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STUDY PROTOCOL

Maternal prenatal stress and its neuropsychological sequelae in infants and mother–infant dyadic quality: A systematic review and meta-analysis protocol

[version 1; peer review: 1 approved with reservations]

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Abstract

Background

Prenatal maternal stress represents a significant public health concern within the Developmental Origins of Health and Disease (DOHaD) framework. Unlike transient adaptive stress, chronic prenatal stress triggers sustained hypothalamic–pituitary–adrenal (HPA) axis dysregulation, elevating maternal glucocorticoid levels and enabling cortisol transfer across the placenta. Reduced placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) activity — potentiated by epigenetic silencing of the NR3C1 glucocorticoid receptor gene — amplifies fetal cortisol exposure and disrupts neurodevelopmental programming. Hair cortisol concentration (cHCC), recognised as the gold standard for retrospective assessment of chronic HPA activation, provides an integrated, non-invasive measure applicable to both mothers and neonates.

Methods

This protocol follows the Preferred Reporting Items for Systematic

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Approval Status ?

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1. **Nickie Niforatos Andescavage**, Children's National Hospital, Washington, USA

Any reports and responses or comments on the article can be found at the end of the article.

Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines. We will search seven electronic databases (PubMed/MEDLINE, PsycINFO, Web of Science, Scopus, CINAHL, LILACS/BVS, and EBSCO Academic Search Ultimate), supplemented by grey literature and citation tracking. Prospective cohort and case-control studies including pregnant women (≥18 years) with validated assessments of chronic prenatal stress — via psychometric instruments (PSS-10, EPDS, STAI, PRAQ-R) or HPA biomarkers (cHCC, salivary/serum cortisol, CAR) — and reporting neurodevelopmental outcomes in infants at 6, 12, or 24 months will be eligible. Risk of bias will be assessed with the ROBINS-E tool. Quantitative synthesis will employ random-effects models (DerSimonian–Laird estimator; Hedges's g; Fisher's r-to-z) in R (meta and metafor packages). Statistical heterogeneity, meta-biases (Egger's test; trim-and-fill), and certainty of evidence (GRADE framework) will be formally evaluated.

Registration

This protocol is published in Open Research Europe. The formal pre-registration is deposited in OSF (https://doi.org/10.17605/OSF.IO/2Y3RC).

Keywords
prenatal stress, chronic stress, neuropsychological development, mother-infant dyad, hair cortisol, HPA axis, systematic review, meta-analysis

This article is included in the COST Actions gateway.

This article is included in the Maternal Perinatal Stress collection.

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1. Introduction

1.1 Background and theoretical framework

The Developmental Origins of Health and Disease (DOHaD) paradigm, grounded in the fetal programming hypothesis (Barker, 1995), posits that the intrauterine environment shapes the developmental trajectory of the fetus, with lasting implications for health across the life course. During gestation, the maternal organism undergoes normative neuroendocrine fluctuations that facilitate physiological adaptation to pregnancy. It is essential to draw a clear ontological and physiological distinction between this adaptive stress response and chronic prenatal distress. Whereas the former constitutes a necessary allostatic response, chronic distress represents a pathological exposure characterised by the failure of the maternal system to restore homeostasis (Van den Bergh et al., 2020; Monk et al., 2019; Gluckman et al., 2008).

The biological mechanism underlying this transmission of adversity involves dysregulation of the maternal hypothalamic–pituitary–adrenal (HPA) axis. Chronic distress induces sustained cortisol secretion that overwhelms the buffering capacity of the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) (Glover, 2014). This down-regulation exposes the fetus to supraphysiological glucocorticoid levels, catalysing epigenetic modifications — particularly methylation of the glucocorticoid receptor gene (NR3C1). These structural and functional alterations preferentially affect the development of glucocorticoid receptor-rich regions, including the limbic system and the prefrontal cortex (Monk et al., 2012; Moog et al., 2017; Sandman et al., 2012).

Fetal vulnerability to these neuroendocrine insults exhibits marked temporal sensitivity. Exposure during the first trimester is predominantly associated with alterations in cognitive development and learning, whereas distress in the third trimester tends to manifest as phenotypes of emotional reactivity and difficult temperament (Bergman et al., 2010; Davis & Sandman, 2010; Sandman et al., 2012). To capture this chronic exposure, hair cortisol concentration (cHCC) has emerged as the gold-standard retrospective biomarker, enabling quantification of systemic glucocorticoid accumulation over extended periods and thereby overcoming the limitations of single time-point measures (Caparros-Gonzalez et al., 2017; Russell et al., 2012).

1.2 Rationale and research gaps

Despite the proliferation of studies on prenatal stress, the literature lacks a rigorous synthesis that simultaneously integrates psychological and biological assessment. No existing systematic review or meta-analysis has jointly evaluated maternal distress using validated self-report instruments and HPA-axis biomarkers as dual exposure measures. This omission precludes determining whether variance in neurodevelopmental outcomes is attributable to the subjective perception of distress or to the objective allostatic burden (Huizink et al., 2003; Laplante et al., 2004; Riquelme-Gallego et al., 2023).

Furthermore, prior research has disproportionately prioritised infant outcomes, relegating maternal neuropsychological outcomes in the postpartum period (Kingston et al., 2012). The quality of the mother–infant dyadic interaction — encompassing constructs such as maternal sensitivity and attachment — remains underrepresented in models of fetal programming, despite its critical role as a mediator of infant development (Thiel et al., 2021). The absence of pre-specified moderator analyses comparing measurement modality (self-report versus biomarker) constitutes a methodological gap that this protocol aims to address.

1.3 Objectives

Primary objective:

To quantify the association between chronic prenatal maternal stress (assessed via validated psychometric instruments and/or HPA biomarkers) and neurodevelopmental outcomes in infants at 6, 12, and 24 months of age.

Secondary objectives:

1. To compare the predictive validity of subjective stress assessments (psychometric scales) versus objective biomarker-based assessments (cHCC and related HPA measures) for infant neurodevelopmental outcomes.

2. To evaluate the association between chronic prenatal maternal stress and maternal neuropsychological functioning in the postpartum period.

3. To examine the relationship between chronic prenatal maternal stress and the quality of mother–infant dyadic interaction (sensitivity, responsiveness, attachment).

4. To investigate potential moderating factors including trimester of exposure, sex of the infant, gestational age, and country income level (HIC vs. LMIC).

2. Methods

2.1 Protocol and registration

This methodological protocol was designed in accordance with the PRISMA-P guidelines (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) (Shamseer et al., 2015). The protocol is pre-registered in the Open Science Framework (OSF; https://doi.org/10.17605/OSF.IO/2Y3RC) and published in Open Research Europe as its formal dissemination record.

2.2 Eligibility criteria (PECOS framework)

Studies will be eligible for inclusion if they meet the following PECOS criteria.

P	Pregnant women ≥18 years (any trimester, parity, and nationality) with a formal prenatal stress assessment. No restriction on gestational age or country of origin.
E	Chronic prenatal maternal stress assessed by: (a) validated psychometric tools (PSS-10, EPDS, STAI, PRAQ-R, PDQ, life-event scales) or (b) HPA-axis biomarkers (hair cortisol concentration [cHCC], salivary/serum/plasma cortisol, cortisol awakening response [CAR], urinary catecholamines).
C	Women with low or normative prenatal stress levels on the same measurement instruments (validated scales or biomarker values within reference ranges).
O	Primary: Neurodevelopmental outcomes in infants at 6, 12, and 24 months (Bayley-III, ASQ-3, CBCL, Mullen Scales). Secondary: maternal neuropsychological postpartum outcomes; mother–infant dyadic interaction quality (sensitivity, responsiveness, attachment).
S	Longitudinal observational designs (prospective cohorts) and retrospective designs (case-control). Peer-reviewed articles and preprints. No language or date restrictions. Animal studies, purely clinical/obstetric outcomes, and cross-sectional designs excluded.

*PECOS: Population, Exposure, Comparator, Outcome, Study design.

Exclusion criteria: Animal or in vitro studies; participants <18 years; studies assessing stress exclusively in the postpartum period; outcomes limited to obstetric parameters (gestational age, birthweight, Apgar); cross-sectional designs; secondary literature (narrative reviews, editorials).

2.3 Information sources and search strategy

The selection of information sources follows the guidance set out in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2022) and the PRESS 2015 Evidence-Based Checklist for Librarian Peer Review of Electronic Search Strategies (McGowan et al., 2016), with the dual aim of maximising both sensitivity and specificity. The seven databases searched encompass biomedical, psychological, nursing, and Latin American scientific literature, thereby ensuring adequate coverage of the heterogeneous disciplinary landscape in which research on prenatal distress, HPA axis dysregulation, and infant neurodevelopment is published. The search queries were constructed by combining controlled vocabulary terms—MeSH headings in PubMed, Emtree terms in Scopus, and thesaurus descriptors in PsycINFO and CINAHL—with free-text terms applied to title and abstract fields. This dual approach is methodologically necessary: reliance solely on controlled indexing terms would systematically exclude studies indexed inconsistently or prospectively, particularly those from non-English or emerging research groups, a recognised limitation that has been extensively documented in the information retrieval literature.

Two distinct rounds of searching were conducted. The first round (November 2025) employed the full primary search string across all seven databases, retrieving a combined total of 2,083 records. The second round (February 2026) was a targeted complementary search, deliberately designed to capture studies on mother–infant interaction, maternal sensitivity, and attachment outcomes that may have been underrepresented in the first round owing to the keyword emphasis on cortisol concentrations and neuropsychological outcomes. This second round contributed an additional 725 records across five databases (PubMed, PsycINFO, Web of Science, Scopus, and EBSCO). Across both rounds, searches yielded a combined total of 2,808 raw records. Following automated deduplication within each database platform prior to export and cross-database deduplication in Rayyan (Ouzzani et al., 2016), the final unique record set submitted for title and abstract screening comprised 1,476 records. Table 1 presents the complete search record by database, interface, and round.

Table 1. Records retrieved per database across both search rounds.

Database	Interface/ platform	Search 1 date	Records (S1)	Search 2 date	Records (S2)	Total
PubMed/MEDLINE	NCBI	25 Nov 2025	21	03 Feb 2026	7	28
PsycINFO	ProQuest	26 Nov 2025	416	—	481*	897
Web of Science Core Collection	Clarivate Analytics	27 Nov 2025	426	05 Feb 2026	128	554
Scopus	Elsevier	27 Nov 2025	258	05 Feb 2026	48	306
CINAHL	EBSCOhost	25 Nov 2025	7	—	—	7
LILACS/BVS	VHL Regional Portal	27 Nov 2025	448	—	—	448
EBSCO (Academic Search Ultimate)	EBSCOhost	27 Nov 2025	507	05 Feb 2026	61	568
TOTAL			**2,083**		**725**	**2,808**

The primary search string is structured around three conceptual Boolean blocks. Concept block A captures prenatal stress and adversity exposure, incorporating both psychological constructs (perceived stress, psychological distress, anxiety) and physiologically operationalised adversity (perinatal stress, intrapartum stress, maternal stress transfer). Concept block B retrieves neurodevelopmental and neuropsychological outcomes in the offspring and in the mother herself, covering cognitive development, motor milestones, language acquisition, executive function, emotion regulation, and behavioural outcomes. Concept block C functions as a biological pathway precision filter, targeting studies that operationalise HPA axis activity through cortisol measurement—whether salivary, urinary, serum, or hair—or through related glucocorticoid markers. The decision to include Concept block C as a mandatory element of the primary string reflects the conceptual specificity of this review: by requiring all three blocks to co-occur, the strategy retrieves studies that explicitly link prenatal psychosocial adversity to offspring outcomes through a measurable biological mechanism, substantially reducing the retrieval of studies that address behavioural correlates of prenatal stress without any neuroendocrine component.

The second-round search relaxed Concept block B and replaced it with dyadic and relational outcome terms—mother–infant interaction, maternal sensitivity, maternal responsiveness, parent–child interaction, attachment, bonding, and caregiving behaviour—while retaining Concept block A (prenatal stress exposure) and Concept block C (cortisol/HPA markers). This design reflects the recognition that studies examining maternal sensitivity and mother–infant dyadic quality as outcomes of prenatal neuroendocrine dysregulation occupy a partially distinct literature from those focused on infant neurodevelopmental milestones, and would not be reliably retrieved by the primary string alone.

Across all databases, the Boolean NOT operator was applied exclusively to publication types (systematic reviews, meta-analyses, narrative reviews) and methodological designs incompatible with the longitudinal exposure–outcome framework of this review (cross-sectional studies). Critically, NOT was not applied to content terms, in order to prevent inadvertent exclusion of relevant primary studies in which secondary study type terms appear incidentally in title or abstract fields. This conservative application of exclusionary logic is consistent with best-practice recommendations for high-sensitivity systematic review search design.

In addition to the primary database searches, grey literature was systematically canvassed through several complementary channels. Open Grey (www.opengrey.eu) and ProQuest Dissertations & Theses Global were searched to retrieve unpublished reports, conference proceedings, and doctoral dissertations relevant to the review topic. Clinical trial registries—specifically ClinicalTrials.gov and the International Standard Randomised Controlled Trial Number (ISRCTN) registry—were searched to identify ongoing or recently completed trials that may yield eligible data prior to formal publication. To supplement database retrieval, the reference lists of all studies included after full-text review will be manually screened (backward citation tracking), and forward citation tracking will be conducted via Google Scholar and Web of Science for key included studies, in order to capture relevant work not indexed in the primary databases.

Deduplication was performed in two sequential stages. First, within each database platform, automated deduplication was carried out prior to record export to remove intra-database duplicates arising from multiple index versions of the same article. Second, cross-database deduplication was performed in Rayyan (Ouzzani et al., 2016), an AI-assisted web and mobile application purpose-built for systematic review management, which applies smart deduplication algorithms to identify and merge duplicate records across sources. Following completion of both stages, the final set of unique records submitted for title and abstract screening comprised 1,476 records.

The complete search strings for all databases and both search rounds are provided in Supplementary Material S1.

2.4 Study selection process

Study selection will follow PRISMA 2020 guidelines (Page et al., 2021). Two independent reviewers will screen titles and abstracts using the Rayyan platform (Ouzzani et al., 2016). Articles passing the screening stage will be evaluated at full-text level by the same two reviewers. Discrepancies will be resolved by consensus; in cases of persistent disagreement, a senior third reviewer (R.A. Caparrós-González or M.A. Muñoz-Garcia) will adjudicate. Where required data are missing, corresponding authors will be contacted following a standardised two-attempt protocol with a 15–30-day interval.

2.5 Data extraction

Data extraction will be performed independently by two investigators (V.M. Salmeron-Vega and L. Leonardo-Encabo) using a standardised, pilot-tested form. The following variables will be extracted: bibliometric information; sample sociodemographic characteristics; methodological details of exposure assessment (instrument type, trimester of assessment, biomarker type and protocol); neurodevelopmental assessment tools and time points; statistical estimators required for meta-analysis (means, standard deviations, effect sizes, confidence intervals, correlation coefficients); and data relevant to dyadic quality outcomes.

2.6 Risk of bias

The methodological quality and risk of bias of included observational studies will be assessed using the **ROBINS-E tool** (Risk Of Bias In Non-randomized Studies – of Exposures; Sterne et al., 2019). Seven critical domains will be examined: (1) confounding; (2) selection of participants; (3) classification of the exposure; (4) co-exposures; (5) missing data; (6) measurement of outcomes; and (7) selection of the reported result. Assessments will be conducted independently by two reviewers; discrepancies will be resolved by consensus.

2.7 Statistical synthesis and meta-analytic strategy

Quantitative analyses will be performed in the R programming environment (version ≥4.3.0) using the **meta** and **metafor** packages. A **random-effects model** with the DerSimonian and Laird (1986) estimator will be used to calculate between-study variance (τ^2), with the restricted maximum likelihood (REML) method applied in sensitivity analyses. Effect sizes will be standardised using **Fisher's r-to-z transformation** for correlations and **Hedges's g** for standardised mean differences between groups.

Statistical heterogeneity will be quantified using Cochran's Q test and the I^2 statistic (Higgins et al., 2003), interpreting I^2 values of 25%, 50%, and 75% as indicative of low, moderate, and high heterogeneity, respectively. Meta-regression and subgroup analyses have been pre-specified to explore sources of heterogeneity, including: **(a)** trimester of exposure; **(b)** measurement modality (self-report vs. biomarker); **(c)** neuropsychological domain assessed; **(d)** infant age at outcome measurement; and **(e)** country income level (HIC vs. LMIC) (Baroutis et al., 2025).

2.8 Assessment of meta-biases

Publication bias and small-study effects will be evaluated visually through contour-enhanced funnel plots and statistically by Egger's test, provided that a minimum of 10 studies per outcome are available. The trim-and-fill method will be applied to impute theoretically missing studies and assess the robustness of pooled estimators. The Doi plot and LFK index will be used as a complementary non-asymmetry test.

2.9 Certainty of the evidence

Overall confidence in the body of evidence will be assessed using the **GRADE framework** (Grading of Recommendations Assessment, Development and Evaluation). Observational evidence will begin at a 'low' certainty rating and may be downgraded for risk of bias, inconsistency, indirectness, imprecision, or publication bias, or upgraded in the presence of large effect sizes (OR > 5 or < 0.2) or a dose–response gradient.

3. Discussion

3.1 Expected contributions

This systematic review will provide the first quantitative synthesis directly contrasting the predictive validity of subjectively perceived maternal stress against objective allostatic burden measured via HPA-axis biomarkers. By integrating the assessment of the mother–infant dyad, the findings will clarify whether alterations in infant neurodevelopment operate independently or are mediated by disruptions in maternal sensitivity and postpartum attachment.

From a clinical and applied perspective, these findings may inform screening strategies in perinatal settings by clarifying whether subjective or biological measures of stress should be prioritised, or whether a combined approach provides greater predictive value. This has direct implications for early detection and targeted intervention in populations at risk.

3.2 Limitations

Considerable methodological heterogeneity is anticipated, arising from variability in the psychometric instruments employed and biomarker collection protocols across primary studies. Furthermore, the observational nature of the available literature limits the capacity to draw definitive causal inferences, requiring cautious interpretation of the pooled effect sizes.

Additionally, variability in biomarker assessment protocols (e.g., hair segment length, timing of sampling, and laboratory procedures) may limit comparability across studies. Publication bias and selective reporting may also influence the observed effect sizes, particularly in studies reporting significant associations. These factors should be considered when interpreting the findings.

3.3 Dissemination

The results of this systematic review will be submitted for publication in a high-impact international peer-reviewed journal in psychoneuroendocrinology or paediatrics. Findings will be presented at relevant national and international scientific conferences. Executive summaries for perinatal health professionals and policy-relevant briefs will be produced to ensure translation of findings into clinical practice.

Ethics and consent

Ethical approval and consent were not required. This is a systematic review and meta-analysis protocol involving secondary analysis of previously published data. No primary data collection involving human participants will be undertaken as part of this study.

Registration

This protocol is published in Open Research Europe. The formal pre-registration is deposited in OSF (https://doi.org/10.17605/OSF.IO/2Y3RC).

Ethics

No ethics committee approval is required for this systematic review, as no primary data are collected. Only published literature will be analysed.

Data availability

No primary data are generated during this protocol phase.

Extended data

Zenodo. *Maternal Prenatal Stress and Its Neuropsychological Sequelae in Infants and Mother–Infant Dyadic Quality: A Systematic Review and Meta-Analysis Protocol.*

This project contains the following extended data:

- *PRISMA-P 2015 Compliance Checklist.* (Completed PRISMA-P 2015 checklist mapping each reporting item to its location in the protocol manuscript.) https://doi.org/10.5281/zenodo.19682153 Sandman et al., 2012 https://doi.org/10.5281/zenodo.19682153 (Salmeron-Vega et al., 2026b)

- *List of Abbreviations.* (Complete list of abbreviations used in the systematic review and meta-analysis protocol.) https://doi.org/10.5281/zenodo.19694951 (Shamseer et al., 2015) https://doi.org/10.5281/zenodo.19694951 (Salmeron-Vega et al., 2026c)

- Supplementary Material S1: *Full Boolean Search Strings for All Databases.* (Full Boolean search strings for all 7 databases used in the November 2025 and February 2026 search rounds.) https://doi.org/10.5281/zenodo.19695458 (Sterne et al., 2019) https://doi.org/10.5281/zenodo.19695458 (Salmeron-Vega et al., 2026d)

Data are available under the terms of the Creative Commons Zero v1.0 Universal (CC0) license.

Operational study materials (screening instructions, decision tree, data extraction forms) are available at the Open Science Framework (Salmeron-Vega et al., 2026a): Russell et al., 2012: https://doi.org/10.17605/OSF.IO/2Y3RC under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) license.

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In accordance with the F1000 AI Policy, the authors disclose that AI-assisted tools (Perplexity Computer, November 2025 – April 2026) were used to support organizational tasks during the preparation of this manuscript, including screening workflow management and document structuring. All scientific content, analytical decisions, and conclusions were developed, reviewed, and approved exclusively by the human authors.

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I enjoyed reading the protocol for a metanalysis of prenatal maternal stress and the effects on infant outcomes.
Overall, the theoretical framework is very well articulated and captures both the importance of prenatal stress exposures on infant development and clearly identifies gap in the literature – namely the integration of subjective and objective measures of stress and the proposed metanalysis would be of great interest to the research community.

While the premise is well justified, the authors could strengthen this proposal by stating the research question more clearly in the abstract and introduction. The introduction also could potentially be expanded so that the knowledge gap, research question and primary (and secondary) objectives have stronger alignment and allow the reader to more readily understand the direction the authors are taking. For example, the framework and rational emphasize independence of subjective vs. objective/biomarker measures of stress, but is unclear if the research objective is to synthesize, compare, integrate or assess these independently? Similarly, the framework primarily discusses cortisol as the objective biomarker, but the objectives seem to allude to broader biomarker pool. If the authors could elaborate the rationale and research gaps, this would help the reader better understand the proposed protocol. Many of these details emerge in the strategy but introducing this sooner would make it easier for the reader to follow.

Some additional comments.

It would be helpful to also better understand how the primary objective is distinct from the first secondary objective. Additional rationale for the additional secondary objectives would be helpful in both the background and the rationale. Provision of hypothesis for the stated objectives would also strengthen the protocol.

The PECOS research question is very nicely specified, including details of the population, the exposure, the comparator and outcomes. It would be helpful to expand on the rationale for the a priori decisions made (e.g. the rationale for exclusion of pregnant women < 18 years old, how is

stress being defined; how were stress measures identified; how were the HPA axis biomarkers selected; what biomarkers/stress measures were excluded and why? Similarly, expand the rationale for the selected ages of infant assessments and the selection of developmental measures used?)

The search strategy is well detailed. Databases identified were appropriate, especially in the inclusion of gray literature; the strategy appears reproducible and the search terms align with the PECOS question and are comprehensive in that context (though addressing why the outcomes were restricted in the PECOS question would strengthen this approach further). Study selection procedures are clear and well defined, as well as data extraction, risk of bias assessment and statistical analysis, though could potentially be expanded with greater specificity around the secondary objectives.

This is minor but the links embedded to the references do not always link to the cited article. I do also think there are some nuances in phrasing that occasionally are unclear to the reader and may be revised for clarity (especially for Section 1)

Is the rationale for, and objectives of, the study clearly described?

Partly

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Prenatal exposure, infant neurodevelopment, DoHAD

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.