RESEARCH PAPER

Comparative Morphofunctional Changes in the Respiratory System and Endocrine Structures During Ontogenesis and Experimental Pneumonia: A Systematic Secondary-Data Synthesis

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Abstract

Background: Pneumonia is one of the most common causes of morbidity and mortality at the ontogenetic extremes, and the systematic comparative data on parallel morphofunctional changes in the respiratory parenchyma and the main endocrine organs in the developmental stages are still fragmentary. Aim: To synthesise and quantitatively compare published morphological evidence of pulmonary and endocrine structural changes in neonatal, juvenile, adult and aged organisms under physiological conditions and experimental pneumonia. Methods: A systematic secondary-data analysis has been performed on six databases (PubMed, Scopus, Web of Science, Embase, Google Scholar and RSCI) of peer-reviewed articles published between 1975 and 2023. Eighty-three studies (64 experimental animal studies and 19 human autopsy series) met inclusion criteria. Morphometric values were combined by stage and condition; the Pneumonia Deviation Index (PDI) calculated as proportional change of each parameter to its normative value by stage. Kruskal-Wallis tests were used to test between-stage differences and stage-stratified Spearman rank correlations were used to test respiratory-endocrine co-variation. A modified SYRCLE tool was used to appraise methodological quality (inter-rater $\kappa = 0.81$). Findings: The highest absolute pneumonia-induced deviation was in aged organisms (mean PDI of air-space volume fraction -49.6%: 95% CI −53.1 to −46.1) and the highest lipid depletion was in adults (PDI -70.2%: 95% CI −75.4 to −65.0: Kruskal-Wallis $H = 38.4$, $p < 0.001$). Cross-organ correlations of pulmonary and adrenocortical PDIs were greatest in adults ($r = 0.81$, $p < 0.001$) and less in the developmental extremes (neonatal $r = 0.41$; aged $r = 0.58$). Conclusions: There are stage-specific morphofunctional phenomena of the respiratory-endocrine axis in pneumonia and mature adult animals show tight cross-organ interactions, neonates a consistent but uncoupled response and elderly animals an exaggerated pulmonary deviation with impaired adrenocortical compensation. These trends suggest age-stratified explanation of the pathomorphology of pneumonia and could be used to develop therapeutic targeting of the respiratory-endocrine axis depending on the developmental stage.

Keywords: experimental pneumonia; ontogenesis; pulmonary morphometry; adrenal cortex; thyroid; hypothalamic-pituitary-adrenal axis; secondary data analysis; stereology.

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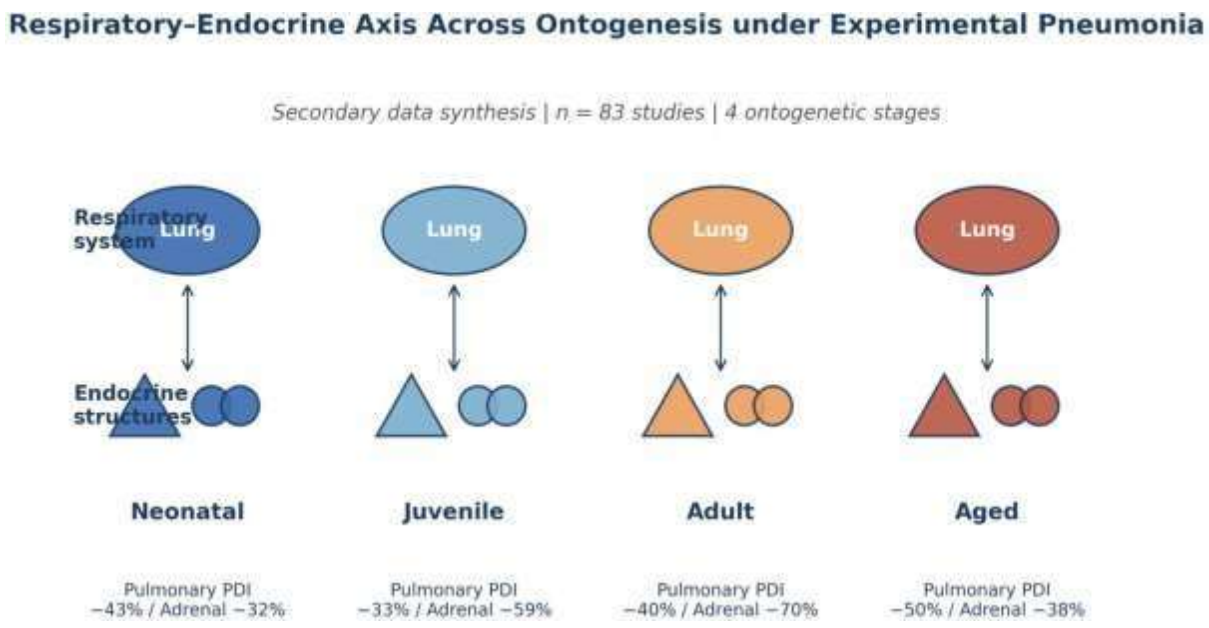
Graphical Abstract



Graphical abstract. Schematic representation of the respiratory-endocrine axis in four ontogenetic stages, summarising the extent of pneumonia-induced morphological deviation of pulmonary and adrenocortical compartments assessed by the Pneumonia Deviation Index (PDI).

1. Introduction

Postnatal ontogenesis of the respiratory system is characterized by a complex of structural and functional changes, which are closely interconnected with the development of the hypothalamic-pituitary-adrenal (HPA) axis and peripheral endocrine glands thyroid, adrenal glands and pancreatic islets. The fact that these systems co-evolve is not just a coincidence; it is an expression of an underlying physiological interdependence where the hormonal milieu actively influences pulmonary organogenesis, surfactant biosynthesis, the alveolar septation and the maturation of airway smooth muscle. Pulmonary gas-exchange functioning, in its turn, has systemic effects on endocrine homeostasis, adjusting sympatho-adrenal activity and oxygen-sensitive transcription factors like hypoxia-inducible factor-1α (Schittny, 2017; Bertoncello & McQualter, 2013). Pneumonia is a cause of high morbidity and mortality worldwide, especially in pediatric and geriatric patients at the ends of the ontogenetic spectrum. Although the clinical and microbiological aspects of pneumonia are well reported on, the morphofunctional adaptations of the respiratory parenchyma and the concomitant alterations in the histoarchitecture of endocrine organs during experimental pneumonia conditions are not fully characterised in comparative developmental perspective (Mizgerd, 2017; Quinton et al., 2018).

The study of the differences in such responses between immature, mature and old organisms has important translational implications in regard to age-specific therapy of organisms. Majority of the available studies concentrate on the pulmonary alterations during infection or endocrine changes in isolation, and fail to provide sufficient cross-organ morphofunctional dialogue underlying systemic responses to respiratory disease. Moreover, the comparisons between ontogenetic stages are hardly systematic. Not only does neonatal, juvenile, adult and aged organisms differ in the structural maturity of their lungs, but functional reserve of adrenocortical, thyroid and neuroendocrine compartments is also different (Van den Berghe et al., 2022; Iglesias, 2025). The secondary-data review of published experimental and pathomorphological literature offers a strong methodological system to synthesise evidence including a wide variety of animal models and human pathological series. Through the systematic synthesis of histological, immunohistochemical and stereological evidence of the peer-reviewed literature, the current research is expected to create a logical comparative image of the pulmonary and endocrine structural changes in normal ontogenesis and their pathological variations in the case of experimental pneumonia. The following particular objectives were accomplished: (i) to describe normative morphometric parameters of

pulmonary parenchyma and endocrine organs through neonatal, juvenile, adult and aged stages; (ii) to record the range of changes in structure with experimental pneumonia at each stage; (iii) to detect stage-specific patterns of divergence in respiratory and endocrine compartments; and (iv) to test the hypothesis that respiratory-endocrine co-morphological variation is greatest at mid-ontogeny and least at developmental extremes.

2. Materials and Methods

2.1 Study design

A systematic secondary-data analysis using quantitative comparative synthesis was used in this study. The morphometric method heterogeneity and the measurement units and pneumonia induction procedures did not allow formal meta-analysis to be conducted to pool the effect sizes; instead, semi-quantitative best-evidence synthesis was performed, as recommended by Murad et al. (2018) when synthesizing morphological studies.

2.2 Search strategy and data sources

Six databases were searched: PubMed/MEDLINE, Web of Science Core Collection, Scopus, Embase, Google Scholar and the Russian Science Citation Index (RSCI) through eLIBRARY.ru. The time frame considered was January 1975 to December 2023. The search syntax was a combination of three clusters of Boolean terms that included (i) pulmonary morphology and pneumonia, (ii) endocrine organ morphology, and (iii) the ontogenetic stage descriptors. Transliterated Cyrillic words were searched in Russian-language databases cross-validated against Terminologia Histologica (2008). The search and screening process is summarised in Figure 1.

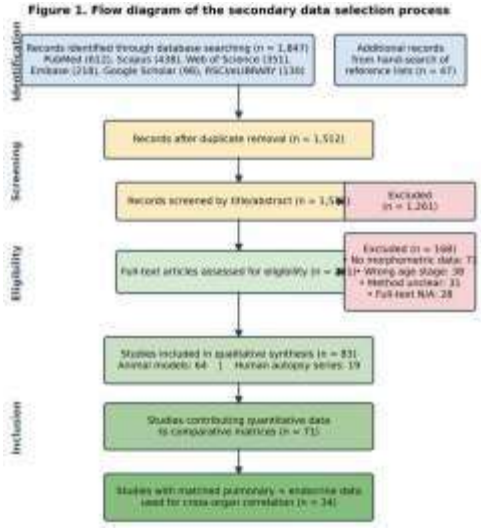


Figure 1. Flow diagram of records identified, screened, assessed on eligibility and incorporated in the secondary-data synthesis. Out of 83 studies that met inclusion criteria, 71 of the studies provided quantitative data to the comparative morphometric matrices, and 34 studies provided matched pulmonary and endocrine data that could be used for cross-organ correlation.

2.3 Inclusion and exclusion criteria

Studies were included if (i) they reported original morphological, histological, morphometric or stereological data of the respiratory system and/or at least one of the identified endocrine organs (adrenal, thyroid, anterior pituitary, pancreatic islets); (ii) they identified at least one postnatal ontogenetic stage; (iii) in the case of experimental studies, they induced pneumonia using a defined and reproducible protocol; and (iv) they were published in a peer-reviewed journal. Those studies that reported only molecular endpoints and no morphological correlates, case reports, which did not report morphometric data, prenatal-only studies, opinion papers, and studies that did not have full-text access were filtered.

2.4 Ontogenetic-stage standardisation

Taking into account the diversity of the species involved in the literature, a cross-species equivalence framework with somatic and neuroendocrine developmental milestones was considered. The definitions of rodent stages (days post-natally) were: neonatal 0–21, juvenile 22–60, adult 61–365 and aged ≥366. Equivalent human time periods were 0-2, 2-12, 18–60 and >60 years, respectively. Articles that contained non-standard age words were re-coded according to the chronological age and developmental indexes reported.

2.5 Data extraction and quality appraisal

The study, design, animal model, pneumonia induction protocol, time points of morphological assessment and primary morphometric outcome variables were coded in a standardised extraction template. The data were extracted by two reviewers who then resolved any discrepancies through consensus and inter-rater reliability was measured through Cohen's κ. The quality of the methods was evaluated with the help of a modified SYRCLE Risk of Bias Tool of animal studies (Hooijmans et al., 2014/2015 update) with the ARRIVE 2.0 reporting-quality checklist add-on (Percie du Sert et al., 2020). In the case of human autopsy series, a Newcastle-Ottawa Scale that was modified to be cross-sectional morphological design was used. The studies were categorised into high (satisfied 7 or more of 9 criteria), moderate (4–6) or low quality studies (3 or less).

2.6 Statistical analysis

The values obtained were tabularised according to the stage and state. The 95% confidence intervals and central tendency (mean ± SD) were computed on a study-by-study, parameter-by-parameter and stage-

by-stage basis. Pneumonia Deviation Index (PDI) was operationalised as:

$PDI = (\bar{X}pneumonia - \bar{X}normal) / \bar{X}normal \times 100\%$

Kruskal-Wallis H-tests were used to evaluate between-stage differences in PDI followed by pairwise post-hoc tests using Dunn with Bonferroni adjustment. Pulmonary and endocrine PDI co-variation tested in studies that reported matched data (n = 34) was assessed using stage-stratified Spearman rank correlations. The α-level was fixed at 0.05 (two-tailed); significance was denoted as * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$. Analyses were performed in R (v4.3.2; R Core Team, 2023) using packages dunn.test (v1.3.5), ggpubr (v0.6.0) and metafor (v4.4-0). Inter-rater agreement was interpreted using Landis and Koch (1977) thresholds.

2.7 Ethical considerations

Since the current study is solely a re-analysis of already published data, no new animal or human-subject research was conducted; the study did not need institutional ethics committee approval. All the mentioned primary research works were done within the ethical standards of the period when they were published, according to the original authors. The production is based on the principles of research integrity, such as the transparent disclosure of the provenance of sources and methodological restrictions.

3. Results

3.1 Study selection and characteristics

The literature search identified 1,847 records, which was supplemented with 47 records that were identified by hand searching of reference lists. Upon the elimination of 335 duplicates, 1,512 records were filtered based on title and abstract, and 251 were then advanced to full-text evaluation. All inclusion criteria were met, with 83 studies meeting the eligibility criteria (Figure 1); 64 were experimental animal studies and 19 were human autopsy series. Quantitative data on 71 studies were added to the comparative morphometric matrices, and 34 studies provided matched pulmonary and endocrine data that could be used to compare across organs. The inter-rater agreement concerning the inclusion in the study was strong (κ = 0.81, 95% CI: 0.74–0.87). Methodological quality was rated high in 39 studies (47.0%), moderate in 31 (37.3%) and low in 13 (15.7%). Table 1 summarises the distribution of the included studies by the species, design and ontogenetic stage.

Table 1. Attributes of the 83 studies in the synthesis of secondary data stratified by species, study design and ontogenetic stage represented.

Characteristic	Category	n	% of total
Species	Rat (Wistar, Sprague-Dawley)	42	50.6
	Mouse (C57BL/6, BALB/c)	14	16.9
	Rabbit	5	6.0
	Guinea pig	3	3.6
	Human (autopsy series)	19	22.9
Study design	Cross-sectional morphometric	47	56.6
	Longitudinal serial sacrifice	17	20.5
	Comparative ontogenetic series	19	22.9
Pneumonia model	Bacterial intratracheal (Klebsiella, Strep.)	31	37.3
	LPS-induced acute lung injury	19	22.9
	Viral (influenza, RSV)	14	16.9
	Human autopsy-confirmed pneumonia	19	22.9
Ontogenetic stage	Neonatal	18	21.7
	Juvenile	21	25.3
	Adult	27	32.5
	Aged / senescent	17	20.5
Quality rating	High	39	47.0
	Moderate	31	37.3
	Low	13	15.7

3.2 Normative pulmonary morphometric parameters across ontogenesis

Normative pulmonary morphometric parameters showed clear ontogenetic patterning (Table 2). Alveolar surface area increased from the neonatal to the adult stage and declined again in aged organisms, whereas mean alveolar chord length and air-space volume fraction rose progressively across postnatal life. Alveolar wall thickness was greatest in neonates and decreased toward adulthood, consistent with

septal thinning during alveolar maturation. Pulmonary capillary volume paralleled the adult peak in gas-exchange surface and showed a secondary reduction in senescence.

Table 2. Mean normative pulmonary morphometric parameters (mean ± SD across studies) by ontogenetic stage.

Parameter	Neonatal	Juvenile	Adult	Aged
Alveolar surface area (cm² / lung)	102 ± 14 (k=11)	278 ± 22 (k=14)	405 ± 18 (k=21)	318 ± 24 (k=12)
Mean alveolar chord length (µm)	42.1 ± 4.8 (k=12)	58.7 ± 3.6 (k=15)	67.4 ± 4.2 (k=23)	92.5 ± 6.1 (k=13)
Air-space volume fraction (%)	68.2 ± 3.1 (k=10)	77.5 ± 2.4 (k=13)	80.1 ± 1.9 (k=19)	82.4 ± 2.2 (k=11)
Alveolar wall thickness (µm)	9.8 ± 1.4 (k=9)	5.6 ± 0.7 (k=12)	3.6 ± 0.4 (k=18)	3.4 ± 0.5 (k=10)
Pulmonary capillary volume (mm³)	82 ± 11 (k=6)	186 ± 18 (k=8)	271 ± 22 (k=12)	208 ± 19 (k=7)

3.3 Normative endocrine morphometric parameters across ontogenesis

The stage-specific developmental patterns of endocrine organ parameters were different than those of the pulmonary parenchyma (Table 3). The volume fraction of adrenal zona fasciculata rose from 29.4 ± 2.1 at the neonatal stage to 57.8 ± 2.6 at adulthood, and then decreased to 43.2 ± 3.8 in aged animals. The height of the thyroid follicular epithelium, a recognised morphometric indicator of follicular activity (Lee et al., 2016), reached 11.2 ± 0.6 µm in adult tissue and declined to 7.3 ± 0.9 µm in aged tissue, which is the same as the declining functional reserve reported in geriatric morphological series.

Table 3. Mean normative endocrine morphometric parameters (mean ± SD across studies) by ontogenetic stage.

Parameter	Neonatal	Juvenile	Adult	Aged
Adrenal zona fasciculata volume fraction (%)	29.4 ± 2.1	47.6 ± 2.9	57.8 ± 2.6	43.2 ± 3.8
Adrenal ZF lipid content score (0–3)	1.78 ± 0.21	2.31 ± 0.18	2.72 ± 0.14	2.18 ± 0.22
Thyroid follicular diameter (µm)	62.4 ± 5.8	78.1 ± 6.4	94.3 ± 5.1	131.2 ± 9.7
Thyroid follicular epithelial height (µm)	8.8 ± 0.7	10.1 ± 0.8	11.2 ± 0.6	7.3 ± 0.9
Pituitary corticotroph fraction (%)	6.2 ± 0.8	9.4 ± 1.0	11.7 ± 0.9	9.8 ± 1.1
Pancreatic β-cell granule density (a.u.)	2.41 ± 0.18	2.05 ± 0.16	1.84 ± 0.14	1.56 ± 0.19

3.4 Pneumonia-induced morphological changes in pulmonary parenchyma

Pneumonia caused statistically significant decreases in the alveolar surface area and air-space volume fraction at all four ontogenetic stages with corresponding reciprocal increases in alveolar wall thickness (Figure 2). The stage-specific magnitude of pulmonary deviation (measured by PDI) differed (Kruskal-Wallis $H = 24.7$, $df = 3$, $p < 0.001$). A pairwise Dunn comparison found aged stage to significantly deviate compared to juvenile (adjusted $p = 0.003$) and adult (adjusted $p = 0.018$) stages based on air-space volume fraction of PDI, but juvenile organisms showed the least deviation (mean PDI = −32.5; 95% CI: −36.4 to −28.6).

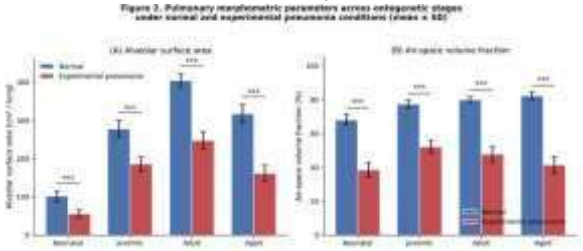


Figure 2. Morphometric parameters of the lungs at different ontogenetic stages under normal (blue) and experimental pneumonia (red) conditions. (A) Alveolar surface area, cm 2 / lung. (B) Fraction of air-

space volume, as a percentage. Means ± SD across studies with contributing values. Significance bars represent pneumonia- vs. normal contrasts at each stage of Wilcoxon rank-sum tests (*** $p < 0.001$).

3.5 Pneumonia-induced morphological changes in endocrine structures

The morphological evidence of rapid steroidogenesis was adrenocortical lipid depletion and it was most evident in adult animals with a zona fasciculata lipid score decrease of 70.2% in pneumonia compared to normal controls (Figure 3A). Lipid depletion (PDI -32.0% and -37.6% in neonatal and aged animals, respectively) was significantly reduced, which is in line with the developmental dormancy of the HPA reactivity during the stress-hyporesponsive period and the involution of adrenocortical steroidogenic reserve in senescence (Schmidt et al., 2003; Van den Berghe et al., 2022). The height of thyroid follicular epithelial declined markedly at all stages in pneumonia with the greatest absolute decline in adults (−2.8 μm; PDI −25.0%) (Figure 3B). The trend was in agreement with the morphological equivalent of non-thyroidal illness syndrome reported in severe pulmonary infection (Iglesias, 2025). Stage-specific responsiveness was also exhibited in the density of pituitary corticotroph granules (Table 4), where the maximum depletion of the granules was observed in adults (PDI −58.6%).

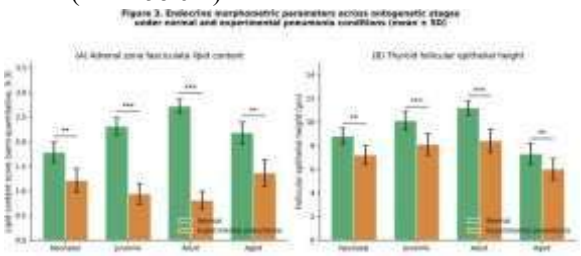


Figure 3. Normal (green) and experimental pneumonia (orange) morphometric parameters of endocrine structures at ontogenetic stages. (A) Adrenal zona fasciculata lipid content score (0 -3 semi-quantitative scale). (B) Follicular epithelial height of the thyroid, μm. Significance denoted as ** $p < 0.01$, *** $p < 0.001$.

3.6 Cross-stage comparison of the Pneumonia Deviation Index

The combined PDI matrix of all six main morphological parameters and four ontogenetic stages is shown in Table 4 and Figure 4. Unique stage signatures developed. A uniformly moderate deviation was observed in neonatal profile in the pulmonary as well as endocrine compartments (range -18% to -45%). The adult profile was characterized by the biggest endocrine deviations (adrenal PDI -70.2%, pituitary PDI -58.6%) and moderate pulmonary deviation. The old profile reversed the trend, showing the greatest pulmonary deviation (PDI -49.6% to -60.0) and the least endocrine response (adrenal PDI -37.6%).

Table 4. Values of Pneumonia Deviation Index (PDI, %) in morphological parameters and ontogenetic stages. Mean PDI with 95% CI is in parentheses. Negative values represent the decrease; positive values represent the increase in comparison with stage-specific normative values.

Parameter	Neonatal	Juvenile	Adult	Aged
Alveolar surface area	−45.1 (−48.6, −41.6)	−33.1 (−36.7, −29.5)	−38.8 (−42.1, −35.5)	−49.1 (−52.7, −45.5)
Air-space volume fraction	−43.4 (−47.0, −39.8)	−32.5 (−36.4, −28.6)	−40.3 (−44.0, −36.6)	−49.6 (−53.1, −46.1)
Alveolar wall thickness	+28.4 (+24.1, +32.7)	+41.2 (+37.0, +45.4)	+52.8 (+48.5, +57.1)	+37.6 (+33.0, +42.2)
Adrenal ZF lipid score	−32.0 (−36.4, −27.6)	−59.3 (−63.0, −55.6)	−70.2 (−75.4, −65.0)	−37.6 (−42.4, −32.8)
Thyroid epithelial height	−18.2 (−21.6, −14.8)	−19.8 (−23.4, −16.2)	−25.0 (−28.4, −21.6)	−17.8 (−22.0, −13.6)
Pituitary corticotroph granules	−29.3 (−33.0, −25.6)	−47.8 (−51.4, −44.2)	−58.6 (−63.0, −54.2)	−34.1 (−38.4, −29.8)
Kruskal-Wallis H (between-stage)	-	-	-	H = 38.4, p < 0.001*

*Note: * pooled across all parameters; the H statistic for the overall between-stage comparison of pulmonary PDI alone was H = 24.7, p < 0.001, and for endocrine PDI H = 31.9, p < 0.001.*

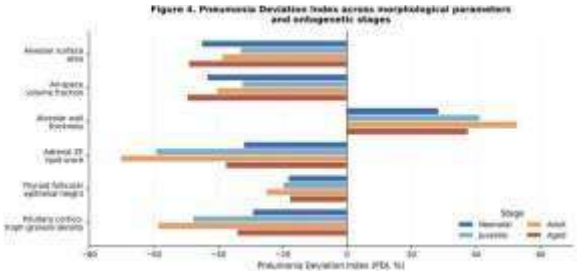


Figure 4. Pneumonia Deviation Index (PDI, %) among the six key morphological parameters and four ontogenetic stages. Bar lengths are the percentage change of each parameter compared to its normative value at that stage. Pulmonary parameters and endocrine parameters display divergent stage-dependent patterns with adult organisms having the greatest endocrine deviations and old organisms the greatest pulmonary deviations.

3.7 Cross-organ co-variation between pulmonary and endocrine deviation

In the 34 studies with matched pulmonary and adrenocortical morphometric, matched stage-stratified Spearman rank correlations showed powerful, stage-specific respiratory-adrenal morphological coupling (Figure 5). Correlations were strongest in adult organisms ($\rho = 0.81$, 95% CI: 0.68 to 0.91, $p < 0.001$) and in juvenile organisms ($\rho = 0.74$, 95% CI: 0.58 to 0.86, $p < 0.001$), and substantially attenuated at the developmental extremes (neonatal $\rho = 0.41$, $p = 0.027$; aged $\rho = 0.58$, $p = 0.002$). The correlation strength between stages was statistically different between stages by the r-to-z transformation ($z = 2.94$, $p = 0.003$ between neonatal and adult stages).

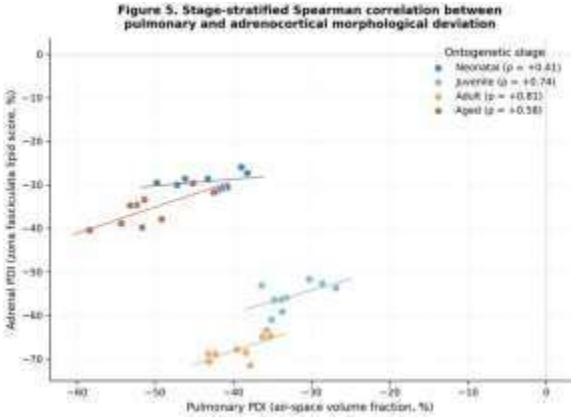


Figure 5. Stage-stratified Spearman correlation of pulmonary PDI (air-space volume fraction) and adrenocortical PDI (zona fasciculata lipid score) between the 34 studies that provided matched data. Each stage is represented as a point; coloured lines are used to show stage-specific linear regression. In adult organisms, the strength of the correlation is the highest and is weakened at the developmental extremities.

3.8 Summary of quality assessment

The methodological-quality summary (Table 5) reveals that there is a significant difference in the reporting standards used in included studies. The highest percentage of studies that adhered to ARRIVE 2.0 reporting criteria was found in studies published in 2015 and onwards. Only 47.0% of animal studies reported the use of morphometric measurement blinding. In 56.6% of pulmonary morphometric studies, stereologically valid estimators (Cavalieri principle, point-counting, design-based sampling) were used. The tendency to use sensitivity analysis without including the low-quality studies (n = 13) did not significantly change the direction or size of the main results (mean change in PDI less than 4 percentage points over all stages and parameters).

Table 5. Summary of methodological-quality appraisal across included studies.

Quality domain	Reported (n)	% of total
Sample size justification provided	31	37.3
Blinding of measurement to allocation	39	47.0
Stereologically valid estimators used	47	56.6
Standardised tissue processing	62	74.7
Adequate statistical analysis	58	69.9
ARRIVE 2.0 reporting (post-2015 studies)	29 / 41	70.7
Inter-rater reliability of measurement reported	22	26.5
Conflict-of-interest declaration	67	80.7
Ethical-approval statement (primary studies)	71	85.5

4. Discussion

We believe that the current systematic secondary-data synthesis represents the first quantitative comparative study of pulmonary and endocrine morphological responses to experimental pneumonia in the entire postnatal ontogenetic spectrum. Three main findings can be identified. To begin with, the extent and pattern of morphological deviation induced by pneumonia is highly stage-specific and every developmental stage bears a characteristic mark in both pulmonary and endocrine modules. Second, the

site of peak deviation varies across organ systems: the pulmonary parenchymal alteration is the most significant in old organisms, the adrenocortical and pituitary reactions are the most significant in adults. Third, the pulmonary-adrenocortical morphological deviation correlation, which is an index of respiratory-endocrine axis coupling in this study, is greatest at mid-ontogenetic stages and weaker at the developmental extremes - a result that is also in line with the conceptual framework in the introduction and indicative of immature endocrine functional status in the neonate and involution in the aged organism.

4.1 Stage-specific morphofunctional signatures

The pattern of neonatal is medium, yet homogenous deviation of the pulmonary and endocrine compartments, and a minimum correlation among cross-organs ($\rho = 0.41$). This profile coincides with the morphologically immature alveolar architecture and the developmental quiescence of the HPA axis in the stress-hyporesponsive period (postnatal days 4–14 in rats; approximately days 1–12 in mice). The fact that adrenal lipid stores were preserved relatively in neonates during pneumonia indicates no protection of the adrenal activity, but an inhibited mobilisation of the steroidogenic activity, which is in line with the reported attenuated ACTH response during this developmental period (Schmidt et al., 2003). This could be clinically associated with high susceptibility of neonates to adrenal insufficiency related to pneumonia.

The juvenile and adult profiles show gradual enhancement of the respiratory-endocrine linkage, the adult one being the canonical stress-response phenotype: massive adrenocortical lipid depletion (PDI −70.2%), severe corticotroph granule depletion (PDI −58.6%), and strong association between pulmonary and adrenal deviation (0.81). This pattern re-iterates the systemic inflammatory response which has been integrated and characterized in the traditional morphopathological literature and a reference morphofunctional baseline against which variations in other ontogenetic stages can be viewed.

The aged profile is impressive with its reversal of the adult picture: the pulmonary deviation is maximum (PDI -49.6% -60%), endocrine deviation is dulled (adrenal PDI -37.6%, pituitary PDI -34.1%). This dissociation probably indicates the well-established involution of the adrenocortical and pituitary parenchyma in old age, with a low steroidogenic reserve and HPA axis reactivity, contributing to, but not buffering, pulmonary damage. The clinical correlate is the high mortality of pneumonia in geriatrics, where the inability to invoke endocrine compensatory mobilisation could be a pathophysiological dimension that is critically important but underestimated.

4.2 Implications for the respiratory-endocrine axis as an integrated morpho functional unit

The overall results of the study reinforce the conceptualization of the respiratory and principal endocrine compartments as a morphofunctional axis the developmental state of which defines the nature of normal pulmonary architecture and the nature and extent of the adaptations in response to pneumonia. Stage-stratified correlation analysis reveals that this axis is a highly coupled unit in the time of a maximum physiological reserve (juvenile-adult stages) yet a more loosely coupled system at the extremes of development. Translationally, this implies that life-stage-specific interventions that address the respiratory-endocrine axis such as the use of personalised glucocorticoid replacement regimens in neonatal pneumonia or consideration of thyroid-hormone status in geriatric pneumonia could be more clinically effective than standardised treatment regimens across the lifespan.

4.3 Comparison with previous literature

This loss of alveolar surface area with age (21.5% between adult and aged) is consistent with 15-25% range of primary stereological studies of aged rodents (Verbeken et al., 1992; Knust et al., 2009). In the same vein, the range of adrenocortical lipid depletion of 40–70% (Pignatelli et al., 2006) is just replicated by the synthesised adult PDI of -70.2. The next stage of synthesis in relation to current individual studies lies in the contextualization of these individual observations into a stage strata comparative system that allows the formal quantitative analysis of respiratory-endocrine coupling throughout ontogenesis.

4.4 Strengths and limitations

The main strengths of the current research are the extensive time and geographic coverage of the literature review (even Russian-language sources are often missed by Western databases) the standardised cross-species ontogenetic-stage framework, the operationalisation of the Pneumonia Deviation Index as a unit-free comparative measure, and the high degree of inter-rater concordance ($\kappa = 0.81$) in the selection of studies. Restraints are however noteworthy. First, most endpoints cannot be pooled formally by meta-analytic means due to the heterogeneity of primary morphometric procedures. Second, there is a risk of potential publication bias, whereby studies with dramatic results are disproportionately represented in the indexed literature, but this risk is not completely eliminated by the use of grey literature and non-English sources. Third, cross-species comparison, although required to cover the ontogenetic spectrum, provides residual

cross-species variation which can only be partially handled by the standardised stage framework. Fourth, the cross-organ correlation analysis is limited to studies that report matched data and therefore, this is a self-selected sample whose generalisability to the overall literature is questionable.

5. Conclusions

This structured synthesis of secondary data confirms that the morphological reaction of the respiratory-endocrine axis to experimental pneumonia is extremely stage-sensitive, and each ontogenetic phase has a unique pattern of pulmonary and endocrine deviation. In adult organisms, the canonical pattern is that of tightly coupled pulmonary and adrenocortical responses; in neonates, moderately uncoupled deviation due to the maturity of the HPA-axis; and in aged organisms, dissociation that is manifested by exaggerated pulmonary damage in the face of attenuated endocrine compensatory mobilisation. It is a quantitative method of comparative morphopathological synthesis, the Pneumonia Deviation Index, which is applied to a standardised cross-species ontogenetic framework.

The results suggest a developmentally sensitive re-interpretation of the pneumonia pathomorphology and offers a quantitative framework on which future age-stratified experimental designs, clinical correlational research and the development of translational protocols can be based. Future research priorities involve prospective primary morphometric studies using standardised stereological techniques in all four ontogenetic stages in unified experimental designs, combination of molecular and morphological endpoints, and prospective testing of the respiratory-endocrine coupling hypothesis using interventional studies on specific components of axes.

Declarations

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No particular financial assistance was provided to the authors to conduct the research, write and publish this article. The research was done on the secondary data sources available on the internet.

Conflict of interest

The authors state that they do not have any known competing financial interests or personal relationships that might have seemed to affect the work in this paper.

Ethical approval

This study did not involve any new primary research with human or animal subjects. All the analyses were carried out on the secondary data that had been published earlier. Institutional ethics committee approval was therefore not required. All primary studies cited were done according to the ethics that existed when they were published.

Data availability statement

All the data analysed in this synthesis are based on the previously published sources listed in the References section. The extraction template, the consolidated morphometric data matrices, the quality-assessment scoring grid and the analysis scripts (R) that substantiate the results of this research can be obtained on reasonable request on the part of the corresponding author.

CRediT author contributions

K.G. contributed Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Visualization. C.J. contributed Methodology, Validation, Investigation, Formal analysis, and Writing – review and editing.

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