecal s-IgA concentrations (p <.05). • These lower s-IgA levels yielded a large effect size in older infants (p <.05). • None associations were observed for maternal stress symptoms neither in pre nor postnatal periods.

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Table 1 (*continued*)

Authors (Year) Country	Sample Ethnicity	Age[a] Sex Research design	Stressors *Measures*	s-IgA measurement Procedure of sample collection[b, c]	Time of sample extraction (hours)	Statistic approach Reported s-IgA data[d]	Other measures: Biological and Psychological	Findings[e]
Laurent et al. (2015) USA	82 healthy children and adolescents 73% Caucasian 27% NA	7–17 years 49% male Cross sectional	Induced Psychosocial stress- 62% of the participants: *TSST adaptation* (speech, mental arithmetic, mirror tracing; 20 min) - 38% of the participants: Interpersonal stress session (three exclusion challenges; 20 min)	Stress s-IgA reactivity Six salivary samples (*passive drool*): 1. Before the induced stress (-25 min) 2. After task 1 (+10 min) 3. After task 2 (+15 min) 4. After task 3 (+20, +40, +60 min)	Between 14:00 and 17:00	Hierarchical linear modeling *Raw datas* s-IgA (μg/mL) = 155.03 ± 112.48	CBCL Cortisol sAA STAI-C	• S-IgA levels significantly increased during acute stress and started to decrease immediately after the task ended ($p < .001$). • There were differences in s-IgA responses related to youth externalizing behavior ($p = .010$).
Ma et al. (2018) Canada	Study 1: 115 children (wave 1) Study 2: 103 children (waves 1, 2 and 3) 95% Caucasic 5% Latin American, Haitian or other ethnics	Wave one: 10.79 ± 0.92 (9–12) years Wave two: 13.62 ± 1.10 (12–15) years Wave three: 16.95 ± 1.27 (15–18) years 47% male Longitudinal	Exposure to diurnal anxiety and depressive symptoms *CDI* *RCMAS*	s-IgA circadian rhythm 48 salivary samples (eight samples in two consecutive school days per each wave) (*cotton swab*): 1. At awakening 2. 30 min post awakening 3. Every 2 h until bedtime	Throughout the day, from awakening to bedtime	Hierarchical Linear Modelling *Log transformations* s-IgA (μg/mL) Wave one = 1.55 ± 0.33 Wave two = 1.49 ± 0.52 Wave three = 1.76 ± 0.28	Frequency and type of physical illness Medication	• Children's diurnal s-IgA rhythm showed a gradual increase within the first 4 hr post-awakening, followed by a gradual decrease toward the afternoon and a final increase before bedtime ($p < .001$). • Children with higher anxiety had steeper increases in s-IgA compared to those with lower anxiety ($p < .05$). • Higher total anxiety and worries in children between ages 9–12 were associated with diminished global s-IgA levels when they were 12–15 years of age ($p < .05$). Lowered s-IgA levels in turn predicted higher total anxiety symptoms and worries between ages 15–18 ($p < .05$). • In late adolescence, higher total anxiety was associated with lower s-IgA levels. • s-IgA levels at 9–12 years old were associated with s-IgA levels at 12–15 ($p < .01$) but not at 15–18 years old ($p > .05$).
Marques-Feixa et al. (2022) Spain	94 children and adolescent 83% European 17% Latin American,	13.80 ± 2.40 (7–17) years 40% male Cross sectional	Induced Psychosocial stress *TSST-C:* -Habituation period (30 min) - TSST (20 min) -	Stress s-IgA reactivity Five salivary samples (*cotton swab*): 1. Before the task (-30 min)	TSST-C protocol started at 16:00	Mixed model and simple effects test *Log transformations* s-IgA (μg/dL) Children	Cortisol Current infectionK-SADS-PL-5 (Current Psychopathology) Tanner Stage	• Adolescents showed an increase after the stressor and a rapid recovery, while children did not show an s-IgA

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Table 1 (*continued*)

Authors (Year) Country	Sample Ethnicity	Age[a] Sex Research design	Stressors *Measures*	s-IgA measurement Procedure of sample collection[b, c]	Time of sample extraction (hours)	Statistic approach Reported s-IgA data[d]	Other measures: Biological and Psychological	Findings[e]
	Maghrebin and others		Recovery (30 min) History of childhood maltreatment	2. When the task started (0 min) 3. At the end of the task (+20) 4. During the recovery period (+35, +50 min)		Adolescents T1 = 4.30 ± 0.045 T1 = 4.37 ± 0.048 T2 = 4.25 ± 0.042 T2 = 4.44 ± 0.045 T3 = 4.26 ± 0.041 T3 = 4.48 ± 0.044 T4 = 4.21 ± 0.043 T4 = 4.35 ± 0.046 T5 = 4.23 ± 0.045 T5 = 4.37 ± 0.047		response (p =.010). • However, children exposed to maltreatment exhibited an s-IgA pattern more similar to that of adolescents when compared to non maltreated children (p =.017).
Molnar et al. (2018) USA	50 children/ mother dyad NA	5.68 ± 0.26 years 58% male Longitudinal	Pre-postnatal substance exposure Maternal cigarette and/or cannabis consumption during pregnancy TLFB	Basal s-IgA One salivary sample (*passive drool*)	Between 13:00 and 17:00	Hierarchical Multiple Regression *Raw datas* s-IgA (μg/mL) Control group = 101.77 ± 26.75 Cigarette group = 149.60 ± 91.76 Cannabis group = 166.85 ± 81.88	Cotinine Nicotine OHCOT THC	• Children with postnatal cigarette or pre and postnatal cannabis exposure did not have differences in their s-IgA levels (p =.419). • Prenatal cigarette exposure and the combination of cigarette and cannabis in both pre and postnatal timings was correlated with the higher levels of s-IgA (p =.047).
Noakes et al. (2007) Australia	82 infants NA	At 3 and 12 months NA Longitudinal	Prenatal tobacco exposure: Maternal cigarette consumption during pregnancy	Basal s-IgA Two salivary samples (*specimen suction set*): 1. At 3 months old 2. At 12 months old	NA	Mann-Whitney *U* test, Wilcoxon signed Rank tests or Spearman correlation coefficients *Log transformation* Median s-IgA (μg/mL) (approximation) 3 months: 12 months: Non exposed ≈ 10 Unexposed ≈ 5 Exposed ≈ 10 Exposed ≈7	Allergen SPT Specific IgA to pneumococcal PS serotype 14 Urinary cotinine	• Infants exposed to maternal cigarette smoke in pregnancy had significantly higher total IgA levels at 12 months old (p =.026), but not at 3 (0.722) when compared to non exposed. • IgA levels decreased with age in both groups.
Reindl et al. (2022) Germany	Initial sample: 253 (94 children in foster care and 157 biological children) Final sample: 232 (84 children in foster care and 146 biological children) NA	T1: Children in foster care: 3.80 ± 1.57 Biological children: 4.10 ± 1.46 T2: After 6.45 ± 1.59 months T3: After 6.04 ± 1.49 months 50% male in both groups	Caregiving - Foster care vs biological parental care: *Caregiver-child interactions* *Relationship quality* *History of maltreatment and/or neglect*	Basal s-IgA Three salivary samples (*cotton swab*): 1. At T1 2. At T2 (+6 months) 3. At T3 (+1 year)	Between 13:00 and 16:00	Linear mixed models *Log transformation* Total s-IgA (μg/mL) (approximation) Foster care Foster care higher caregiving lower caregiving T1 ≈ 3.75 T1 ≈ 4.00 T2 ≈ 3.80 T2 ≈ 3.80 T3 ≈ 3.85 T3 ≈ 3.75	Cortisol DHEA Progesterone	• No differences were found for s-IgA between foster care and biological care children (p =.50). • However, caregiving quality modulated s-IgA concentrations: children in foster care of lower caregiving quality showed decreasing s-IgA concentrations across the study period (p =.028)

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Table 1 (*continued*)

Authors (Year) Country	Sample Ethnicity	Age[a] Sex Research design	Stressors *Measures*	s-IgA measurement Procedure of sample collection[b, c]	Time of sample extraction (hours)	Statistic approach Reported s-IgA data[d]	Other measures: Biological and Psychological	Findings[e]
		Longitudinal						when compared with children in foster care of higher caregiving quality, which showed s-IgA increments ($p = .049$).
Ulmer-Yaniv et al. (2018a) Israel	125 children NA	9.63 ± 0.65 years NA Longitudinal	Maternal depression Parenting style: *CIB*	Basal s-IgA Three salivary samples (*cotton swab*): 1. After 10 min of acquaintance (baseline) 2. After testing (+80 min from baseline) 3. After CIB (+155 min from baseline)	Between 16:00 and 19:00	Pearson correlations *Raw data and AUCg calculation* Total diurnal s-IgA (NA) Non exposed = $1288.54*10^3 \pm 469.39*10^3$ Exposed = $1893.06*10^3 \pm 451.84*10^3$	CBCL Cortisol	• Children of depressed mothers had higher s-IgA levels than children of non-depressive mothers ($p < .01$). • Children internalizing and externalizing symptoms were significantly associated with higher s-IgA levels ($p < .01$).
Ulmer-Yaniv et al. (2018b) Israel	Initial sample: 232 children (148 war-exposed) Final sample: 177 children (101 war-exposed) NA	9–11 years 48% male Longitudinal	War-exposure Parenting style: *CIB*	Basal s-IgA Nine salivary samples (three samples/time point) (*cotton swab*): 1. Following acquaintance (baseline) 2. After testing (+60 min from baseline) 3. After CIB (+84 min from baseline)	Between 15:00 and 19:00	Pearson correlations *Raw data and AUCg calculation* Child s-IgA (NA) Not exposed = 618.72 ± 413.49 Exposed = 909.03 ± 518.46	DAWBA Oxytocin SCARED	• War-exposed children had higher s-IgA levels ($p < .01$) and anxiety-related symptoms ($p < .01$). • Higher s-IgA levels were associated with lower maternal sensitivity ($p > .05$).
Vermeer et al. (2012) Netherlands	68 children NA	2.5 ± 0.48 years 57% male Cross sectional	Caregiving - Center childcare vs family childcare: *Emotional support provided by the caregiver*	s-IgA circadian rhythm Eight salivary samples (four samples/day) (*cotton swab*): On one childcare days (by the center or the family care) , and on one day at home	Around 7:00, 11:00, 15:00 and 18:00	AUCg calculation and MANCOVAS *Log transformations* s-IgA (μg/mL) Child Care Home Care 7 AM = 4.63 ± 0.89 7 AM = 4.33 ± 0.87 11 AM = 3.48 ± 0.7 11 AM = 3.55 ± 0.61 3 PM = 3.86 ± 0.77 3 AM = 4.06 ± 0.79 6 PM = 3.49 ± 0.69 6 PM = 3.57 ± 0.67	Child use of medicine, mood, naps and food on the collection day	• The diurnal pattern of s-IgA in toddlers showed a steep fall in the morning followed by a flattening out starting at mid-morning, both at childcare and at home ($p < .001$). • Lower caregiver sensitivity was associated with lower s-IgA levels in all time-points ($p < .05$).
Watamura et al. (2010) USA	79 healthy children 64% Caucasian 20% Asian American 9% Black 7% American Indian	3 – 5 years 54% male Longitudinal	Caregiving - Center childcare during the week vs parental care in the weekend: *Number of stressors in the past 6 months*	s-IgA circadian rhythm Twelve salivary samples (three samples/day on two childcare days, and on two weekend days) (*cotton swab*): 1. Mid-morning 2. Mid-afternoon 3. Evening	At 10:30, 15:30 and 20:00	Bivariate correlations and ANOVAS (Adjusted for flow rate) *Log transformations* s-IgA (μg/mL) (approximation) Child Care Day Weekend	Cortisol Parental report of illness frequency	• There was a clear s-IgA diurnal rhythm only on the weekends characterized by s-IgA dropped levels from the afternoon to the evening ($p = .013$), but not on care days ($p > .05$). • Younger children had higher s-IgA

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Table 1 (*continued*)

Authors (Year) Country	Sample Ethnicity	Age[a] Sex Research design	Stressors *Measures*	s-IgA measurement Procedure of sample collection[b, c]	Time of sample extraction (hours)	Statistic approach Reported s-IgA data[d]	Other measures: Biological and Psychological	Findings[e]
						Mid-Morning 35.50 40.98 Mid-Afternoon 34.34 38.37 Evening 35.70 32.04		during child care days evenings compared to older children (p =.007). • Older children presented a diurnal decline both in the week and the weekend (p =.048).
Yirmiya et al. (2018) Israel	111 children (58 war-exposed) from a cohort of 232 children NA	11.66 ± 1.23 years 40% male Longitudinal	War-exposure Parental style *CIB*	Basal s-IgA Three salivary samples (*Cotton swab*): 1. Upon arrival to the lab (baseline) 2. After testing (+10 min from baseline) 3. After CIB (+100 min from baseline)	NA	Pearson correlations *Raw data and AUCg calculations* s-IgA (NA) Not war exposed = $5050.09*10^3 \pm 267.20*10^3$ War exposed = $6205.58*10^3 \pm 360.17*10^3$	Cortisol SCARED	• War-exposed children had significantly higher s-IgA levels than non-exposed (p <.05). • Elevated children's s-IgA levels were correlated with reduced social collaboration (p <.05) and more anxiety symptoms (p <.05).

Abbreviations: APQ, Alabama Parenting Questionnaire; AUC, Area Under the Curve; BMI, Body Mass Index; CBCL, Child Behavior Checklist; CDI, Children's Depression Inventory; CES-D, Center for Epidemiological Studies Depression Scale; CIB, Coding Interactive Behavior Manual; CRP, C-Reactive Protein; DAWBA, Developmental and Well-Being Assessment; DHEA, dehydroepiandrosterone; ELISA, Enzyme-Linked Immunosorbent Assay; EPDS, Edinburgh Postnatal Depression Scale; K-SADS-PL-5, Kiddie-Schedule for Affective Disorders & Schizophrenia, Present & Lifetime Version V; OHCOT, trans-3′-hydroxycotinine; PANAS, Positive and negative Affect Schedule; PSS, Perceived Stress Scal; RCMAS, Revised Children's Manifest Anxiety Scale; sAA, Alpha-Amylase; SCARED, Screen for Child Anxiety Related Emotional Disorders; SPT Skin-Prick Test; STAI, State-Trait Anxiety Inventory; STAI-C, STAI for Children; THC, Tetrahidrocannabinol; TLFB, Timeline Follow Back; TSST-C, Trier Social Stress Test for Children.

[a] Age is specified as either mean age of the sample ± standard deviation (SD) (if available), or age range.

[b] When the stressor was induced, 0 min refers to the starting point of the induced stress task.

[c] s-IgA was determined in all the studies using a enzyme-linked immunosorbent assay (ELISA) kit.

[d] s-IgA concentrations are specified as Mean ± SD of the total sample or the different groups (with the exception of two studies, that reported Median ± SD). When the data were extracted from a graphic, approximated values were reported.

[e] p values are indicated whenever the paper reported them.

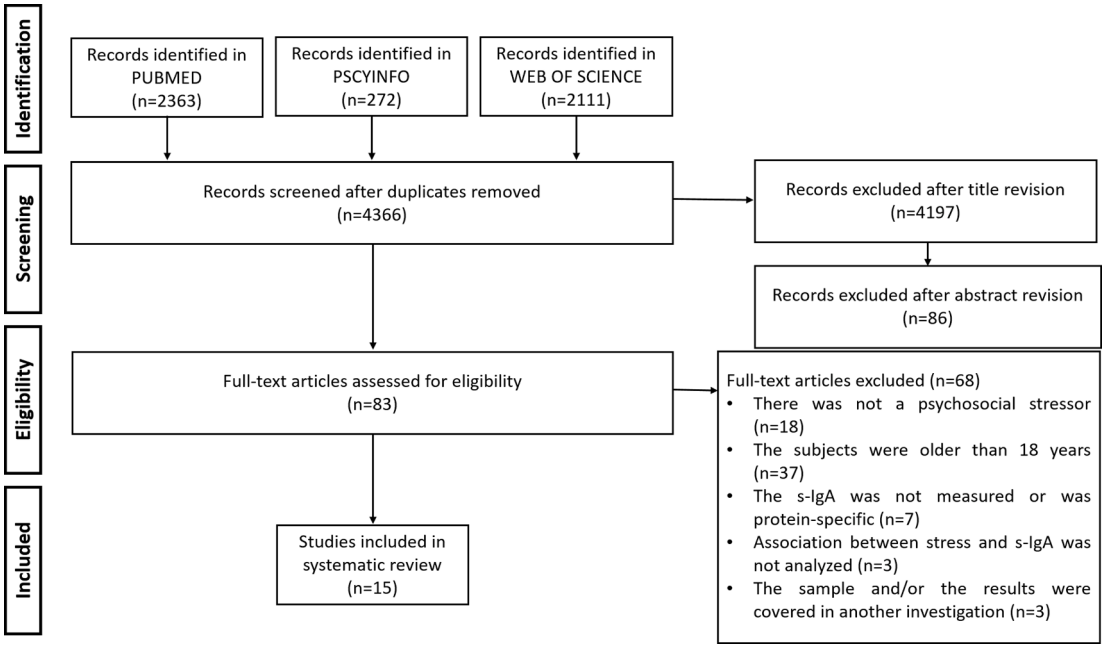

Fig. 2. PRISMA flowchart detailing the filtering steps undertaken to select the studies.

3.2. General characteristics of included studies

The selected studies were conducted in eight different countries: USA (5), Israel (4), Canada (2) Australia (1), Germany (1), Netherlands (1) and Spain (1), and they were published between 2007 and 2022 (Fig. 3 a).

From all evaluated studies, four (27%) were cross sectional and eleven (73%) were longitudinal. Studies characteristics are presented in Table 1.

The number of participants in each study ranged from 47 to 253 with an outlier of 1043 (median = 94) and seven studies assessed more than 100 subjects (Fig. 3 b). The age ranged between 0 and 18 years. Three studies evaluated infants from 0 to 1 year old (Ellberg et al., 2019; Kang et al., 2020; Noakes et al., 2007), five studies included children between 1 and 5 years (Abraham et al., 2021; Molnar et al., 2018; Reindl et al., 2022; Vermeer et al., 2012; Watamura et al., 2010) and seven studies included children and adolescents from 7 to 18 years old (Byrne et al., 2017; Laurent et al., 2015; Ma et al., 2018; Marques-Feixa et al., 2022; Ulmer-Yaniv et al., 2018a,b; Yirmiya et al., 2018). Regarding sex, thirteen studies included both female and male participants (half-half proportion), and two studies did not report the sex of the participants. Six studies reported information about ethnicity, showing a Caucasian predominance.

3.3. Nature of the stressors in the studies reviewed

The nature of the psychosocial stressors described in the included articles is diverse. According to the duration and chronicity of the stressors, they were classified as isolated short-term stressors or acute stressors (e.g., mathematical test, speaking test) and severe long-term exposure stressors or chronic stressors (e.g., parental style, maternal prenatal distress, war exposure).

Ten studies evaluated the impact of only one stressor. Specifically, nine studies included chronic stressors as pre and postnatal maternal distress measured with depression and stress scales (Ellberg et al., 2019; Kang et al., 2020); maternal drug consumption during pregnancy (Noakes et al., 2007) and during pregnancy and postpartum (Molnar et al., 2018); diurnal anxiety and depressive symptoms (Ma et al., 2018); parenting style measured with parent infant-synchrony and interaction (Byrne et al., 2017); and childcare (e.g. center care, family care [family home who carried a license for caring 3 or 4 children], foster care or biological parental care (Reindl et al., 2022; Vermeer et al., 2012; Watamura et al., 2010). One article studied s-IgA reactivity under an induced acute stressor using a performed-orientated task based on an adaptation of the Trier Social Stress Test for Children (TSST-C), consisting on a combination of a speaking, a mental arithmetic and a mirror-tracing task in the 62% of the participants and a interpersonal stress task, consisting on three exclusion challenge, in the 38% of the participants (Laurent et al., 2015).

Additionally, five studies evaluated the impact of two stressors. Three studies included the combination of two chronic stressors as maternal depression and parenting style (Ulmer-Yaniv et al., 2018a) and war and parenting style (Ulmer-Yaniv et al., 2018b; Yirmiya et al., 2018). Finally, two studies included a chronic stressor and an induced acute stressor. Marques-Feixa et al. (2022) performed the TSST-C in children-young population exposed and non-exposed to childhood maltreatment. The TSST-C, is a standardized tool for inducing stress in a controlled environment in which participants are instructed to continue a story and to perform a mental arithmetic task. Before beginning, they are told that the tasks will be recorded and rated by a group of public speaking experts. Abraham et al. (2021), included parenting style but also applied the Fear Eliciting Task ("Mask") to 3 years old children. In this task an experimenter used four increasingly fear-eliciting masks: rabbit, lion, alligator and monster (15 s per mask), while calling children by name and moving her head slowly from side to side. The parents are present but adopt a passive role during the test. In this study, although authors employed diverse tasks to evaluate infants' emotionality and self-regulation abilities, they were not considered as a protocol of stress induction. See Table 1 for more information regarding the specific test questionnaires and measurements used for each stressor.

3.4. Study design and biological samples collection

Every unspecific form of s-IgA assessed in mucosa was considered for this systematic review, however, only one article used feces for s-IgA analysis (Kang et al., 2020), the other 14 studies used saliva.

For the purpose of this review, articles were classified according to the specific aspect of s-IgA functioning that they measured as: measures of basal s-IgA levels, measures of s-IgA circadian rhythm and measures of s-IgA reactivity to acute stress.

There was a high heterogeneity between studies regarding the number of biological samples obtained for each participant, which ranged from one to twelve with an outlier of forty-eight samples per subject. Ten articles assessed s-IgA basal levels, collecting one to three saliva samples throughout a day (Abraham et al., 2021; Byrne et al., 2017; Ellberg et al., 2019; Kang et al., 2020; Molnar et al., 2018; Noakes et al., 2007; Reindl et al., 2022; Ulmer-Yaniv et al., 2018a,b; Yirmiya et al., 2018) Three articles measured s-IgA circadian rhythm by collecting three to eight samples throughout a day (Ma et al., 2018; Vermeer et al., 2012; Watamura et al., 2010). Finally, for assessing s-IgA reactivity to acute stress, two articles collected five to six samples throughout the laboratory stress task (Laurent et al., 2015; Marques-

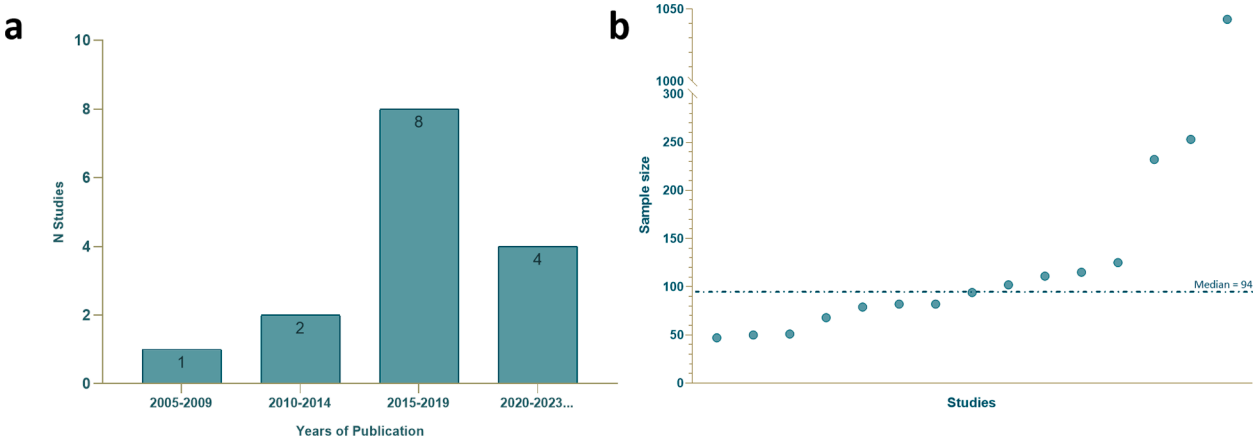

Fig. 3. (a) Year of publication of the selected studies. The studies are grouped in ranges of five years. The last bar represents only the last two years. **(b) Sample Size of the studies reviewed.**

Feixa et al., 2022). Seven articles repeated the collection protocol in an interval of time that varied from one day to six years (Ellberg et al., 2019; Ma et al., 2018; Noakes et al., 2007; Reindl et al., 2022; Ulmer-Yaniv et al., 2018b; Vermeer et al., 2012; Watamura et al., 2010).

Eight of the studies took place in the afternoon (between 3 PM and 6 PM) (Abraham et al., 2021; Ellberg et al., 2019; Laurent et al., 2015; Marques-Feixa et al., 2022; Molnar et al., 2018; Reindl et al., 2022; Ulmer-Yaniv et al., 2018a,b), one took place in the morning (at waking) (Byrne et al., 2017) and in three studies, samples were collected across the day (Ma et al., 2018; Vermeer et al., 2012; Watamura et al., 2010). Three studies did not report timing of sample collection (Kang et al., 2020; Noakes et al., 2007; Yirmiya et al., 2018).

Determination of the s-IgA in the laboratory was performed using an enzyme-linked immunosorbent assay (ELISA) in all the studies. Information of s-IgA concentration is reported in Table 1.

3.5. Additional measures reported in the included articles

Different additional measures were reported together with s-IgA determinations in all the reviewed studies.

Five of the studies reported psychiatric outcomes of their sample including infant emotional and behavior problems evaluated using the Child Behavior Checklist (CBCL), the Kiddie-Schedule for Affective Disorders & Schizophrenia (K-SADS-PL-5) the Developmental and Well-Being Assessment (DAWBA) or the Screen for Child Anxiety Related Emotional Disorders (SCARED) (Laurent et al., 2015; Marques-Feixa et al., 2022; Ulmer-Yaniv et al., 2018a,b; Yirmiya et al., 2018).

Eleven out of the fifteen studies reported information about additional biomarkers (73%). Salivary cortisol concentration was investigated in seven of the fifteen studies (47%), being the most common additional biomarker (Abraham et al., 2021; Laurent et al., 2015; Marques-Feixa et al., 2022; Reindl et al., 2022; Ulmer-Yaniv et al., 2018a; Watamura et al., 2010; Yirmiya et al., 2018). Alpha amylase (sAA) (Laurent et al., 2015), dehydroepiandrosterone (DHEA) and progesterone (Reindl et al., 2022) were explored together with cortisol. Additionally, C-reactive protein (CRP), Body Max Index (BMI) (Byrne et al., 2017) and oxytocin (Ulmer-Yaniv et al., 2018b) were measured. Moreover, when prenatal maternal smoking exposure was studied, cotinine and nicotine were assessed (Molnar et al., 2018; Noakes et al., 2007).

When prenatal maternal distress was assessed, infant birth weight and length were reported (Ellberg et al., 2019; Kang et al., 2020). In this line, two studies explored child use of medicine (Vermeer et al., 2012) and infant illness frequency (Watamura et al., 2010) and one study reported information regarding children medication and frequency and type of physical illness (Ma et al., 2018).

3.6. Main findings

The main findings of the studies are summarized in Fig. 4.

Firstly, ten studies that evaluated basal s-IgA levels observed differential s-IgA directions. Specifically, 7 studies reported increased s-IgA levels under stressful conditions (Abraham et al., 2021; Byrne et al., 2017; Molnar et al., 2018; Noakes et al., 2007; Ulmer-Yaniv et al., 2018a,b; Yirmiya et al., 2018), 2 studies reported a decrease on s-IgA basal levels (Ellberg et al., 2019; Kang et al., 2020) and one study did not observe differences among groups (Reindl et al., 2022). Thus, these results suggest that basal s-IgA levels under stress may depend on participant's age, the type of stressor and the methodological design employed.

Secondly, three studies evaluated the impact of caregiving type (Vermeer et al., 2012; Watamura et al., 2010) and diurnal anxiety (Ma et al., 2018) on s-IgA circadian rhythm, pointing out to the existence of s-IgA diurnal pattern characterized by a gradual decrease throughout the day. However, authors differed on the age of appearance and the environmental conditions.

Finally, two studies evaluated s-IgA reactivity under a psychosocial acute stressor in children and adolescents employing a laboratory-based task (Laurent et al., 2015; Marques-Feixa et al., 2022). Both studies indicated that salivary s-IgA shows reactivity to acute stress, characterized by a fast increase upon the beginning of the stress task followed by a fast decline on s-IgA levels during the recovery period.

3.7. Risk of bias

The risk of bias of the 15 articles reviewed was assessed according with the criteria mentioned in the section "2.4. Data collection process and risk of bias assessment". A summary of the risk of bias present in each manuscript can be found in Table 2. Two studies presented scores below 50% and were considered of low-quality (Molnar et al., 2018; Noakes et al., 2007; Watamura et al., 2010), six studies achieved a percentage of risk of bias between 50% and 74% and were considered of

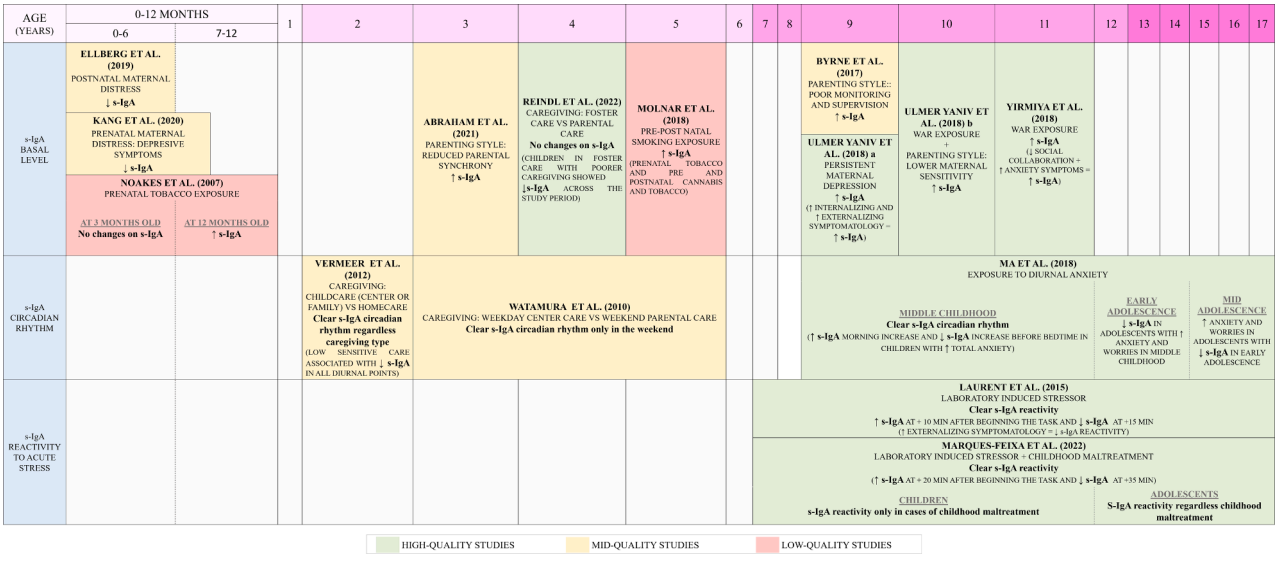

Fig. 4. Summary of the main findings of the reviewed studies. Studies are classified according to the age of the subjects (0–18 years) and the aspect of s-IgA functioning measured (basal level, circadian rhythm and reactivity to acute stress). The quality of the study extracted from the risk of bias is indicated in colors (high-quality, green; mid-quality, yellow; low-quality, red).

Table 2
Quality of the reviewed articles (n = 15). Items are scored as 2 (best possible score), 1 (medium score), or 0 (worst score) and the sum of the 6 items represent the final punctuation for each article. An overall score was calculated for each study by summing the scores of each criterion and expressing it as a percentage, considering the total possible score. The quality of the study was classified, as low when the total score was lower than 50%, as mid when the total score was between 50% and 74% and as good when the total score was equal or higher than 75%.

	Selection		Outcome Assessment			Comparability	Total (%)
	Population sample size[a]	Quality of stress definition[b]	Quality of sample collection[c]	Timing of sample collection[d]	Adequate number of samples[e]	Control for covariables[f]	
Abraham et al., 2021	0	2	2	2	2	0	67
Byrne et al., 2017	2	1	2	1	0	2	67
Ellberg et al., 2019	0	1	2	2	1	2	67
Kang et al., 2020	2	1	2	0	0	2	58
Laurent et al., 2015	1	2	2	2	2	2	92
Ma et al., 2018	2	2	1	2	2	2	92
Marques-Feixa et al., 2022	2	2	2	2	2	2	100
Molnar et al., 2018	0	0	2	2	0	0	33
Noakes et al., 2007	1	0	2	0	1	1	42
Reindl et al., 2022	2	1	2	2	1	2	83
Ulmer-Yaniv et al., 2018a	2	1	2	2	2	0	75
Ulmer-Yaniv et al., 2018b	2	1	2	2	2	1	83
Vermeer et al., 2012	0	1	1	1	2	2	58
Watamura et al., 2010	1	1	1	1	1	1	50
Yirmiya et al., 2018	2	1	2	2	2	1	83

[a] Population sample size punctuation: 2, a sample size higher than 97, calculated considering unlimited population with a confident level of 0.95 and an error of 0.10 (Marrugat & Vila, 2012); 1, a sample size between 69 and 97, calculated considering an infinite population with a confident level of 0.90 and an error of 0.10; 0, a sample size between 1 and 69.

[b] Quality of stress definition punctuation: 2, laboratory stress induction or direct measures of participants stress; 1, standardized environmental stress measures; 0, non-standardized measure.

[c] Quality of sample collection punctuation: 2, samples collected by professionals following adequate instructions; 1, self-collection following adequate instructions; 0, self-collection with no previous instructions.

[d] Timing of sample collection punctuation: 2, sample collection throughout the day and at least one at awakening and one before going to bed (s-IgA circadian rhythm) or in the evening (s-IgA reactivity to acute stress or basal levels); 1, sample collection throughout the day (s-IgA circadian rhythm) or in the morning (s-IgA reactivity to acute stress or basal levels); 0, the time was not indicated.

[e] Adequate number of samples punctuation: 2, at least two (s-IgA basal levels), three (s-IgA reactivity to acute stress) or four (s-IgA circadian rhythm) samples per day; 1, repeated measures across the study (s-IgA basal levels) or two (s-IgA reactivity to acute stress) or three (s-IgA circadian rhythm) samples per day; 0, one sample across the study (s-IgA basal levels) or one (s-IgA reactivity to acute stress) or two (s-IgA circadian rhythm) samples per day.

[f] Control by covariates punctuation: 2, control by sex, age and other variables related to the sampling;1, control by sex and/or age; 0, not controlling by covariates).

mid-quality (Byrne et al., 2017; Ellberg et al., 2019; Kang et al., 2020; Vermeer et al., 2012) and seven of them presented a percentage equal or higher than 75%, so they could be considered of high-quality (Abraham et al., 2021; Laurent et al., 2015; Ma et al., 2018; Marques-Feixa et al., 2022; Reindl et al., 2022; Ulmer-Yaniv et al., 2018a,b; Yirmiya et al., 2018).

4. Discussion

To the best of our knowledge, this is the first systematic review to date that explores s-IgA reactivity to psychological stress during the first stages of life including 15 empirical studies. The different articles evaluated: i) s-IgA basal level, ii) s-IgA circadian rhythm and iii) s-IgA reactivity to acute stress.

4.1. s-IgA basal level

Results from the ten articles evaluating the impact of stress on s-IgA basal levels seem to indicate that consequences may vary depending on the type of stressor and children age (Abraham et al., 2021; Byrne et al., 2017; Ellberg et al., 2019; Kang et al., 2020; Molnar et al., 2018; Noakes et al., 2007; Reindl et al., 2022; Ulmer-Yaniv et al., 2018a,b; Yirmiya et al., 2018).

When exploring tobacco exposure during pregnancy, Noakes and colleagues (2007) did not find significant differences on s-IgA basal levels between exposed and non-exposed infants at 3 months old. Curiously, exposed infants showed significant higher s-IgA levels at 12 months of age when compared with non-exposed children. In this line, Molnar et al. (2018) reported increased s-IgA levels among 5-year-old children born to mothers who smoked tobacco during pregnancy or combined tobacco and cannabis during pregnancy and postnatal period. Higher s-IgA levels in children exposed during pregnancy could be due to the immunogenic components of the cigarette, which could cross the placental barrier and have a direct effect in the fetal immune system, which could be reflected in later children's s-IgA reactivity and health (Sandin et al., 2011). Interestingly, as reported by Noakes et al. (2007), children exposed to maternal tobacco presented a higher prevalence of chest infections, which could explain the increased s-IgA levels. Although the prenatal period seems to be a sensitive stage for the immune system programming, other factors as breastfeeding should be considered, since maternal milk is a source of different immunoglobulins that protect infants against pathogens (Rio-Aige et al., 2021). According to Noakes and colleagues (2007), the length of breastfeeding was shorter in the group of smokers, impacting on their susceptibility to infections and their postnatal immune system development. However, these results should be interpreted with caution taken in to account some methodological limitations of both studies.

Secondly, with regard to perinatal maternal distress, Ellberg et al. (2019) and Kang et al. (2020) reported lower s-IgA levels in 1 to 8 months old infants exposed to different forms of pre or postnatal maternal distress. Specifically, Kang and colleagues (2020) observed that prenatal and persistent depression are associated with reduced s-

IgA levels in offspring's feces. Interestingly, when analyzing the impact of infant's age, s-IgA concentrations were only significantly lower in infants older than 4 months whose mothers showed depression during pregnancy. These results suggest that maternal depressive status during pregnancy could be a risk factor for the optimal fetal immunity system development. Different maternal immune and neuroendocrine mediators have been proposed as mechanisms underlying these associations (Merlot et al., 2008). Furthermore, maternal and infant gut microbiome has been also suggested to be modified under maternal distress, which might affect infant's intestinal s-IgA production (Jašarević et al., 2015; Mu et al., 2021).

On the other hand, Ellberg and colleagues (2019), employing a composite measure of depression and stress, proposed that maternal postnatal distress was associated with lower s-IgA levels in infants between 1 and 6 months of age. In accordance with previous literature, maternal well-being and caregiving in early stages of life might influence infant emotional and physiological functioning (Barclay et al., 2022; Buhler-Wassmann & Hibel, 2021). Moreover, these results are in line with other studies included in this review, which point out that poor family caregiving downregulates s-IgA diurnal secretion (Vermeer et al., 2012; Watamura et al., 2010). Notably, further studies must deeply explore the role of s-IgA levels in maternal breast milk, since those levels could be altered in the presence of different psychosocial stressors.

Contrary, Ulmer-Yaniv et al. (2018a) reported that maternal depression at any time-point of child's life was associated with increased evening s-IgA basal levels at 10 years old. Interestingly, higher children s-IgA levels were also associated with more internalizing and externalizing symptoms. This is in line with previous studies indicating that both early life adversity and psychopathological symptoms are associated with increased activity of the immune system (Coelho et al., 2014; Mitchell & Goldstein, 2014; Slopen et al., 2013). Beyond increased s-IgA levels, Ulmer-Yaniv and colleagues (2018a) observed elevated cortisol levels in children from depressed mothers, suggesting a crosstalk between neuroendocrine and immune system. These results are in great accordance with previous literature indicating the existence and HPA axis-related immune modulation (Mueller et al., 2022; Ziemssen & Kern, 2007).

In regard to parenting and caregiving, worse parenting resulted in increased s-IgA basal levels in the studies of Abraham et al. (2021) and Byrne et al. (2017) while not differences were found in Reindl et al. (2022) study. In line with the study by Ulmer-Yaniv et al. (2018a), Abraham et al. (2021) found that poor parental caregiving was associated with increased levels of both s-IgA and cortisol in three-year-old children, highlighting once again that parents play an important role on infant stress regulation. Moreover, children with better self-regulation abilities showed lower s-IgA basal levels, as reported in previous studies which claim that personality traits modulates the impact that stress have on immune system functioning (Kubitz et al., 1996; Segerstrom & Miller, 2004). In this line, Byrne and colleagues (2017) identify that poor monitoring and supervision predict higher s-IgA and C-Reactive Protein (CRP) levels in nine-year-old children, suggesting an hyper activation of the immune system under situations that can be interpreted as social rejection. On the other hand, Reindl et al. (2022) indicated that familial foster care might mitigate the impact of early life adversity since no differences on s-IgA and cortisol levels were found between 4-year old children in foster and biological parental care. Contrary to expected, authors found that children in foster care with higher caregiving quality showed an increasing s-IgA pattern across the one-year study period. Meanwhile, children in foster care with lower caregiving quality showed decreasing s-IgA concentrations, suggesting that long-term stressors could downregulate s-IgA production. Further studies are needed to determine whether poor caregiving disrupts the expected age-related increase on s-IgA levels.

Finally, the studies by Ulmer-Yaniv et al. (2018b) and Yirmiya et al. (2018) indicated that war exposure increased basal s-IgA levels in nine- to eleven-year old children. Furthermore, both studies observed that increased s-IgA levels lead to higher anxiety symptoms and reduced social collaboration skills, indicating that s-IgA could be a biomarker of perceived anxiety in children exposed to chronic stress. Moreover, when studying the impact of maternal caregiving among children exposed to war, greater maternal sensitivity was associated with lower s-IgA levels in both studies. These results are in line with previous literature claiming that mothers might buffer children stress response throughout multiple physiological and social cues (Ruttle et al., 2011).

Therefore, the above-mentioned studies highlight the difficulty of exploring the impact of different stressors on s-IgA basal levels. Most of the studies, including those with high quality, point out to increased s-IgA basal levels after exposure to stressors, especially in children older than 9 years old. However, it should be noticed that there are several confounding factors that might be mediating this association. In this line, the nature and chronicity of stressors might differentially affect immune system functioning. Moreover, it should be explored whether participation in the study is acting as an acute stressor that rapidly increases s-IgA levels. Importantly, other aspects as age and sex must be consider in further studies as it has been well stablished that s-IgA levels increased throughout life span in a sex specific way. Finally, considering that s-IgA secretion varies throughout the day, timing of sampling may contribute to the inconsistency of these findings.

4.2. *s-IgA circadian rhythm*

The three studies exploring the impact of parenting, caregiving and psychopathological symptoms on s-IgA circadian rhythm suggest that these stressors could modulate the existing diurnal pattern depending on children's age (Ma et al., 2018; Vermeer et al., 2012; Watamura et al., 2010).

With regard to s-IgA rhythmicity, the three reviewed studies identified the existence of a diurnal pattern, although the curves presented noticeable differences between studies. The only similarity identified in all the studies was the decrease of s-IgA levels during late afternoon and evening. However, it is important to highlight that the methodological differences regarding the number of samples and collection time hinder the comparison of the patterns across studies. For instance, despite evaluating children around 3 years old with similar stressors, Watamura et al. (2010) and Vermeer et al. (2012) obtained contradictory findings. Specifically. Vermeer and colleagues (2012) determined that 2- to 3-year old children presented circadian rhythm both during weekdays and weekends characterized by a morning decrease, a slight afternoon increase and a final evening decline. Contrary, Watamura and colleagues (2010) only reported rhythmicity on the weekends. This circadian pattern was characterized by a gradual decrease from mid-morning to evening, with a sharper decline on mid-afternoon. These discrepancies may be explained by the methodological design, especially related to differences on the time of sample collection. On the other hand, Ma and colleagues (2018), employing a high-quality design, reported the existence of a well-defined s-IgA circadian rhythm in 9-to-12 year old children. According to these authors, s-IgA presented a slight increase within the first four hours post-awakening and a gradual decrease toward the afternoon followed by a final increase before bedtime. This study presents the greatest reliability as eight saliva measures per day were obtained, in two consecutive days, starting at awakening, 30 min after and then collecting samples every two hours until bedtime. This approach seems to be more suitable for studying s-IgA diurnal rhythmicity since it considers children's awakening time and has continued measures.

In spite of the above-mentioned methodological differences between the studies, the type of stressor also seems to play a role on s-IgA rhythmicity. Regarding caregiving, both Vermeer and colleagues (2012) and Watamura and colleagues (2010) agree that s-IgA circadian pattern is better defined in the weekends, when children are cared for at home. Additionally, according to Vermeer and colleagues (2012) lower caregiver emotional support is associated with lower s-IgA levels in all

daytime points during weekdays and weekends. These findings suggest that children could benefit from a warm atmosphere and secure environments to self-regulate their s-IgA diurnal secretion. In this line, Watamura et al. (2010) reported an increase on this immunoglobulin in the weekdays evening in young children when they are at home with their parents. This result is in great accordance with the increased s-IgA levels during the afternoon that Vermeer et al. (2012) reported. However, the mediating role of children's age should not be underestimated. Particularly, Watamura et al. (2010) observed that 3- to 4- year old children only presented the expected s-IgA circadian rhythm during weekends, while 4- to 5- year old children showed rhythmicity independently of the day. Thus, while the ability to regulate s-IgA secretion seem to depend on environmental clues in young children, older children s-IgA rhythmicity could be independent of the received care. Interestingly, when studying cortisol profiles, Watamura et al. (2010) observed that young and old children presented a well defined circadian rhythm in both weekdays and weekends, suggesting that s-IgA rhythmicity presents greater differences according to children's age.

Furthermore, in regard with children's anxiety, Ma and colleagues (2018) observed that psychological anxiety symptoms, including worries and social concern, predicted a higher s-IgA level's increase in the morning and lower s-IgA evening levels in 9 to 12 year old children. However, physiological anxiety symptoms (e.g. nausea, headaches, and muscle tension) were not associated with s-IgA diurnal slopes, suggesting that cognitive anxiety might have great impact on biological systems at these ages. Nevertheless, the effect of anxiety on s-IgA seems to be mediated also by age. Specifically, authors reported the existence of a continuous loop between anxiety and s-IgA levels in the different stages. Higher total anxiety and worries in children in late childhood (between 9 and 12 years old) were associated with diminished global s-IgA levels when they reached the adolescence (between 12 and 15 years old), which in turn seems to predict higher total anxiety symptom and worries in late adolescence. Furthermore, in late adolescence (between 15 and 18 years old), higher total anxiety was associated with lower s-IgA levels. S-IgA levels in late childhood were significantly associated with s-IgA levels in early adolescence, but these levels were not associated with those presented in late adolescence. These results indicate that children with persistent worries over time may be at risk for compromised mucosal immunity, reflected by lowered overall levels of s-IgA. The findings further illustrate the mutual regulation between chronic anxiety symptoms and immunity over several years. These results, together with previous evidence, point out that stress produces maladaptive responses that lead to the downregulation of the immune system, especially when it is chronic. It has been also proved that chronic stress dysregulates cortisol secretion which in turn leads to altered immune responses (Johnston-Brooks et al., 1998; Juster et al., 2010).

Due to the methodological differences, the nature of the explored stressors and the age of the participants, it is not possible to conclude that stress modifies s-IgA rhythmicity in a specific way. Further studies are needed to determine s-IgA rhythmicity and possible psychological stress related disturbances. Moreover, an optimal design would include at least four saliva samples to measure s-IgA circadian rhythm according with participant's awakening time and routines.

4.3. S-IgA reactivity to acute stress

The two studies assessing s-IgA reactivity under acute stress using variations of the TSST-C observed that s-IgA levels significantly increased during the stress task and then gradually decreased until the end of the acute stress protocol in participants between 7 and 17 years (Laurent et al., 2015; Marques-Feixa et al., 2022).

Both studies analyzed s-IgA in combination with other biomarkers, i.e., cortisol (Laurent et al., 2015; Marques-Feixa et al., 2022) and salivary alpha amylase or SAA (Laurent et al., 2015). The results of both studies reinforce the idea that, when faced with acute stress, s-IgA levels increase faster when compared to both cortisol and SAA. In fact, s-IgA peaks around 5 to 6 min after facing the stressor (Benham, 2007) and this response ends approximately 30 min after the exposure. Notably, cortisol, which is the most widely used stress biomarker, peaks around 20 to 30 min after exposure to the stressor (Giacomello et al., 2020). Interestingly, Laurent et al. (2015) reported that s-IgA and cortisol were positively associated, suggesting a cross-system linkages in humans.

Although the immediacy of the s-IgA response makes it a good candidate for exploring acute stress responses, some confounding variables should be considered. Firstly, it should be highlighted that s-IgA reactivity seems to vary according to the developmental stage of the participants. In that sense, Marques-Feixa et al. (2022) observed that s-IgA levels increased after the stress task in adolescents, although this response was not observed in children between the ages of 7–11, suggesting this population group might not be able to release s-IgA after a stressor. These results are in line with previous reports indicating that puberty is a key period for the reprograming of the immune system. Interestingly, the immune system is immature in the first stages of life and goes throughout different changes during childhood and puberty in order to adapt and optimize its function to the environment (Simon et al., 2015).

Despite the importance of age, early life adversities seem to advance the abovementioned immune changes and modulate s-IgA reactivity prematurely. According to Marques-Feixa et al (2022) children with a history of childhood maltreatment did show a moderate s-IgA reactivity, similar to the one observed in adolescents, suggesting a precocious adaptive immunological response. Additionally, authors claimed that adolescents who have suffered maltreatment showed a slightly flattened s-IgA response, which may also be indicative of an immune dysregulation associated with chronic relational trauma. In accordance with these results, Laurent et al. (2015) reported that youth behavioral problems also have the ability to downregulate s-IgA reactivity. Specifically, youth with high externalizing symptoms exhibited lower s-IgA responses during the stressor when compared with youth with low externalizing behaviors. However, the impact of the developmental stage was not explored in this study. These results are in accordance with previous literature indicating that rumination and neuroticism traits flatten s-IgA stress response in adulthood (Reza et al., 2016). Alterations in other biological systems have been also reported in people exposed to early adverse experiences; for instance, the anticipation of menarche (Boynton-Jarrett et al., 2013), increased cellular aging (Colich et al., 2020) and epigenetic aging (Palma-Gudiel et al., 2019). Furthermore, cortisol reactivity in front stress seems to be strongly regulated by childhood maltreatment and psychopathological status, but not by pubertal stages (Laurent et al., 2015; Marques-Feixa et al., 2022). These changes might have a major and long lasting impact on both brain and immune system (McCrory et al., 2010), contributing significantly to a poorer mental and physical health later in adulthood (O'Connor et al., 2014). Thus, these findings suggest that the combined use of different biomarkers, particularly cortisol, could provide complementary information regarding acute stress response in humans.

To sum up, s-IgA reactivity patterns vary throughout the ontogenic stages, although early adverse events dysregulate this response. The robustness of the two high-quality studies reviewed (Laurent et al., 2015; Marques-Feixa et al., 2022) highlights s-IgA as a potential non-invasive salivary acute stress biomarker to be used in pediatric and childhood-adolescent psychiatry research. For an optimal design, we recommend the use of standardized stress protocols, the collection of different salivary samples across the test, taking into consideration that s-IgA peaks around 6 min. Conducting the study in the afternoon or evening is also recommended in order to avoid possible bias related to s-IgA circadian rhythm.

5. Conclusion

The present review highlights that s-IgA basal levels, s-IgA circadian rhythm and s-IgA reactivity to acute stress could be used as biomarkers

of psychosocial stress in childhood. However, the variety of stressors together with the different group of ages evaluated makes it difficult to obtain generalizable conclusions.

Firstly, the reviewed studies suggest that s-IgA basal levels is an accurate approach to study the impact of psychosocial stress in late childhood (Abraham et al., 2021; Byrne et al., 2017; Ellberg et al., 2019; Kang et al., 2020; Molnar et al., 2018; Noakes et al., 2007; Reindl et al., 2022; Ulmer-Yaniv et al., 2018a,b; Yirmiya et al., 2018). Specifically, stress generally resulted on increased s-IgA levels in children older than 9 years old. Secondly, the studies that explored s-IgA rhythmicity suggest that s-IgA levels varied throughout the day with a tendence to decrease throughout the afternoon and the evening, although the curves were slightly different between studies (Ma et al., 2018; Vermeer et al., 2012; Watamura et al., 2010). Noticeably, rhythmicity seems to be better defined in older children, suggesting the possible existence of reprogramming processes at certain ages. Furthermore, reported changes on s-IgA rhythmicity due to psychosocial stressors, although the methodological differences do not allow establishing a specific directionality. Finally, regarding s-IgA reactivity under acute stress, the studies by Laurent et al. (2015) and Marques-Feixa et al. (2022 agreed on the existence of a fast s-IgA response after stress exposure, especially in adolescents. However, this reactivity pattern seems to be modified by childhood maltreatment and current psychopathological status, leading to diminished s-IgA responses after puberty and anticipated responses in childhood.

Independently of the s-IgA measure employed, this review highlights that age influences s-IgA functioning. Previous studies have described an increase on s-IgA levels across the ontogenic periods (Weemaes et al., 2003) but our review additionally suggest that there are different immunological reprogramming periods across lifespan. During the first years of life, s-IgA levels are more dependent on the maternal health and bond, especially due to breastfeeding, while older children rely on themselves to regulate the s-IgA responses to the environmental conditions. Finally, the abovementioned reprograming seems to be especially relevant during pubertal when s-IgA becomes clearly reactive to acute stressor. The findings of the reviewed studies suggest that this age related s-IgA changes could be compromised in the presence of adverse events during these sensitive reprogramming periods.

On the other hand, the type of the stressor evaluated also seems to play a key role on s-IgA dysregulation. The fact that stressors differently affect children's s-IgA responses indicate that stressors could be targeting different biological pathways. For example, tobacco exposure clearly increases the risk of infection and the consequent s-IgA secretion, while relational trauma during infancy seems to be related to glucocorticoid dysregulation that latter compromise immunological functioning. Therefore, the study of additional biomarkers, especially cortisol, would provide a better understanding of the complex nature of stress response in humans and the cross talk of different biological systems.

However, there are several concerns regarding methodological designs that should be addressed in future studies. On the one hand, standardized protocols for salivary collection are needed in order to facilitate comparisons between studies. Moreover, reporting raw s-IgA levels would improve the understanding of the obtained results and would enable to perform meta-analytic approaches. Finally, we consider of great importance to understand how s-IgA reactivity, rhythmicity and basal levels behave in the unexplored ontogenic stages.

To sum up, the present evidences indicate that s-IgA can be considered a reliable biomarker of acute stress. However, further research is needed to determine how psychosocial stress impacts on s-IgA circadian rhythm and basal levels.

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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.

Data availability

No data was used for the research described in the article.

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