



UNIVERSIDADE ESTADUAL PAULISTA “JÚLIO
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MEDICINA

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**Global Patterns in Paediatric Anaesthesia-Related Mortality:
Systematic Review and Meta-Analysis**

Tese apresentada ao Programa de Pós-Graduação em Anestesiologia da Faculdade de Medicina da Universidade Estadual Paulista "Júlio de Mesquita Filho" (UNESP), Câmpus de Botucatu, como parte dos requisitos para a obtenção do título de Doutora em Anestesiologia.

Orientador: Prof. Associado Leandro Gobbo Braz

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C828g	Cortez, Williany Dark Silva Serafim Global Patterns in Paediatric Anaesthesia-Related Mortality: Systematic Review and Meta-Analysis / Williany Dark Silva Serafim Cortez. -- Botucatu, 2026 84 f. : il., tabs. Tese (doutorado) - Universidade Estadual Paulista (UNESP), Faculdade de Medicina, Botucatu Orientador: Leandro Gobbo Braz 1. Child. 2. Anesthesia. 3. Mortality. 4. Global Health. I. Título.
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Botucatu, 31 de julho de 2026

Ao meu marido,

Existem pessoas que celebram as conquistas quando elas acontecem. Você fez muito mais do que isso: esteve presente em cada dia que tornou esta conquista possível.

Nunca caminhei sozinha. Quando a dúvida parecia maior que a coragem, encontrei em você um olhar tranquilo, uma palavra serena, um abraço que dizia, sem precisar de voz, que eu conseguiria continuar.

Compreendeu minhas ausências, acolheu minhas inseguranças, respeitou meus silêncios, comemorou cada pequena vitória e permaneceu ao meu lado até mesmo quando eu já não conseguia enxergar a linha de chegada.

Há um tipo de amor que se declara em palavras. O seu sempre se revelou em atitudes.

Se hoje concluo este doutorado, é porque encontrei em você muito mais do que um companheiro. Encontrei meu porto seguro, meu lugar de paz.

Você foi o meu refúgio em todas as horas.

Esta conquista é nossa.

Com todo o amor que cabe em mim, e com uma gratidão que nenhuma palavra será capaz de traduzir, dedico este trabalho a você.

A Deus,

Por ter sustentado meu coração nos dias difíceis, iluminado meus caminhos nas incertezas e permitido que eu chegasse até aqui cercada de amor, cuidado e propósito.

E, com todo o amor que existe em mim, aos meus pais e ao meu irmão,
meu lugar de afeto, verdadeiras bênçãos em minha vida.

Nada nesta trajetória teria sentido sem o amor imenso, silencioso e constante que
sempre recebi de vocês.

Cada conquista carrega um pedaço do cuidado, da renúncia, das orações e da ternura
que dedicaram a mim ao longo da vida.

A vocês, todo o meu amor, minha eterna gratidão

Ao Professor Leandro,

Quando concluí o mestrado, eu ainda não sabia quais seriam os próximos capítulos da minha história. Foi então que encontrei no senhor o respeito de um grande profissional, a inteligência de um professor admirável e o abraço acolhedor de um amigo.

Ao aceitar orientar-me neste doutorado, o senhor fez mais do que abrir uma porta: deu um novo sentido ao caminho que eu desejava seguir. Naquele instante, senti-me profundamente abençoada.

Sempre que leio *Sou feita de retalhos*, de Cris Pizzimenti, lembro-me de que somos construídos pelos encontros que a vida nos oferece. Hoje sei que um dos retalhos mais preciosos da minha trajetória acadêmica nasceu quando o senhor acreditou em mim e decidiu caminhar ao meu lado.

Obrigada por compartilhar seu conhecimento com generosidade, por me ensinar com excelência e, sobretudo, por mostrar que a grandeza de um professor também se revela na forma como acolhe seus alunos.

Minha eterna gratidão.

Agradecimentos

Ao Prof. Emérito Dr. José Reinaldo Cerqueira Braz, por sua generosidade em dividir seu conhecimento e experiência, sempre nos incentivando a buscar o melhor em cada trabalho e a acreditar que a excelência é construída com dedicação e partilha.

À Prof.^a Titular Norma Suely Pinheiro Módolo, docente do Departamento de Especialidades Cirúrgicas e Anestesiologia e ex-coordenadora do Programa de Pós-graduação em Anestesiologia, pelo ensino, carinho e dedicação, e por todo o aprendizado que me foi proporcionado.

Ao Prof. Titular Paulo do Nascimento Junior, docente do Departamento de Especialidades Cirúrgicas e Anestesiologia e atual coordenador do Programa de Pós-graduação em Anestesiologia, pelo ensino e dedicação para garantir a excelência da Residência Médica em Anestesiologia e da Pós-graduação.

Aos docentes do Departamento de Especialidades Cirúrgicas e Anestesiologia da Faculdade de Medicina de Botucatu, que não apenas ensinaram, mas também acolheram, inspiraram e aconselharam com generosidade.

À Joana Jacirene Costa Teixeira, secretária da Divisão de Anestesiologia da Faculdade de Medicina de Botucatu, UNESP, por sempre estar presente, pelo carinho, comprometimento e generosidade.

Ao André Renato Passaroni, funcionário do serviço de computação da Divisão de Anestesiologia da Faculdade de Medicina de Botucatu, UNESP, cujos serviços são imprescindíveis para a pesquisa clínica deste departamento.

À Ligia Stefani Tomazelli, supervisora da Secção Técnica de Pós-Graduação em Anestesiologia da Faculdade de Medicina de Botucatu - UNESP, pela disponibilidade em ajudar e orientar sobre toda a regulamentação, etapas da Pós-Graduação, além do olhar necessário em todos os momentos.

À Márcia Fonseca Piagentini Cruz, Secretária do Programa de Pós-Graduação em Anestesiologia Faculdade de Medicina de Botucatu - UNESP, pela disponibilidade e orientação com prazos, em todos os momentos que precisei, além da condução afetuosa em todas as etapas.

À Dra. Marluci Betini, bibliotecária da Universidade Estadual Paulista – UNESP, que com seu amplo conhecimento e experiência nos auxiliou na pesquisa, sendo uma colaboradora fundamental para o trabalho.

Ao Prof. Associado José E. Corrente, sempre doando seu conhecimento e experiência para que os trabalhos sejam excepcionais.

À Ketillyn Nayara de Macedo Silveira, meu agradecimento mais sensível. Sua presença constante e suas palavras de sabedoria e incentivo foram fundamentais nesta jornada. Pelos momentos dedicados ao aprendizado mútuo, pelos ensaios para cada apresentação, e pela amizade que torna cada desafio mais leve: muito obrigada. Esta conquista também pertence a você.

“O Senhor guarda os pequeninos.”

— Salmo 116:6^a

Abstract

Background: Infants face a substantially higher perioperative mortality risk than older children and adults. Anaesthesia safety is closely linked to a country's Human Development Index (HDI). This review examined global trends in paediatric anaesthesia-related mortality rates (ARMRs), stratified by HDI, age group, and time period.

Methods: We searched electronic databases for studies reporting early-onset (24-hour postoperatively) and short-term (30-day postoperatively or in-hospital) ARMRs (per 10,000 anaesthetics). Outcomes were analysed by HDI category (HDI <0.800 vs HDI $\geq$ 0.800), time period (pre-2001 vs 2001-2025), and age (overall paediatric population, <1 year vs $\geq$ 1 year) using systematic review, meta-regression, and meta-analysis.

Results: Forty-four studies (6,217,524 anaesthetics) reported 232 early-onset and 67 short-term deaths. Both ARMRs were inversely correlated with HDI ($P=0.0087$ and $P=0.033$, respectively) but not with time ($P=0.25$ and $P=0.34$, respectively). In HDI $\geq$ 0.800 countries, early-onset ARMRs remained stable across periods (0.77 vs 0.36; $P=0.067$), whereas in HDI <0.800 countries they increased (0.43 vs 3.44; $P<0.0001$). During 2001-2025, early-onset and short-term ARMRs were higher in HDI <0.800 than in HDI $\geq$ 0.800 settings (3.44 vs 0.36; $P=0.0001$ and 4.35 vs 0.42; $P=0.0047$, respectively). Both ARMRs were consistently higher in infants <1 year compared with older children in HDI $\geq$ 0.800 (adjusted odds ratio (aOR) 11.58 and aOR 8.02, respectively; both $P<0.0001$) and HDI <0.800 countries (aOR 4.59 and aOR 5.29, respectively; both $P<0.0001$) across 2001-2025.

Conclusions: Over six decades, paediatric ARMRs have remained consistently low and stable in HDI $\geq$ 0.800 countries but increased substantially in HDI <0.800 settings, with infants under one year consistently at greatest risk across both HDI levels.

Keywords: children; developed countries; developing countries; mortality; systematic review

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1. INTRODUCTION

Peri-operative mortality depends not only on patient-specific factors (e.g., underlying disease) but also on process-related aspects such as anaesthesia and surgical management. A pioneering study by Rackow and colleagues¹ reported markedly different anaesthesia-related mortality rates (ARMRs) in children according to postnatal age: 11.6 per 10,000 anaesthetics in infants younger than one year old, 3.6 per 10,000 in older children, and 4.6 per 10,000 across the overall paediatric population.

Since then, advances in anaesthesia and surgical safety—technological, pharmaceutical, and infrastructural—have reduced risks, though implementation varies widely by country. This disparity is strongly influenced by the Human Development Index (HDI),² ranging from 0 to 1, representing the lowest and highest levels of development. HDI ≥ 0.800 countries adopted safety measures from the late 20th century onwards, whereas HDI < 0.800 countries continue to face limited implementation.^{3,4}

The association between HDI and anaesthesia safety has been demonstrated across age groups⁵⁻⁷ and specifically in children.^{8,9} A systematic review⁸ comparing pre-2001 with 2001-2022 data found anaesthesia-related cardiac arrest rates inversely related to HDI, with no overall temporal improvement. Differences between countries with HDI ≥ 0.800 and those with HDI < 0.800 became more pronounced in the later period, and rates were consistently higher in infants under one year than in older children. The implications of these findings for ARMAR remain unclear, particularly when stratified by age, HDI, and time period. Rare adverse events such as anaesthesia-related mortality (ARM) are difficult to study, as they occur unpredictably and too infrequently within single institutions to yield robust data. Large-scale analyses of global studies are therefore essential to clarify ARMAR patterns across diverse settings.

We hypothesised that ARMARs in children vary according to HDI, postnatal age, and time period. To examine this, we undertook a systematic review and meta-analysis of global studies reporting early-onset and short-term ARMARs, defined as occurring within 24 hours postoperatively and within 30 days postoperatively or in-hospital, respectively. Data were analysed for the overall paediatric population, and with specific comparisons between infants younger than one year and older children across two time periods (pre-2001 vs 2001-2025) and by country HDI (HDI ≥ 0.800 vs HDI < 0.800).

2. METHODS

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist¹⁰ and the Joanna Briggs Institute's (JBI) critical appraisal checklist for studies reporting prevalence data.¹¹ The review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD420251119505).

2.1 Outcomes

2.1.1 Primary Outcomes

The primary outcomes were early-onset ARM, defined as ARM events occurring within 24 hours postoperatively, and short-term ARM, defined as ARM events occurring within 30 days postoperatively or during hospitalisation (in-hospital). Because most studies reporting intra-operative ARMs also included deaths in the Post-Anaesthesia Care Unit (PACU) without clearly defined time frames, early-onset ARM was assumed to encompass these deaths. Outcomes were based on available data from included studies, following surgery or procedures performed under anaesthesia in either operating theatre settings or non-theatre settings.

ARM events were categorised as entirely and partially-related. The “entirely ARM” subgroup included events exclusively attributed to anaesthesia personnel or the anaesthetic process (e.g., ventilatory depression with hypoxaemia, cardiac arrest, and death following intravenous opioid injection in a stable child without comorbidities). The “partially ARM” subgroup included events where anaesthesia personnel or the anaesthetic process contributed, but other factors related to the underlying disease or surgical complications also played a role (e.g., cardiac arrest and death immediately after induction of anaesthesia in a hypovolaemic child). ARM events were classified according to the authors of the included studies. Since most included studies did not distinguish between entirely and partially ARM, both categories were aggregated for analysis.

2.1.2 Secondary Outcomes

Secondary outcomes included aetiology of the ARM events: respiratory-related, cardiocirculatory-related, or medication-related, stratified by country HDI and time period (pre-2001 vs 2001-2025), as well as ARMs by American Society of Anaesthesiologists physical status (ASA-PS) ≥ 3 , stratified by HDI in 2001-2025.

2.1.3 Eligibility criteria

We included observational studies that adhered to the ‘Participants-Exposure of interest-Outcomes’ (PEO) framework:¹² Participants: children; Exposure of interest: anaesthetic procedures; Outcome: peri-operative ARM.

Studies were eligible if they were available as full-text articles, had an observational design (including population-based or database studies), reported ARMRs in a mixed paediatric population encompassing all types of surgery, anaesthesia, and procedures performed under sedation or anaesthesia, and provided sufficient information to allow outcome calculation according to postnatal age groups.

No minimum sample size was imposed to avoid excluding studies from smaller centres with lower paediatric surgical volumes. Age limits of the paediatric population were defined according to the authors’ classification. Where multiple studies reported data from the same population sample during the study period, only the most recent and/or more complete study was included.

Studies were excluded if they were published solely in abstract form or remained unpublished; if they focused on selective populations such as patients with specific conditions (e.g., cardiac disease), or restricted ASA-PS classifications (e.g., ASA-PS 1); if they were confined to particular surgical interventions such as cardiac or emergency procedures; if they were limited to specific anaesthesia techniques, such as regional anaesthetic blocks; or if they lacked sufficient information to allow outcome calculation.

Exclusions were documented and presented in the PRISMA flow diagram.

2.1.4 Literature search strategy

A comprehensive search strategy was developed by a research librarian in cooperation with two authors. We systematically searched for studies reporting peri-operative and/or anaesthesia-related cardiac arrest or mortality rates from inception up to June 30, 2025 across PubMed, Scopus, Embase, LILACS, and Web of Science Core Collection. Search strategies incorporated thesaurus terms (MeSH and Emtree) and keywords, including variants of ‘an(a)esthesia’, ‘cardiac arrest’ and ‘mortality’ supplemented by synonyms. Strategies were adapted for each database (see Supplementary Methods). No restrictions were applied regarding language, year of publication, or study/population. Duplicate records were removed using EndNote (X9.2/2019 version; Clarivate Analytics, Philadelphia, PA, USA) by an experienced information specialist.

2.1.5 Study selection process

Two researchers independently screened titles, abstracts, and full-texts articles, applying eligibility criteria in a stepwise manner. Disagreements were resolved by a third author. Translation services were used when necessary.

2.1.6 Data extraction

Data were extracted independently by two reviewers using standardized forms (Supplementary Table 1). Discrepancies were resolved with input from a third reviewer.

2.1.7 Assessment of study quality

Methodological quality of included studies was assessed independently by two reviewers using the JBI Prevalence Critical Appraisal Tool,¹¹ which evaluates nine domains: target population, sampling, sample size, participants and setting description, coverage, outcome identification, measurement reliability, statistical analysis, and response rate. The overall methodological quality was categorised arbitrarily as good (equal to or more than seven 'yes' answers), fair (five or six 'yes' answers), or poor (< 5 'yes' answers). A minimum score of ≥ 5 was required for study inclusion. Disagreements were resolved by discussion or adjudication by a third author.

2.1.8 Allocation of Human Development Index

Countries were categorised according to the HDI established by the United Nations Development Programme.² As HDI values vary over time and studies often report data for specific periods, the mean HDI for each study was calculated by averaging the values from its first and last years;^{5,6,8} if HDI was unavailable, the closest year's value was used. For multicentre studies, HDI was determined by averaging across participating countries.

2.1.9 Allocation of the study period

The study period was divided into two intervals: pre-2001 and 2001-2025. This division reflects the gradual adoption of major advancements in anaesthesia and surgical safety, including monitoring technologies including oxygenation, carbon dioxide, anaesthetic gases, and haemodynamic monitoring; intra-operative warming devices, supraglottic airway devices, ultrasound-guided blocks, new agents (sevoflurane, propofol, dexmedetomidine, remifentanyl, ropivacaine), improved anaesthesia and surgery safety protocols, and expanded paediatric surgical and ICU capacity. Thus, the 2001-2025 period provides a contemporary perspective on

ARMR literature. Studies were allocated to these periods based on their median patient recruitment interval.^{5,6,8}

2.2 Statistical analyses

Analyses were conducted in three steps:

2.2.1. Descriptive statistics

Numbers and proportions were used to characterise studies: investigator, publication year, data source, recruitment period, country, design, study period, median year of the recruitment, demographics and procedures, such as average HDI, number of anaesthetic procedures, and age groups (< 1 year, $\geq$ 1 year, and the all overall paediatric population), mortality outcomes, including time period of ARM occurrence (within 24 hours postoperatively and/or within 30 postoperative days or in-hospital), peri-operative ARMs by age groups and ASA-PS score, aetiology of the ARM events (respiratory-related, cardiocirculatory-related, or medication-related), and excluded or non-included surgeries.

2.2.2. Meta-regression analysis

A random-effects model with restricted maximum likelihood estimation was applied, using observed log-odds ratios to assess associations between ARMRs, HDI, and time, all treated as continuous variables. Regression models and bubble plots were weighted by the standard error of the log-odds. Meta-regression analyses were conducted only when ten or more studies were available. All analyses were performed in SAS for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as $P < 0.05$, with 95% confidence intervals (CIs).

2.2.3 Proportional meta-analysis

Weighted event rates and proportions were calculated using random-effects models.¹³ Variances were stabilised with the inverse double arcsine square root method¹⁴ Analyses were performed in StatsDirect® software (StatsDirect Ltd., Altrincham, Cheshire, UK).

2.2.3.1 Subgroup analyses

Subgroup analyses examined ARMRs by HDI level, provided at least two studies reported data for a given outcome. Aggregate ARMRs (per 10,000 anaesthetic procedures) were subdivided by time period (pre-2001 *vs* 2001-2025) and HDI level (HDI <0.800 *vs* HDI $\geq$ 0.800), stratified by age (<1 year, $\geq$ 1 year, and the overall paediatric population), ASA-PS,

and event aetiology. Differences in effect sizes were tested using adjusted logistic regression with binomial distribution and overdispersion correction.¹⁵ Results were expressed as adjusted odds ratios (aORs) with 95% CIs, with $P < 0.05$ considered statistically significant.

Finally, ARMRs were analysed by quartiles (median, 25%, and 75%) to detect potential regional differences (geographic subgroup analysis).

2.2.3.2 Sensitivity analyses

Sensitivity analyses tested the robustness of the findings by comparing ARMRs across HDI quartiles and excluding outlier studies. These adjusted analyses were pooled to provide the most conservative estimates.

2.2.3.2 Publication bias and heterogeneity

Publication bias was assessed with Egger's test.¹⁶ Heterogeneity was evaluated using visual inspection of forest plots, non-parametric Cochran's Q test, with significance set at a $P \leq 0.1$, and I^2 statistic,¹⁷ where values greater than 40% indicate substantial heterogeneity.¹⁸ All analyses were performed in SAS for Windows v.9.4.

3. RESULTS

3.1 Description of the included studies

The search strategy identified 82,866 citations. After removing 52,216 duplicates and excluding 30,336 irrelevant studies, 314 full-text articles were retrieved for detailed evaluation. Of these, 54 studies met the predefined inclusion criteria; 10 studies were excluded after quality assessment (Supplementary Table 2), leaving 44 studies for analysis (Fig. 1).

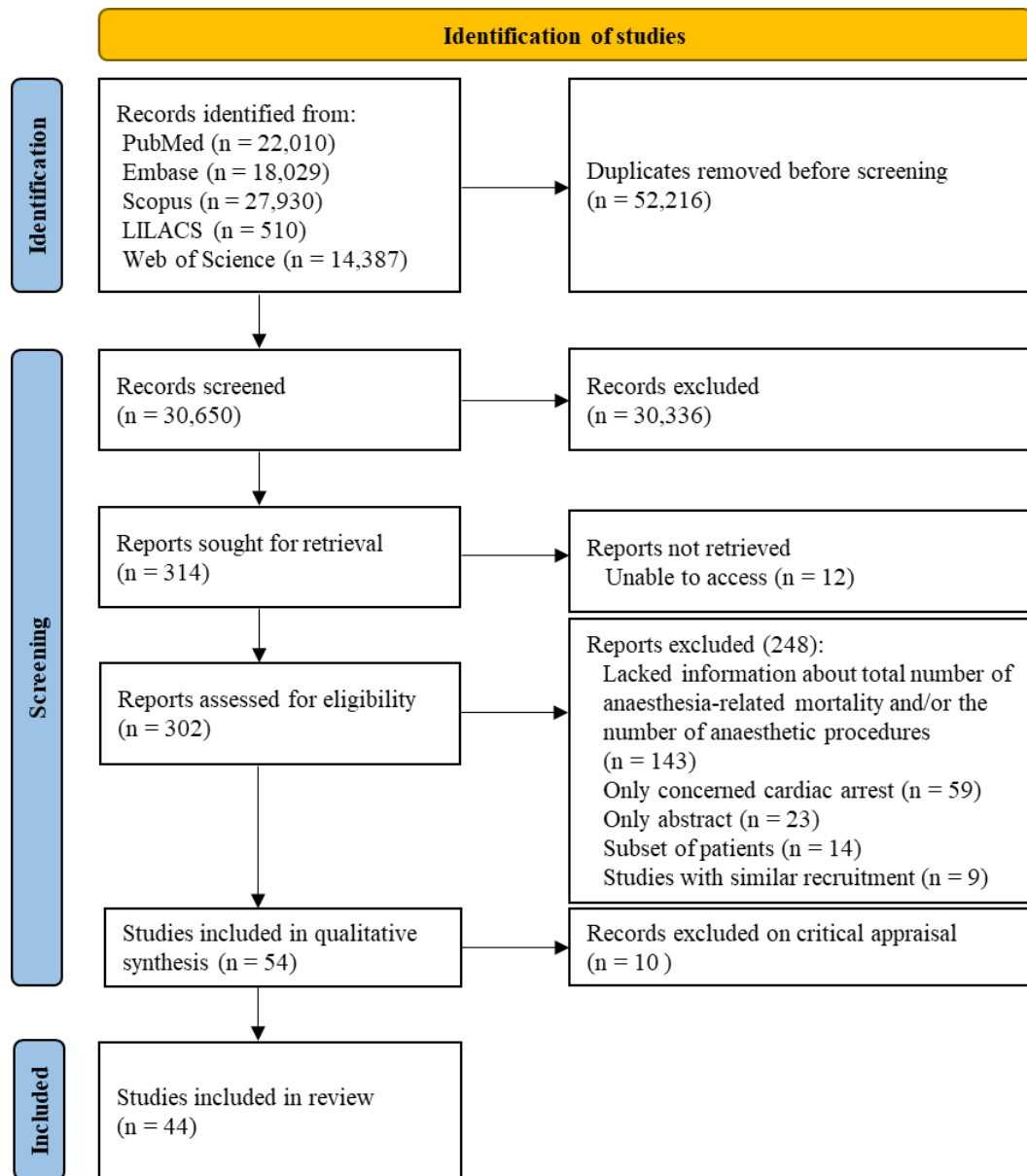


Fig 1. PRISMA flow diagram of the study identification, screening, and inclusion process.

The earliest study included was published in 1961,¹ and the most recent in 2025.¹⁹ Together, the 44 studies encompassed 6,217,524 anaesthetic procedures performed in children across five continents (America, Europe, Asia, Africa, and Oceania). In the overall paediatric population, early-onset ARM Rs were documented in 43 (97.7%) studies, whereas short-term ARM Rs were documented in 15 (34.1%) studies; one study reported only short-term outcomes and therefore did not contribute to the early-onset analysis. Age-stratified analyses (<1 year, ≥ 1 year) indicated that early-onset ARM Rs were reported in 26 (59.1%) studies, while short-term ARM Rs were reported in 12 (27.3%) studies. Overall, 232 ARM s occurred within 24 hours postoperatively (early-onset ARM Rs) and 67 within 30 days postoperatively or in-hospital (short-term ARM Rs). The dataset comprised 18 prospective studies (40.9%; n=4,821,341) and 26 retrospective studies (59.1%; n=1,358,191). Thirty-three studies (75%) were single-centre (n=1,456,383), and 11 (25%) were multicentre (n=4,761,141). Fourteen studies reported early-onset ARM Rs prior to 2001 (12 HDI ≥ 0.800 and 2 HDI < 0.800), whereas 29 studies reported early-onset ARM Rs between 2001 and 2025 (18 HDI ≥ 0.800 and 11 HDI < 0.800). Study characteristics are reported in Supplementary Table 3.

3.1.1 Meta-regression analyses

Meta-regression analyses in the overall paediatric population indicated inverse correlations between early-onset ($P=0.0087$; Fig. 2A) and short-term ARM Rs ($P=0.033$; Supplementary Fig. 1) with HDI, whereas no significant correlations with time were observed ($P=0.25$; Supplementary Fig. 2 and $P=0.34$; Supplementary Fig. 3, respectively).

HDI-stratified analyses showed no significant correlation between early-onset ARM R and time in HDI ≥ 0.800 countries ($P = 0.0727$; Fig. 2B), but a significant increase over time in HDI < 0.800 countries ($P = 0.0082$; Fig. 2C).

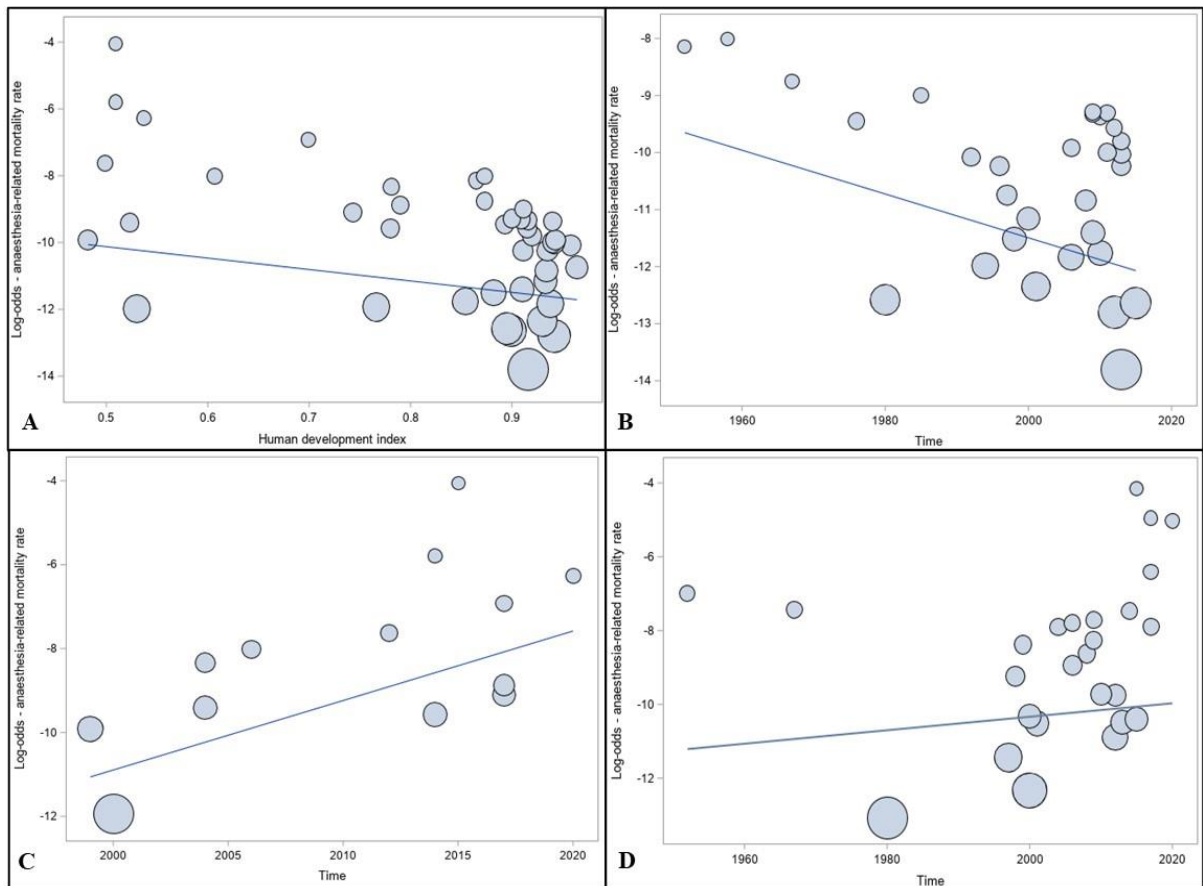


Fig 2. A. Meta-regression of early-onset anaesthesia-related mortality rates by country Human Development Index (HDI) (slope: -6.65, 95% CI -11.39 to -1.92; $P=0.0087$); B. Meta-regression of early-onset anaesthesia-related mortality rates by time in $HDI \geq 0.800$ (slope: -0.038, 95% CI -0.08 to 0.002; $P=0.0727$); C. Meta-regression of early-onset anaesthesia-related mortality rates by time in $HDI < 0.800$ countries (slope: 0.166, 95% CI 0.065 to 0.266; $P=0.0082$); D. Meta-regression of early-onset anaesthesia-related mortality rates of children younger than one year by time (slope: 0.070, 95% CI 0.022 to 0.119; $P=0.0091$).

Age-stratified analyses showed a significant increase over time in early-onset ARMOR unadjusted for HDI among children <1 year ($P=0.0091$; Fig. 2D), whereas no significant correlation among children ≥ 1 year ($P=0.48$; Supplementary Fig. 4). Meta-regression analyses indicated an inverse correlation between early-onset ARMOR among children <1 year with HDI ($P=0.022$; Supplementary Fig. 5), but no significant correlation among children ≥ 1 year ($P=0.083$; Supplementary Fig. 6).

Age-stratified analyses found no significant correlations by HDI or over time in short-term ARMOR among children <1 year ($P=0.55$, Supplementary Fig. 7; $P=0.33$, Supplementary Fig. 8). Among children ≥ 1 year, there was an inverse correlation between short-term ARMOR and HDI ($P=0.024$, Supplementary Fig. 9), but not with time ($P=0.88$, Supplementary Fig. 10).

3.1.2 Proportional meta-analysis

3.1.2.1 Early-onset ARMOR

Across all postnatal age groups and unadjusted for HDI, early-onset ARMORs did not differ significantly between the two study periods ($P=0.89$). After adjustment for HDI, rates increased significantly in HDI <0.800 countries ($P<0.0001$) but remained stable in HDI ≥ 0.800 countries ($P=0.067$). Prior to 2001, these rates did not differ between HDI ≥ 0.800 and HDI <0.800 countries ($P=0.49$). However, between 2001-2025, early-onset ARMORs were significantly higher in HDI <0.800 compared with HDI ≥ 0.800 countries ($P=0.0001$; Table 1). Forest plots are provided in the Supplementary Figures 11-12.

3.1.2.2 Short-term ARMOR

Meta-analysis was not feasible for the pre-2001 period due to insufficient studies. Across 2001-2025, short-term ARMORs adjusted for HDI were significantly higher in HDI <0.800 compared with HDI ≥ 0.800 countries ($P=0.0047$) (Table 1). Forest plots summarising the data are provided in the Supplementary Figures 13-14.

Table 1. Proportional meta-analysis of early-onset and short-term anaesthesia-related mortality rates (per 10,000 anaesthetic procedures) stratified by time period and country Human Development Index status in children

	Studies n	Events n	Children n	Proportional meta-analysis (95% CI)	P value for subgroup			
					Per time period*	HDI ≥0.800 vs. HDI <0.800	HDI <0.800 per time period*	HDI ≥0.800 per time period*
Early-onset anaesthesia-related mortality rates								
Pre-2001	14	119	1,951,702	0.72 (0.29-1.34)	0.89			
HDI <0.800	2	1	35,469	0.43 (0.02-1.39)		0.49	<0.0001	
HDI ≥0.800	12	118	1,916,233	0.77 (0.29-1.48)				0.067
2001-2025	29	113	4,257,497	0.69 (0.41-1.04)				
HDI <0.800	11	38	183,504	3.44 (1.57-6.05)		0.0001		
HDI ≥0.800	18	75	4,073,993	0.36 (0.18-0.60)				
Short-term anaesthesia-related mortality rates								
2001-2025	14	55	915,129	0.92 (0.45-1.56)				
HDI <0.800	6	24	86,488	4.35 (1.60-8.44)		0.0047		
HDI ≥0.800	8	31	828,641	0.42 (0.19-0.74)				

CI = confidence interval; vs = versus; HDI = Human Development Index; *Pre-2001 versus 2001-2025

3.1.2.3 Early-onset and short-term ARMORs by age group

Proportional meta-analysis and adjusted odds ratios (aORs) consistently showed higher early-onset ARMORs in children <1 year compared with ≥ 1 year, across both HDI strata and time periods (Table 2; Supplementary Table 4).

Due to the insufficient number of studies, it was not possible to perform a meta-analysis for the pre-2001 period of short-term ARMRs. For 2001–2025, odds of short-term ARMRs were significantly higher in children <1 year compared with ≥ 1 year, regardless of HDI, and across both HDI ≥ 0.800 and HDI <0.800 countries (Table 2; Supplementary Table 4). Forest plots are provided in the Supplementary Figures (Supplementary Figs. 15-20).

Table 2. Proportional meta-analysis of early-onset and short-term anaesthesia-related mortality rates (ARMRs) (per 10,000 anaesthetic procedures) by age group, period and Human Development Index

	Proportional meta-analysis (95% CI)	Odds ratio (95% CI)	P value
Early-onset ARMRs			
Pre-2001			
< 1 year	1.41 (0.20-3.70)	2.96 (2.28 – 3.84)	<0.0001
≥ 1 year	0.30 (0.08-0.66)	Ref	
2001-2025			
< 1 year	3.22 (1.64-5.33)	7.71 (6.11 -9.73)	<0.0001
≥ 1 year	0.49 (0.17-0.98)	Ref	
HDI ≥ 0.800 Pre-2001			
< 1 year	1.33 (0.08-4.06)	2.62 (1.99-3.45)	<0.0001
≥ 1 year	0.34 (0.07-0.81)	Ref	
HDI ≥ 0.800 2001-2025			
< 1 year	1.93 (1.02-3.13)	11.58 (8.32-16.11)	<0.0001
≥ 1 year	0.18 (0.05-0.38)	Ref	
HDI <0.800 Pre-2001			
< 1 year	2.09 (0.10-6.66)	22.16 (4.02-122.17)	0.0004
≥ 1 year	0.18 (0.03-1.01)	Ref	
HDI <0.800 2001-2025			
< 1 year	8.88 (3.26-17.27)	4.59 (3.26-6.47)	<0.0001
≥ 1 year	1.88 (0.41-4.43)	Ref	
Short-term ARMRs			
2001-2025			
< 1 year	4.82 (1.92-9.03)	6.97 (5.82-8.34)	<0.0001
≥ 1 year	0.60 (0.14-1.37)	Ref	
HDI ≥ 0.800 2001-2025			
< 1 year	2.47 (1.18-4.24)	8.84 (6.94-11.25)	<0.0001
≥ 1 year	0.23 (0.09-0.75)	Ref	
HDI <0.800 2001-2025			
< 1 year	14.82 (3.76-33.17)	5.29 (4.01-6.99)	<0.0001
≥ 1 year	1.78 (0.30-4.51)	Ref	

HDI: Human Development Index

3.1.2.4 Comparison of early-onset vs short-term ARMs in the overall paediatric population (2001-2025)

In the studies reporting both early-onset and short-term ARMRs, unadjusted rates did not differ significantly (aOR 1.50; 95% CI 0.99-2.36; $P=0.052$). After HDI adjustment, differences remained non-significant in both HDI ≥ 0.800 countries (aOR 1.48; 95% CI 0.85-

2.57; $P=0.165$) and $HDI < 0.800$ (aOR 1.61; 95% CI 0.91-3.23; $P=0.170$, Supplementary Table 5). Forest plots are provided in the Supplementary Fig. 21.

3.2 ARMRs quartiles by country HDI (2001-2025)

3.2.1 Early-onset ARMRs

Infants (<1 year)

The median and quartiles values of early-onset ARMR were 3.13 (0.0 to 11.14) per 10,000 anaesthetic procedures. In the first quartile (best rates), all four studies were from $HDI \geq 0.800$ countries,²⁰⁻²³ consistently reporting 0.00 per 10,000 anaesthetic procedures. In contrast, the fourth quartile (worst rates), comprised exclusively studies from $HDI < 0.800$ countries in Asia²⁴ and Africa,²⁵⁻²⁷ with ARMRs ranged from 16.56 to 156.25 per 10,000 anaesthetic procedures (Table 3).

Table 3. Early-onset anaesthesia-related mortality rates in children younger than one year old by HDI and quartile distribution in the 2001-2025 period

Investigator/year of publication	Country/Continent	Anaesthesia-related mortality rate (per 10,000 anaesthetics)	Quartile
Murat et al., 2004	France	0.00	Q1: 0.00
Montobbio et al., 2012	Italy	0.00	
Hohn et al., 2019	Germany	0.00	
Habre et al., 2015	33 European countries	0.00	
Talabi et al., 2018	Nigeria	0.00	Q2 (median): 3.13
Jansen et al., 2021	Germany	0.50	
van der Griend et al., 2011	Australia	1.31	
Hauser et al., 2023	Australia	1.80	
Sanabria-Carretero et al., 2013	Spain	2.56	
Bunchungmongkol et al., 2009	Thailand	3.70	
Rattana-Arpa et al., 2023	Thailand	3.72	Q3: 11.14
Bharti et al., 2009	India	4.11	
de Bruin et al., 2015	The Netherlands	4.48	
Morais et al., 2025	Brazil	5.72	
Kan et al., 2021	China	16.56	
Talabi et al., 2021	Nigeria	64.94	
Cronjé et al., 2022	South Africa	70.18	
Nizeyimana et al., 2024	Rwanda	156.25	

HDI: Human Development Index; Q1, Q2 and Q3: first, second and third quartiles, respectively. Blue highlight indicates $HDI \geq 0.800$ country, and yellow highlight indicates $HDI < 0.800$ country.

Older children (≥ 1 year)

The median and quartiles of early-onset ARMOR were 0.00 (0.0 to 1.55) per 10,000 anaesthetic procedures. The first quartile (best rates) included only HDI ≥ 0.800 countries,²⁰⁻²³ all reporting 0.00 per 10,000 anaesthetic procedures. Conversely, the fourth quartile (worst rates) included HDI < 0.800 countries in Asian^{28,29} and Africa,^{25,27} with ARMORs ranging from 2.03 to 177.0 per 10,000 anaesthetic procedures (Table 4).

Table 4. Early-onset anaesthesia-related mortality rates in children one year and older by HDI and quartile distribution in the 2001-2025 period

Investigator/year of publication	Country/Continent	Anaesthesia-related mortality rates (per 10,000 anaesthetics)	Quartile
Murat et al., 2004	France	0.00	Q1: 0.00
Hauser et al., 2023	Australia	0.00	
de Bruin et al., 2015	The Netherlands	0.00	
Montobbio et al., 2012	Italy	0.00	
Hohn et al., 2019	Germany	0.00	Q2 (median): 0.00
Morais et al., 2025	Brazil	0.00	
Habre et al., 2015	33 European countries	0.00	
Cronjé et al., 2022	South Africa	0.00	
Kan et al., 2021	China	0.00	
Talabi et al., 2021	Nigeria	0.00	Q3: 1.55
van der Griend et al., 2011	Australia	0.35	
Jansen et al., 2021	Germany	0.50	
Sanabria-Carretero et al., 2013	Spain	0.57	
Rattana-Arpa et al., 2023	Thailand	1.07	
Bunchungmongkol et al., 2009	Thailand	2.03	
Bharti et al., 2009	India	2.74	
Talabi et al., 2018	Nigeria	8.36	
Nizeyimana et al., 2024	Rwanda	177.00	

HDI: Human Development Index; Q1, Q2 and Q3: first, second and third quartiles, respectively. Blue highlight indicates HDI ≥ 0.800 country, and yellow highlight indicates HDI < 0.800 country.

3.2.2 Short-term ARMORs (overall paediatric population)

The median and quartiles of short-term ARMOR were 0.84 (0.16 to 4.23) per 10,000 anaesthetic procedures. In the first quartile (best rates), all three studies were from HDI ≥ 0.800 countries,^{22,23,30} reporting ARMORs between 0.00 and 0.12 per 10,000 anaesthetic procedures. In contrast, the fourth quartile (worst rates), comprised exclusively African HDI < 0.800

countries,^{25,26,31} with ARMRs ranging from 4.86 to 19.80 per 10,000 anaesthetic procedures. Supplementary Table 6 provides further details.

3.2.3 Aetiology and associated factors of ARM events

Data from 185 ARM events revealed significant differences in aetiology by HDI and time period (Table 5). In HDI ≥ 0.800 countries, respiratory-related causes predominated before 2001 (54.17%) but decreased markedly in 2001-2025 (15.90%; $P < 0.0001$); cardiovascular-related causes became the leading aetiology in 2001-2025 (84.10% vs 26.72% pre-2001; $P < 0.0001$).

Table 5. Proportional meta-analysis of aetiology (%) of anaesthesia-related mortality rates by time period and by country Human Development Index (HDI) status in children.

Cause/mortality n	Proportional meta-analysis (95% CI)	P value for subgroup	
		HDI ≥0.800 vs. HDI <0.800	HDI <0.800 per time period* HDI ≥0.800 per time period*
Respiratory-related			
Pre-2001			
HDI <0.800	-	-	-
HDI ≥0.800	65/111	54.17 (25.79-81.14)	<0.0001
2001-2025			
HDI <0.800	24/48	50.38 (37.19-63.54)	<0.0001
HDI ≥0.800	3/26	15.90 (5.18-31.01)	
Cardiovascular-related			
Pre-2001			
HDI <0.800	-	-	-
HDI ≥0.800	34/111	26.72 (6.50-54.32)	<0.0001
2001-2025			
HDI <0.800	21/48	40.28 (23.89-57.87)	<0.0001
HDI ≥0.800	23/26	84.10 (68.99-94.82)	
Medication-related			
Pre-2001			
HDI <0.800	-	-	-
HDI ≥0.800	12/111	17.81 (4.45-37.48)	0.84
2001-2025			
HDI <0.800	3/48	8.38 (2.51-17.16)	0.81
HDI ≥0.800	0/26	5.08 (0.22-15.72)	

In HDI < 0.800 countries (2001-2025), respiratory-related causes (50.38%) remained predominant, followed by cardiovascular-related causes (40.28%), with no significant difference ($P = 0.71$; Supplementary Table 7).

Frequent respiratory-related factors included: loss of airway/unable to ventilate,^{32,33} aspiration of vomitus or blood,^{19,33-36} respiratory depression due to central nervous system

depression or neuromuscular blockade,³⁴ inadequate ventilation after tracheal extubation,^{1,26,28,37,38} difficult intubation/ventilation,^{28,38,39} and laryngospasm.³⁸⁻⁴⁰

Cardiovascular-related factors included: drug-induced myocardial depression,^{34,38,41,42} haemorrhage,^{1,30,36,38} hyperkalaemia,^{30,33} anaesthetic hypotension with cardiac ischaemia,³⁸ cardiac arrhythmia,^{34,35,38} and inadequate fluid therapy.^{1,34,35,38}

Medication-related ARM events were predominantly linked to older volatile anaesthetic agents (halothane, ether).^{1,28,32,38}

3.3 ARMRs by HDI and ASA-PS status (2001-2025)

Between 2001 and 2025, ARMRs exhibited substantial disparities when stratified by HDI and ASA-PS. Among low-risk patients (ASA-PS 1-2), no ARM events were recorded (0/439,868) in HDI ≥ 0.800 countries, yielding a proportional meta-analysis estimate of 0.02 (95% CI 0.00-0.08), whereas in HDI < 0.800 countries ARM events occurred (4/58,378), yielding a proportional meta-analysis of 1.70 (95% CI 0.42-6.47). Among higher-risk patients (ASA-PS ≥ 3), differences were even more pronounced, with a markedly greater adjusted odds ratio in HDI < 0.800 (aOR 10.24; 95% CI 9.16–11.44; $P < 0.0001$) compared with HDI ≥ 0.800 countries (Supplementary Table 8).

3.3.1 Sensitivity analyses

Sensitivity analyses excluding studies identified as outliers for early-onset outcomes (Supplementary Fig. 22)^{25-27,32} demonstrated no material changes in the pooled proportional meta-analysis estimates. These findings supported the decision to retain all identified studies in the final analysis.

3.3.2 Publication bias and heterogeneity (overall paediatric population)

Without HDI adjustment: in pre-2001, no evidence of publication bias was found for early-onset ARMRs (aOR 0.72; 95% CI 0.29-1.34; $P = 0.11$). Between 2001 and 2025, publication bias was evident for both early-onset ARMRs (aOR 0.69; 95% CI 0.41-1.04; $P < 0.0001$) and short-term ARMRs (aOR 0.92; CI 95% 0.45-0.56; $P = 0.0008$).

HDI-adjusted analyses: pre-2001 showed no evidence of publication bias for early-onset ARMR (aOR 0.77; 95% CI 0.29-1.48; $P = 0.11$). In 2001-2025, publication bias was evident for early-onset ARMRs in both HDI < 0.800 (aOR 3.44; 95% CI 1.57-6.05; $P = 0.0002$) and HDI ≥ 0.800 countries (aOR 0.36; 95% CI 0.18-0.6; $P = 0.002$). No bias was detected for short-term

ARMRs in either HDI <0.800 (aOR 4.35; 95% CI 1.60-8.44; $P=0.072$) or HDI ≥ 0.800 countries (aOR 0.42; 95% CI 0.19-0.74; $P=0.066$).

Publication bias was not assessed for short-term ARMRs pre-2001 (all studies, regardless of HDI) or for early-onset and short-term ARMRs in HDI <0.800 countries, due to insufficient data.

3.3.3 Heterogeneity

Substantial heterogeneity was identified in the most outcomes ($P<0.01$), with the exception of studies conducted in HDI ≥ 0.800 countries during the period 2001-2025. In these settings, the analyses of early-onset ARMRs in infants aged <1 year ($P=0.70$) and ≥ 1 year ($P=0.22$), as well as short-term ARMR in infants aged <1 year ($P=0.72$), demonstrated consistency.

4. DISCUSSION

4.1 Major findings and global disparities

Our analysis demonstrated persistent global disparities in paediatric anaesthesia safety throughout the 21st century. Early-onset and short-term ARMRs were inversely correlated with national HDI but showed no overall temporal trend. In HDI ≥ 0.800 countries, early-onset ARMRs remained consistently low, whereas they rose sharply in HDI < 0.800 settings. The gap between HDI ≥ 0.800 and HDI < 0.800 countries of ARMRs widened from 2001 to 2025 and was consistently greater in infants under one year than in older children, across both HDI groups and time periods. Over time, early-onset ARMRs increased significantly in infants under one year but remained stable in older children, while short-term rates were stable across both age groups. Age-specific analyses showed that, among infants under one year, early-onset ARMRs correlated inversely with HDI, whereas in older children only short-term ARMRs demonstrated this pattern. The close similarity between early-onset and short-term ARMRs indicates that most ARM events occurred within the first 24 postoperative hours.

In HDI ≥ 0.800 countries, the odds ratio for early-onset ARMR among infants under one year of age compared with older children, increased substantially, rising from 2.62 in the period prior to 2001 to 11.58 across 2001-2025. Early-onset and short-term ARMRs in 2001-2025 were approximately 1 per 5,000 and 1 per 4,000 anaesthetics, respectively, in children younger than 1 year, whereas in those aged ≥ 1 year the corresponding rates were substantially lower, at about 1 per 55,000 and 1 per 43,000 anaesthetics, respectively. These findings underscore the persistent vulnerability of infants even in resource-rich settings.

This likely reflects greater case-mix complexity, as advances in surgical and anaesthetic techniques are now applied to critically ill infants who were previously considered inoperable.⁴³ Although ARMRs have plateaued in HDI ≥ 0.800 countries, overall paediatric anaesthesia has become markedly safer. This progress is exemplified by quality improvement initiatives such as the Wake-Up Safe database, which, according to Kanjia et al. (2024),⁴⁴ has reported no ARM events in healthy children since 2009 across more than 4 million cases. Consistent with these findings, during 2001-2025, our review identified no ARM events in 44.4% of studies involving children < 1 year and in 66.7% of studies involving those ≥ 1 year from HDI ≥ 0.800 countries (Tables 3 and 4). Additionally, no ARM events were reported among children classified as ASA-PS 1-2 in studies from HDI ≥ 0.800 countries, whereas those classified as ASA-PS ≥ 3 showed markedly lower odds of ARMRs in HDI ≥ 0.800 compared with HDI < 0.800 countries.

By contrast, the highest ARMRs between 2001 and 2025 were reported in HDI < 0.800 countries, particularly in Africa and Asia, and were most pronounced among infants < 1 year.²⁵⁻

^{26,28,29,35,36} Contributing factors included poverty, weak healthcare infrastructure, rapid population growth, limited paediatric surgical and ICU capacity, and a severely constrained anaesthesia and surgical workforce.^{3,45-47} Collectively, these challenges have resulted in persistently high ARMRs, especially among infants <1 year. During 2001-2025, early-onset and short-term ARMRs were substantially higher, at approximately 1 per 1,100 and 1 per 650 anaesthetics, respectively, in children younger than 1 year, whereas in those aged ≥1 year the corresponding rates were similar, at about 1 per 5,500 anaesthetics.

The elevated ARMRs observed in the present century in HDI <0.800 countries are likely influenced by the inclusion of African and Asian studies only in this later period, as no significant differences between HDI ≥0.800 and HDI <0.800 groups were observed previously. Persistently high ARMRs in these regions underscore structural deficiencies rather than protocol-related gaps. The temporal rise in ARMRs and the persistence of ARM events even in children with lower ASA-PS classification in HDI <0.800 countries, despite global safety initiatives, suggests that systemic and workforce-related failures remain insufficiently addressed.

4.2 Aetiology shift and safe advancements

In HDI ≥0.800 countries, the primary aetiology of ARM events has shifted from respiratory to cardiocirculatory causes, reflecting advances in ventilation monitoring and cardiovascular technologies. Cardiocirculatory-related events are now more frequent, particularly in children with underlying heart disease^{38,48,49} with hypovolaemia, haemorrhage, and ischaemia secondary to anaesthetic-induced hypotension increasingly reported.^{30,41,42}

The decline in respiratory-related ARMRs in HDI ≥0.800 countries is largely attributable to widespread adoption of pulse oximetry, capnography, modern anaesthesia workstations with advanced ventilators, supraglottic airway devices, and indirect laryngoscopy technologies. These improvements have been reinforced by the expansion of the anaesthesia workforce, particularly paediatric specialists, and the establishment of hospital-based safety programmes with standardised reporting.⁴⁴

By contrast, respiratory-related causes remained the predominant aetiology of ARM in HDI <0.800 countries during 2001-2025, resembling the earlier profile of HDI ≥0.800 nations. This highlights the urgent need to strengthen airway management and ventilation monitoring in resource-limited settings. Moreover, unlike HDI ≥0.800 countries, which no longer report medication-related ARM events, such events continue to be documented in Asian and African HDI <0.800 regions.^{32,45}

4.3 The unique vulnerability of neonates and infants

Anaesthesia in children under one year of age remains particularly demanding, even for experienced paediatric anaesthetists, with premature neonates and infants and those with comorbidities presenting the greatest challenges.^{22,50,51} Their vulnerability reflects physiological fragility: reduced functional residual capacity, heightened metabolic demands, and elevated oxygen consumption, all of which predispose to rapid desaturation during brief episodes of hypoventilation or apnoea.⁵² Airway management is further complicated by anatomical features such as large head and tongue, restricted submandibular space, high laryngeal position, and flaccid epiglottis, which contribute to frequent difficulties tracheal intubation and increase the risk of cardiac arrest and death.^{53,54} Autonomic immaturity further predisposes neonates and infants to profound bradycardia and hypotension in response to anaesthetic agents or surgical stimuli.⁵² In resource-limited settings, infrastructural deficits exacerbate these inherent vulnerabilities, leading to heightened adverse outcomes. Furthermore, prematurity⁵⁵ and congenital abnormalities^{56,57} compound the complexity of anaesthetic management in this population.

4.4 Anaesthesia workforce scarcity in HDI <0.800 countries

Paediatric anaesthesia is rarely recognised as a subspecialty in HDI <0.800 countries, where care is often provided by anaesthesiologists with limited paediatric training. In many African nations, non-physicians deliver paediatric anaesthesia due to the severe workforce shortages.³ Consequently, anaesthesia services are frequently inadequate.^{3,26,45} This scarcity transforms peri-operative complications into fatal events through failure to rescue.

4.5 Future Directions

Ensuring equitable access to safe paediatric surgery is crucial to narrowing global disparities in ARM outcomes. Progress depends on coordinated investment in policy, workforce, infrastructure, education, coordinated international collaboration, supported by appropriate incentives, alongside centralised care by experienced teams to improve safety and outcomes.^{4,22,45}

4.6 Strengths and limitations

This systematic review with meta-analysis is, to our knowledge, the first to demonstrate global safety trends in ARM events in paediatric anaesthesia, stratified by HDI level, time period, postnatal age group, and quartile. By pooling studies across many years, we can observe

real changes over time because they captured technology adoption cycles, policy changes, and evolving clinical practice. It highlights the substantial burden of early-onset and short-term ARMRs in infants under one year of age, revealing marked disparities between countries with differing HDI levels from 2001 to 2025. Importantly, early-onset ARMRs have shown no improvement and, in certain HDI <0.800 contexts, have even increased, highlighting entrenched systemic challenges. The evidence highlights both vulnerability and opportunity: infants under one year consistently face the highest risk, yet the near-elimination of ARM events in healthy children and in those aged one year and above in HDI ≥ 0.800 countries demonstrates that prevention is achievable.

Several limitations must be acknowledged: (1) predominance of retrospective studies, increasing the likelihood of missed ARM events; (2) rarity of ARM events, where even small omissions may affect results; (3) methodological heterogeneity across settings, ARM definitions,⁵⁸ data sources, populations, and surgery types contributing to publication bias, underscoring the variability inherent in global data; notably, this pattern was absent in studies conducted in HDI ≥ 0.800 countries during 2001-2025, highlighting the stabilising effect of more developed healthcare systems; (4) scarcity of high-quality data, particularly absence of pre-2001 short-term outcomes; (5) medicolegal factors may lead to selective or incomplete ARM reporting, especially in settings without mandatory incident disclosure; (6) some publication bias was identified; and (6) insufficient data on key factors, such as cardiac surgery,^{38,48,49} emergency procedures,^{27,59} congenital anomalies,⁵⁰ and prematurity.^{57,60}

Despite the high heterogeneity, which is partly explained by the different HDI levels of the countries, and the publication bias, the consistent trends of the rates of MRA observed across continents and time periods in children, confirmed by both the meta-regression and proportional meta-analysis, underscore the robustness and strengthen the validity of our findings.

5. Conclusions

This systematic review demonstrates that global paediatric ARMRs have remained unchanged over time, while disparities in anaesthesia-related mortality persist, with infants under one year consistently at greatest risk across both HDI levels. Over the past six decades, ARMRs have stabilised at very low levels in resource-rich settings yet continue to reach alarming levels in HDI <0.800 regions, particularly among infants under one year, demanding urgent global attention. These findings emphasise that safe paediatric anaesthesia is not a universal reality, but a privilege shaped by geography and infrastructure.

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Supplementary Data

SUPPLEMENTARY DATA

Title

Global Patterns in Paediatric Anaesthesia-Related Mortality: Systematic Review and Meta-Analysis

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Supplementary Methods. Search strategies (up to June 30, 2025)

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death'/exp OR 'cardiac death' OR 'death, cardiac' OR 'anaesthesia-related mortality' OR 'anesthesia-related mortality') **AND** ('anaesthesia, auto':ab OR 'anaesthetic action':ab OR 'anesthesia, auto':ab OR 'anesthetic action':ab OR autoanaesthesia:ab OR autoanesthesia:ab OR 'drop mask anaesthesia':ab OR 'drop mask anesthesia':ab OR narcosis:ab OR 'short anaesthesia':ab OR 'short anesthesia':ab OR 'short duration anaesthesia':ab OR 'short duration anesthesia':ab OR anesthesia:ab OR anesthetics:ab OR 'anesthetic drugs':ab OR 'drugs, anesthetic':ab OR 'anesthetic agents':ab OR 'agents, anesthetic':ab OR anesthetic:ab OR 'anesthetic effect':ab OR 'effect, anesthetic':ab OR 'anesthetic effects':ab OR 'effects, anesthetic':ab OR anaesthesia:ab OR anaesthetics:ab OR 'anaesthetic drugs':ab OR 'drugs, anaesthetic':ab OR 'anaesthetic agents':ab OR 'agents, anaesthetic':ab OR anaesthetic:ab OR 'anaesthetic effect':ab OR 'effect, anaesthetic':ab OR 'anaesthetic effects':ab OR 'effects, anaesthetic':ab)

SCOPUS

("Heart Arrest" OR "Arrest, Heart" OR "Cardiac Arrest" OR "Arrest, Cardiac" OR "Asystole" OR "Asystoles" OR "Cardiopulmonary Arrest" OR "Arrest, Cardiopulmonary" OR "Anaesthesia-related cardiac arrest" OR "Anesthesia-related cardiac arrest" OR "Mortality" OR "Mortalities" OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Rate, Case Fatality" OR "Rates, Case Fatality" OR "CFR Case Fatality Rate" OR "Crude Death Rate" OR "Crude Death Rates" OR "Death Rate, Crude" OR "Rate, Crude Death" OR "Crude Mortality Rate" OR "Crude Mortality Rates" OR "Mortality Rate, Crude" OR "Rate, Crude Mortality" OR "Death Rate" OR "Death Rates" OR "Rate, Death" OR "Mortality Rate" OR "Mortality Rates" OR "Rate, Mortality" OR "Mortality, Excess" OR "Excess Mortality" OR "Excess Mortalities" OR "Decline, Mortality" OR "Mortality Declines" OR "Mortality Decline" OR "Mortality Determinants" OR "Determinants, Mortality" OR "Determinant, Mortality" OR "Mortality Determinant" OR "Mortality, Differential" OR "Differential Mortality" OR "Differential Mortalities" OR "Age-Specific Death Rate" OR "Age-Specific Death Rates" OR "Death Rate, Age-Specific" OR "Rate, Age-Specific Death" OR "Age Specific Death Rate" OR survival OR death OR "End Of Life" OR "End-Of-Life" OR "Determination of Death" OR "Near-Death Experience" OR "Cardiac Death" OR "Death, Cardiac" OR "Anaesthesia-related mortality" OR "Anesthesia-related mortality") **AND** ("Anesthesia" OR "Anesthetics" OR "Anesthetic Drugs" OR "Drugs, Anesthetic" OR "Anesthetic Agents" OR "Agents, Anesthetic" OR anesthetic OR "Anesthetic Effect" OR "Effect, Anesthetic" OR "Anesthetic Effects" OR "Effects, Anesthetic" OR "Anaesthesia" OR "Anaesthetics" OR "Anaesthetic Drugs" OR "Drugs, Anaesthetic" OR

"Anaesthetic Agents" OR "Agents, Anaesthetic" OR anaesthetic OR "Anaesthetic Effect" OR "Effect, Anaesthetic" OR "Anaesthetic Effects" OR "Effects, Anaesthetic"))

WEB OF SCIENCE

("Heart Arrest" OR "Arrest, Heart" OR "Cardiac Arrest" OR "Arrest, Cardiac" OR "Asystole" OR "Asystoles" OR "Cardiopulmonary Arrest" OR "Arrest, Cardiopulmonary" OR "Anaesthesia-related cardiac arrest" OR "Anesthesia-related cardiac arrest" OR Mortality OR Mortalities OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Rate, Case Fatality" OR "Rates, Case Fatality" OR "CFR Case Fatality Rate" OR "Crude Death Rate" OR "Crude Death Rates" OR "Death Rate, Crude" OR "Rate, Crude Death" OR "Crude Mortality Rate" OR "Crude Mortality Rates" OR "Mortality Rate, Crude" OR "Rate, Crude Mortality" OR "Death Rate" OR "Death Rates" OR "Rate, Death" OR "Mortality Rate" OR "Mortality Rates" OR "Rate, Mortality" OR "Mortality, Excess" OR "Excess Mortality" OR "Excess Mortalities" OR "Decline, Mortality" OR "Mortality Declines" OR "Mortality Decline" OR "Mortality Determinants" OR "Determinants, Mortality" OR "Determinant, Mortality" OR "Mortality Determinant" OR "Mortality, Differential" OR "Differential Mortality" OR "Differential Mortalities" OR "Age-Specific Death Rate" OR "Age-Specific Death Rates" OR "Death Rate, Age-Specific" OR "Rate, Age-Specific Death" OR "Age Specific Death Rate" OR "Survival" OR Death OR "End Of Life" OR "End-Of-Life" OR "Determination of Death" OR "Near-Death Experience" OR "Cardiac Death" OR "Death, Cardiac" OR "Anaesthesia-related mortality" OR "Anesthesia-related mortality") **AND** ("Anesthesia" OR "Anesthetics" OR "Anesthetic Drugs" OR "Drugs, Anesthetic" OR "Anesthetic Agents" OR "Agents, Anesthetic" OR Anesthetic OR "Anesthetic Effect" OR "Effect, Anesthetic" OR "Anesthetic Effects" OR "Effects, Anesthetic" OR anaesthesia OR Anaesthetics OR "Anaesthetic Drugs" OR "Drugs, Anaesthetic" OR "Anaesthetic Agents" OR "Agents, Anaesthetic" OR Anaesthetic OR "Anaesthetic Effect" OR "Effect, Anaesthetic" OR "Anaesthetic Effects" OR "Effects, Anaesthetic"))

LILACS

(parada cardíaca OR heart arrest OR paro cardíaco OR assistolia OR parada cardiopulmonar OR parada cardiorrespiratória OR paralisia cardíaca OR mortalidade OR mortality OR mortalidad OR aumento da mortalidade OR aumento de mortalidade OR coeficiente de mortalidade OR declínio da mortalidade OR determinantes da mortalidade OR determinantes de mortalidade OR diminuição da mortalidade OR estatísticas de mortalidade OR excesso de

mortalidade OR fatores determinantes de mortalidade OR fatores de mortalidade OR letalidade OR mortalidade aumentada OR mortalidade diferencial OR mortalidade excessiva OR mortalidade por faixa etária OR mortalidade por idade OR razão de mortalidade proporcional OR redução da mortalidade OR sobremortalidade OR taxa de casos fatais OR taxa de fatalidade OR taxa de letalidade OR taxa de mortalidade OR taxa de mortalidade por faixa etária OR taxa de mortalidade por idade OR taxas de mortalidade específicas por idade OR índice de casos fatais OR índice de fatalidade OR índice de letalidade OR índice de mortalidade OR morte OR death OR muerte OR experiência pré-morte OR falecimento OR óbito) **AND** (anestesia OR anesthesia OR anestésicos OR anesthetics OR anestésico)

Supplementary Table 1. Standard form used to extract information from the studies

Investigator and year of publication
Data source and recruitment year(s)
Country
Median year patient recruitment interval
Human Development Index average
Child patients: all postnatal age groups (n)
Child patients: < 1 year (n)
Child patients: ≥ 1 year (n)
Early-onset anaesthesia-related mortality: all postnatal age groups (n)
Early-onset anaesthesia-related mortality: < 1 year (n)
Early-onset anaesthesia-related mortality: ≥ 1 year (n)
Short-term anaesthesia-related mortality: all postnatal age groups (n)
Short-term anaesthesia-related mortality: < 1 year (n)
Short-term anaesthesia-related mortality: ≥ 1 year (n)
ASA physical status at baseline (n)
Anaesthesia-related mortality by ASA physical status (n)
Anaesthesia-related mortality by aetiology (n)
Excluded patients

ASA: American Society of Anesthesiologists

Supplementary Table 2. Critical appraisal of the quality results of anaesthesia-related mortality in children from included studies using the Joanna Briggs Institute Prevalence Critical Appraisal Checklist

	Target population	Sampling	Sample size	Description of participants and setting	Coverage of identified sample	Methods to identify outcome	Reliability in outcome measurement	Appropriate statistical analysis	Response rate	Total
Adekola et al., 2016	N	N	N	Y	N	Y	Y	Y	Y	5/9
Ahmed et al., 2009	N	Y	Y	Y	N	Y	N	Y	Y	6/9
Aubas et al., 1991	N	N	Y	Y	N	Y	Y	Y	N	5/9
Bharti et al., 2009	N	Y	Y	Y	N	Y	N	Y	Y	6/9
Biboulet et al., 2001	N	N	Y	Y	Y	Y	N	Y	Y	6/9
Braz et al., 2006	N	N	Y	Y	N	Y	Y	Y	Y	6/9
Bunchungmongkol et al., 2009	Y	Y	Y	Y	Y	Y	Y	Y	N	8/9
Christensen et al., 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	9/9
Christensen et al., 2021	N	N	Y	Y	N	Y	Y	Y	Y	6/9
Cronjé et al., 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	9/9
de Bruin et al., 2015	N	Y	Y	Y	N	Y	N	Y	Y	6/9
de Graaff et al., 2015	N	N	Y	Y	Y	Y	Y	Y	Y	7/9
Flick et al., 2007	N	Y	Y	Y	N	Y	Y	N	N	5/9
Graff et al., 1964	Y	N	Y	Y	N	Y	Y	N	N	5/9
Habre et al., 2017	Y	Y	Y	Y	Y	Y	N	Y	Y	8/9
Haché et al., 2020	Y	N	Y	Y	Y	Y	Y	Y	N	7/9
Hauser et al., 2023	N	Y	Y	Y	N	Y	Y	Y	Y	7/9
Hohn et al., 2019	N	Y	Y	Y	N	Y	Y	Y	Y	7/9
Jansen et al., 2021	N	Y	Y	Y	N	Y	N	Y	N	5/9
Kan et al., 2021	N	Y	Y	Y	N	Y	Y	Y	Y	7/9
Keenan & Boyan, 1985	N	Y	Y	Y	Y	Y	Y	Y	Y	8/9
Khoso et al., 2021	N	N	Y	Y	N	Y	N	Y	Y	5/9
Lim et al., 2016	N	N	Y	Y	N	Y	Y	Y	Y	6/9
Marx et al., 1973	N	Y	Y	Y	Y	Y	Y	N	N	6/9
Meyer et al., 2017	N	Y	Y	Y	Y	Y	Y	Y	Y	8/9
Montobbio et al., 2012	N	Y	Y	Y	Y	Y	Y	Y	N	7/9
Morais et al., 2025	N	Y	Y	Y	N	Y	Y	Y	Y	7/9
Morita et al., 2002	Y	Y	Y	Y	N	Y	Y	N	N	6/9
Murray et al., 2000	Y	N	Y	Y	Y	Y	Y	Y	Y	8/9
Murat et al., 2004	N	Y	Y	Y	Y	Y	N	Y	N	6/9
Newland et al., 2002	N	N	Y	Y	Y	Y	Y	Y	Y	7/9
Nizeyimana et al., 2024	Y	N	N	Y	Y	Y	N	Y	Y	6/9
Rackow et al., 1961	Y	Y	Y	Y	N	Y	Y	N	N	6/9
Rattana-Arpa et al., 2023	N	Y	Y	Y	N	Y	N	Y	Y	6/9
Sanabria-Carretero et al., 2013	N	Y	Y	Y	N	Y	Y	Y	Y	7/9
Schleelein et al., 2016	N	N	Y	Y	N	Y	N	Y	Y	5/9
Talabi et al., 2018	N	Y	Y	Y	N	Y	Y	Y	Y	7/9
Talabi et al., 2021	N	Y	N	Y	Y	Y	Y	Y	Y	7/9
Tay et al., 2001	N	N	Y	Y	Y	Y	Y	N	N	5/9
Tiret et al., 1988	Y	Y	Y	Y	Y	Y	Y	Y	Y	9/9
van der Griend et al., 2011	N	Y	Y	Y	N	Y	Y	Y	N	6/9

Westerkamp et al., 2018	N	N	Y	Y	N	Y	Y	Y	Y	6/9
Williams et al., 2017	N	N	Y	Y	N	Y	Y	Y	N	5/9
Zgleszewski et al., 2016	N	N	Y	Y	Y	Y	Y	Y	Y	7/9

Y: Yes; N: No

Supplementary Table 3. Description of the included studies of early-onset (up to 24-hour postoperatively) and short-term (up to 30-day postoperatively or in-hospital) anaesthesia-related mortality rates in children according to postnatal age group, country Human Development Index, and time period (pre-2001 *versus* 2001-2025).

Investigator(s) and year of publication	Data source, country, and study period	Median year	HDI average	Anaesthetic procedures by postnatal age group N	Early-onset and short-term anaesthesia-related mortality events by postnatal age group N	Early-onset and short-term anaesthesia-related mortality rates by postnatal age group (per 10,000 anaesthetics)	Excluded or not included
Adekola et al. 2016	University hospital Retrospective Nigeria 2013-2014	2014	0.509	≤ 18 yr: 987	≤ 18 yr: 3/NR	≤ 18 yr: 30.40/NR	Cardiac surgery
Ahmed et al. 2009	University tertiary hospital Retrospective Pakistan 1992-2006	1999	0.482	≤ 1yr: 4,376 > 1 to 17 yr: 15,840 ≤ 17 yr: 20,216	≤ 1yr: 1/NR > 1 to 17 yr: 0/NR ≤ 17 yr: 1/NR	≤ 1yr: 2.28/NR > 1 to 17 yr: 0.0/NR ≤ 17 yr: 0.49/NR	Cardiac surgery
Aubas et al. 1991	University tertiary hospital Retrospective France 1983-1987	1985	0.911	≤ 14 yr: 16,207	≤ 14 yr: 2/NR	≤ 14 yr: 1.23/NR	
Bharti et al. 2009	Tertiary teaching paediatric hospital Retrospective India 2003-2008	2006	0.607	< 1 yr: 4,863 1 to 17 yr: 7,295 ≤ 17 yr: 12,158	< 1 yr: 2/NR 1 to 17 yr: 2/NR ≤ 17 yr: 4/NR	< 1 yr: 4.11/NR 1 to 17 yr: 2.74/NR ≤ 17 yr: 3.29/NR	Eye surgery Cardiac surgery

Biboulet et al. 2001	University hospital Prospective France 1989-1995	1992	0.958	≤ 14 yr: 23,832	≤ 14 yr: 1/NR	≤ 14 yr: 0.42/NR	ASA physical status 5
Braz et al. 2006	University tertiary hospital Retrospective Brazil 1996- 2004	2000	0.766	< 1yr: 3,065 1 to 17 yr: 12,188 ≤ 17 yr: 15,253	< 1yr: 0/NR 1 to 17 yr: 0/NR ≤ 17 yr: 0/NR	< 1yr: 0.0/NR 1 to 17 yr: 0.0/NR ≤ 17 yr: 0.0/NR	
Bunchungmongkol et al., 2009	Multicentre: 20 hospitals (Thai study) Prospective Thailand 2003-2004	2004	0.781	≤ 1yr: 5,406 1 to 15 yr: 19,692 ≤ 15 yr: 25,098	≤ 1yr: 2/NR 1 to 15 yr: 4/NR ≤ 15 yr: 6/NR	≤ 1yr: 3.70/NR 1 to 15 yr: 2.03/NR ≤ 15 yr: 2.39/NR	
Christensen et al. 2018	Multicentre: 19 university and private paediatric hospitals Prospective USA 2010-2015	2013	0.911	≤ 17 yr: 1,006,685	≤ 17 yr: 36/NR	≤ 17 yr: 0.36/NR	
Christensen et al. 2021	University tertiary paediatric hospital Retrospective USA 2006-2016	2011	0.940	≤ 17 yr: 109,775	≤ 17 yr: 5/7	≤ 17 yr: 0.45/0.64	

Cronjé et al. 2022	Multicentre: 43 university hospitals Prospective South Africa 2017	2017	0.699	≤ 1 yr: 285 2 to 16 yr: 1,739 ≤ 16 yr: 2,024	≤ 1 yr: 2/4 2 to 16 yr: 0/0 ≤ 16 yr: 2/4	≤ 1 yr: 70.18/140.35 2 to 16 yr: 0.0/0.0 ≤ 16 yr: 9.88/19.80	
de Bruin et al. 2015	University tertiary paediatric hospital Retrospective The Netherlands 2006-2012	2009	0.916	< 1 yr: 8,921 1 to 17 yr: 36,261 ≤ 17 yr: 45,182	< 1 yr: 4/5 1 to 17 yr: 0/0 ≤ 17 yr: 4/5	< 1 yr: 4.48/5.60 1 to 17 yr: 0.0/0.0 ≤ 17 yr: 0.89/1.11	ASA physical status 5
de Graaff et al. 2015	University paediatric hospital Prospective The Netherlands 2007-2013	2010	0.940	≤ 18 yr: 35,190	≤ 18 yr: 3/NR	≤ 18 yr: 0.85/NR	
Flick et al. 2007	University tertiary hospital Retrospective USA 1988-2005	1997	0.964	< 1 yr: 9,258 1 to 17 yr: 83,623 ≤ 17 yr: 92,881	< 1 yr: 0/NR 1 to 17 yr: 2/NR ≤ 17 yr: 2/NR	< 1 yr: 0.0/NR 1 to 17 yr: 0.24/NR ≤ 17 yr: 0.22/NR	
Graff et al. 1964	Multicentre: many hospitals Retrospective USA 1953-1963	1958	0.873	≤ 14 yr: 175,757	≤ 14 yr: 58/NR	≤ 14 yr: 3.30/NR	

Habre et al. 2017	Multicentre: 261 hospitals Prospective (APRICOT study) 33 European countries 2014-2015	2015	0.899	< 1 yr: 3,273	< 1 yr: 0/0	< 1 yr: 0.0/0.0	
				1 to 15 yr: 27,600	1 to 15 yr: 0/0	1 to 15 yr: 0.0/0.0	
				≤ 15 yr: 30,873	≤ 15 yr: 0/0	≤ 15 yr: 0.0/0.0	
Haché et al. 2020	Multicentre: 19 tertiary university and private paediatric hospitals Prospective USA 2010-2015	2013	0.916	≤ 20 yr: 1,964,211	≤ 20 yr: 2/NR	≤ 20 yr: 0.01/NR	
Hauser et al. 2023	Tertiary paediatric hospital Retrospective Australia 2001-2015	2008	0.934	< 1 yr: 16,701	< 1 yr: 3/3	< 1 yr: 1.80/1.80	Transplantation surgeries
				1 to 17 yr: 135,832	1 to 17 yr: 0/0	1 to 17 yr: 0.0/0.0	Highly complex cardiac procedures
				≤ 17 yr: 152,533	≤ 17 yr: 3/3	≤ 17 yr: 0.20/0.20	
Hohn et al. 2019	University tertiary hospital Retrospective Germany 2008-2016	2012	0.942	< 1 yr: 5,346	< 1 yr: 0/NR	< 1 yr: 0.0/NR	
				1 to 18 yr: 30,897	1 to 18 yr: 0/NR	1 to 18 yr: 0.0/NR	
				≤ 18 yr: 36,243	≤ 18 yr: 0/NR	≤ 18 yr: 0.0/NR	
Jansen et al. 2021	University tertiary hospital Retrospective Germany 2008-2018	2013	0.942	< 1 yr: 3,564	< 1 yr: 0/0	< 1 yr: 0.0/0.0	Anaesthesia procedures performed in the NICU or PICU
				1 to 15 yr: 19,806	1 to 15 yr: 1/1	1 to 15 yr: 0.50/0.50	
				≤ 15 yr: 22,650	≤ 15 yr: 1/1	≤ 15 yr: 0.44/0.44	

Kan et al. 2021	Tertiary hospital Retrospective China 2013-2020	2017	0.743	≤ 1 yr: 1,208 1 to 18 yr: 16,708 ≤ 18 yr: 17,916	≤ 1 yr: 2/NR 1 to 18 yr: 0/NR ≤ 18 yr: 2/NR	≤ 1 yr: 16.56/NR 1 to 18 yr: 0.0/0.0 ≤ 18 yr: 1.12/NR	
Keenan & Boyan 1985	University tertiary hospital Prospective USA 1969-1983	1976	0.893	< 12 yr: 12,712	< 12 yr: 1/NR	< 12 yr: 0.79/NR	
Khoso et al. 2021	University hospital Retrospective Pakistan 1992-2016	2004	0.523	≤ 16 yr: 48,828	≤ 16 yr: 4/NR	≤ 16 yr: 0.82/NR	Cardiac surgery and anaesthesia outside the OR
Lim et al. 2016	Tertiary university hospital Retrospective South Korea 2004-2014	2009	0.910	≤ 18 yr: 89,534	≤ 18 yr: 1/1	≤ 18yr: 0.12/0.12	
Marx et al. 1973	Public hospital Retrospective USA 1965-1969	1967	0.873	< 1 yr: 3,396 1 to 20 yr: 9,258 ≤ 20 yr: 12,654	< 1 yr: 2/NR 1 to 20 yr: 0/NR ≤ 20 yr: 2/NR	< 1 yr: 5.89/NR 1 to 20 yr: 0.0/NR ≤ 20 yr: 1.58/NR	
Meyer et al. 2017	Tertiary teaching paediatric hospital Prospective South Africa 2015	2015	0.666	< 1 yr: 1,356 1 to 17 yr: 6,969 ≤ 17 yr: 8,325	< 1 yr: NR/2 1 to 17 yr: NR/1 ≤ 17 yr: NR/3	< 1 yr: NR/14.75 1 to 17 yr: NR/1.43 ≤ 17 yr: NR/3.60	Day surgery cases

Montobbio et al. 2012	Public quaternary paediatric hospital Prospective Italy 2009-2010	2010	0.854	< 1 yr: 1,665 1 to 14 yr: 11,185 ≤ 14 yr: 12,850	< 1 yr: 0/NR 1 to 14 yr: 0/NR ≤ 14 yr: 0/NR	< 1 yr: 0.0/NR 1 to 14 yr: 0.0/NR ≤ 14 yr: 0.0/NR	
Morais et al. 2025	University quaternary hospital Retrospective Brazil 2005-2022	2014	0.780	< 1 yr: 3,496 1 to 17 yr: 25,229 ≤ 17 yr: 28,725	< 1 yr: 2/2 1 to 17 yr: 0/0 ≤ 17 yr: 2/2	< 1 yr: 5.72/5.72 1 to 17 yr: 0.0/0.0 ≤ 17 yr: 0.70/0.70	
Morita et al. 2002	Multicentre: 794 hospitals Retrospective Japan 2000	2000	0.933	< 1 yr: 22,642 1 to 17 yr: 117,801 ≤ 17 yr: 140,443	< 1 yr: 0/NR 1 to 17 yr: 2/NR ≤ 17 yr: 2/NR	< 1 yr: 0.0/NR 1 to 17 yr: 0.17/NR ≤ 17 yr: 0.14/NR	
Morray et al. 2000	Multicentre: 47 university and 25 paediatric hospitals Prospective USA and Canada 1994-1997	1996	0.935	≤ 18 yr: 1,089,200/NR	≤ 18yr: 39/NR	≤ 18 yr: 0.36/NR	
Murat et al. 2004	University tertiary paediatric hospital Prospective France 2000-2002	2001	0.930	< 1 yr: 3,681 1 to 16 yr: 19,362 ≤ 16 yr: 23,043	< 1 yr: 0/NR 1 to 16 yr: 0/NR ≤ 16 yr: 0/NR	< 1 yr: 0.0/NR 1 to 16 yr: 0.0/NR ≤ 16 yr: 0.0/NR	Cardiac surgery Neurosurgery
Newland et al. 2002	University tertiary hospital Prospective USA	1994	0.948	≤ 20 yr: 16,051	≤ 20 yr: 0/NR	≤ 20 yr: 0.0/NR	

	1989-1999						
Nizeyimana et al. 2024	Three public hospitals Prospective Rwanda 2015	2015	0.509	< 1 yr: 128 1 to 5 yr: 226 ≤ 5 yr: 354	< 1 yr: 2/NR 1 to 5 yr: 4/NR ≤ 5 yr: 6/NR	< 1 yr: 156.25/NR 1 to 5 yr: 177.00/NR ≤ 5 yr: 169.50/NR	Cardiac surgery
Rackow et al. 1961	Multicentre: four tertiary hospitals Retrospective USA 1947-1956	1952	0.865	< 1 yr: 4,308 1 to 12 yr: 30,191 ≤ 12 yr: 34,499	< 1 yr: 4/4 1 to 12 yr: 6/8 ≤ 12 yr: 10/12	< 1 yr: 9.28/9.28 1 to 12 yr: 1.98/2.65 ≤ 12 yr: 2.90/3.48	
Rattana-Arpa et al. 2023	University tertiary hospital Retrospective Thailand 2014-2019	2017	0.790	< 1 yr: 5,365 1 to 17 yr: 37,411 ≤ 17 yr: 42,776	< 1 yr: 2/4 1 to 17 yr: 4/8 ≤ 17 yr: 6/12	< 1 yr: 3.72/7.46 1 to 17 yr: 1.07/2.14 ≤ 17 yr: 1.40/2.80	Cardiac surgery
Sanabria-Carretero et al., 2013	University quaternary paediatric hospital Retrospective Spain 2007-2011	2009	0.900	< 1 yr: 7,826 1 to 18 yr: 35,465 ≤ 18 yr: 43,291	< 1 yr: 2/NR 1 to 18 yr: 2/NR ≤ 18 yr: 4/NR	< 1 yr: 2.56/NR 1 to 18 yr: 0.57/NR ≤ 18 yr: 0.09/NR	
Schleelein et al. 2016	University quaternary paediatric hospital Retrospective EUA 2010-2012	2011	0.919	≤ 18 yr: 55,070	≤ 18 yr: 5/NR	≤ 18 yr: 0.90/NR	Cardiac surgery and catheterization cases

Talabi et al. 2018	University tertiary hospital Retrospective Nigeria 2007-2016	2012	0.499	< 1 yr: 1,715 1 to 15 yr: 2,393 ≤ 15 yr: 4,108	< 1 yr: 0/0 1 to 15 yr: 2/2 ≤ 15 yr: 2/2	< 1 yr: 0.0/0.0 1 to 15 yr: 8.36/8.36 ≤ 15 yr: 4.86/4.86
Talabi et al. 2021	University tertiary hospital Prospective Nigeria 2019-2020	2020	0.537	< 1 yr: 154 1 to 15 yr: 376 ≤ 15 yr: 530	< 1 yr: 1/1 1 to 15 yr: 0/0 ≤ 15 yr: 1/1	< 1 yr: 64.94/64.94 1 to 15 yr: 0.0/0.0 ≤ 15 yr: 18.87/18.87
Tay et al. 2001	Tertiary paediatric hospital Prospective Singapore 1977-1979	1978	0.882	< 1 yr: 1,022 1 to 14 yr: 8,978 ≤ 14 yr: 10,000	< 1 yr: 0/NR 1 to 14 yr: 0/NR ≤ 14 yr: 0/NR	< 1 yr: 0.0/NR 1 to 14 yr: 0.0/NR ≤ 14 yr: 0.0/NR
Tiret et al. 1988	Multicentre: 440 university and private paediatric and general hospitals Prospective France 1978-1982	1980	0.895	< 1 yr: 47,388 1 to 14 yr: 244,609 ≤ 14 yr: 291,997	< 1 yr: 0/NR 1 to 14 yr: 1/NR ≤ 14 yr: 1/NR	< 1 yr: 0.0/NR/NR 1 to 14 yr: 0.04/NR ≤ 14 yr: 0.03/NR
van der Griend et al., 2011	University tertiary hospital Retrospective Australia 2003-2008	2006	0.943	< 1 yr: 15,255 1 to 17 yr: 86,630 ≤ 17 yr: 101,885	< 1 yr: 2/3 1 to 17 yr: 3/7 ≤ 17 yr: 5/10	< 1 yr: 1.31/1.97 1 to 17 yr: 0.35/0.80 ≤ 17 yr: 0.49/0.98
Westerkamp et al. 2018	University quaternary hospital Retrospective	2012	0.915	≤ 16 yr: 14,300	≤ 16 yr: 1/NR	≤ 16 yr: 0.70/NR

	The Netherlands 2010-2013						
Williams et al. 2017	University paediatric hospital Retrospective USA 2010-2016	2013	0.920	≤ 17 yr: 54,469	≤ 17 yr: 3/NR	≤ 17 yr: 0.55/NR	
Zgleszewski et al. 2016	University tertiary paediatric hospital Prospective USA 2000-2011	2006	0.938	≤ 18 yr: 276,209	≤ 18 yr: 2/4	≤ 18 yr: 0.07/0.14	Cardiac catheterization laboratories

HDI = Human Development Index; R = not revealed; OR = operating room; NICU = Neonatal Intensive Care Unit; PICU = Paediatric Intensive Care Unit; **green** = HDI <0.800 country pre-2001; **dark red** = HDI ≥0.800 country pre-2001; **blue** = HDI <0.800 country 2001-2025; **black** = HDI ≥0.800 country 2001-2025.

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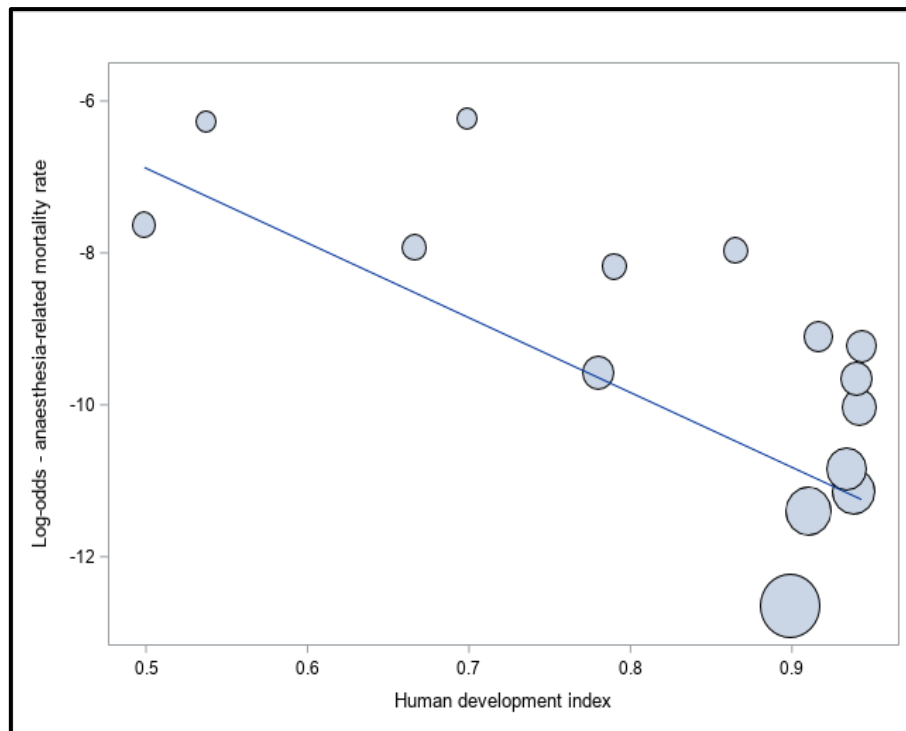
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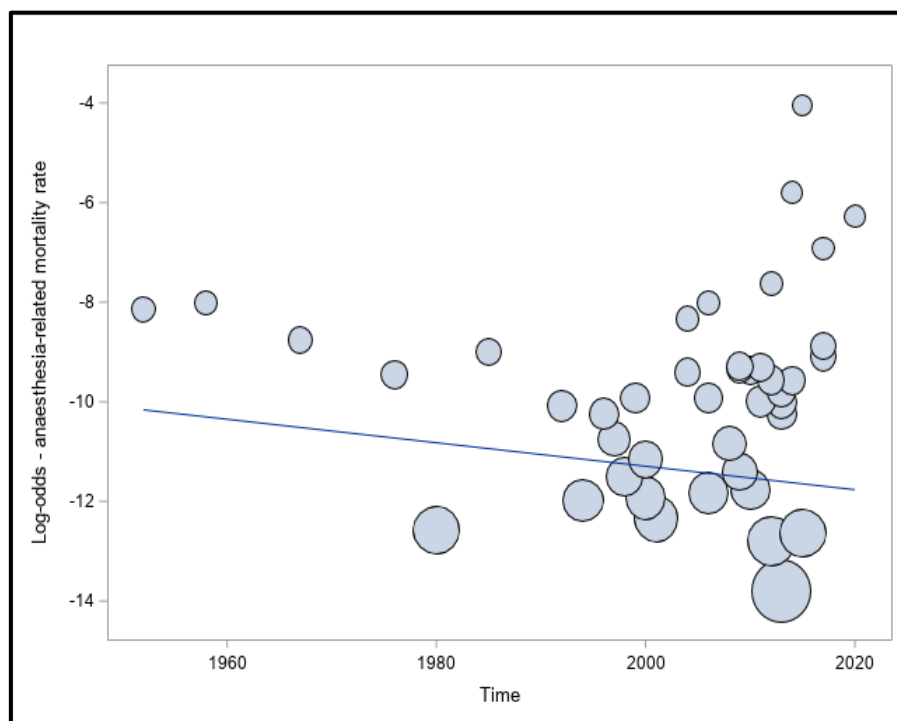
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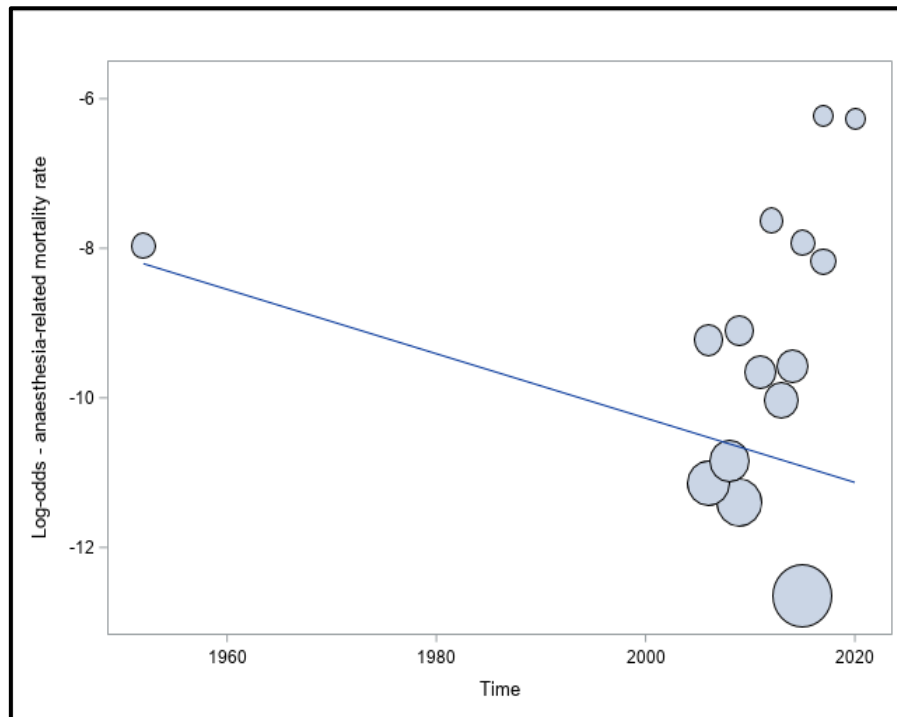
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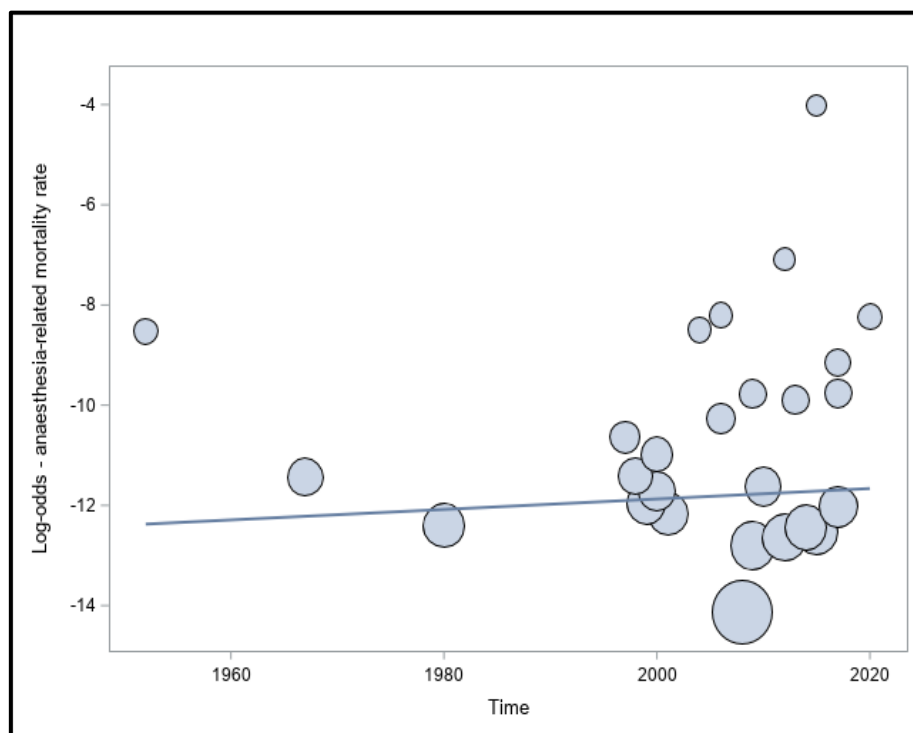
Supplementary Fig. 1. Meta-regression of short-term anaesthesia-related mortality rates in the overall paediatric population by country Human Development Index (slope: -9.84, 95% CI -17.95 to -1.73; $P=0.033$).



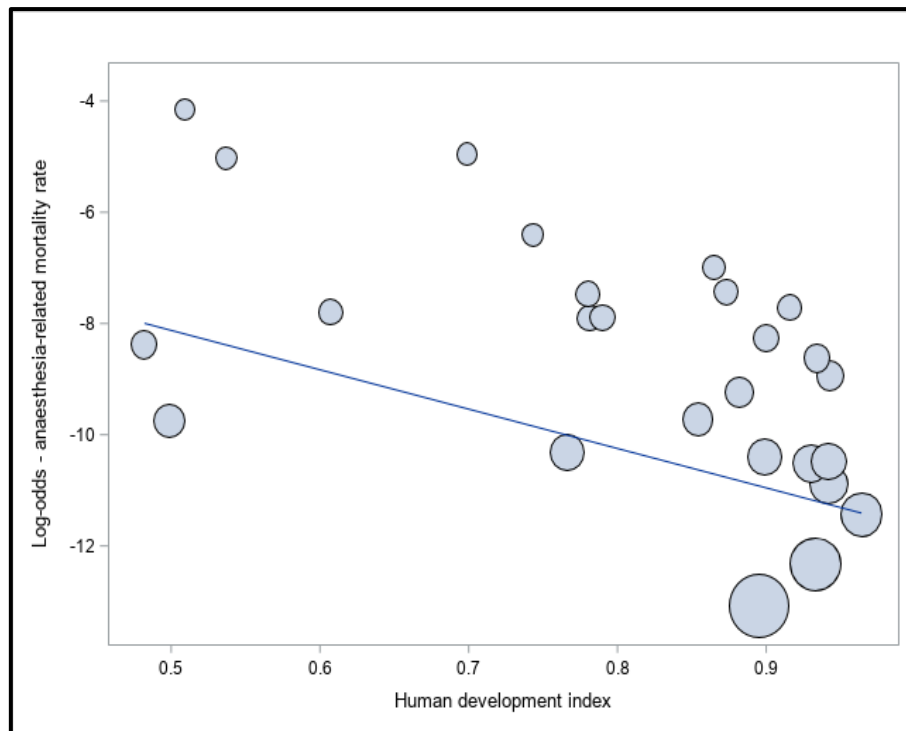
Supplementary Fig. 2. Meta-regression of early-onset anaesthesia-related mortality rates in the overall paediatric population by time (slope: -0.02, 95% CI -0.06 to 0.01; $P=0.25$).



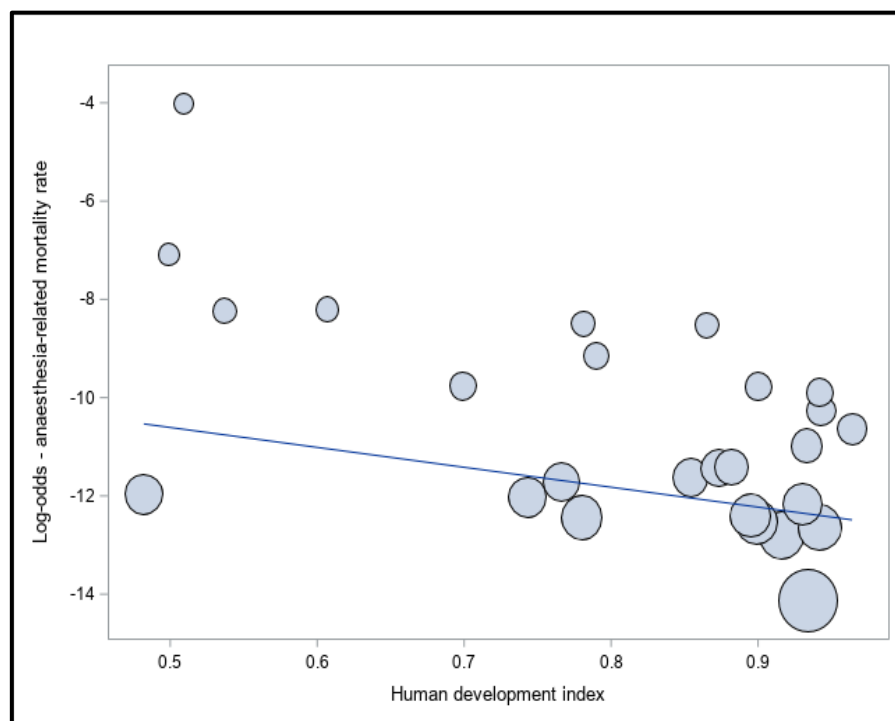
Supplementary Fig. 3. Meta-regression of short-term anaesthesia-related mortality rates in the overall paediatric population by time (slope: -0.04, 95% CI -0.12 to 0.04; $P=0.34$).



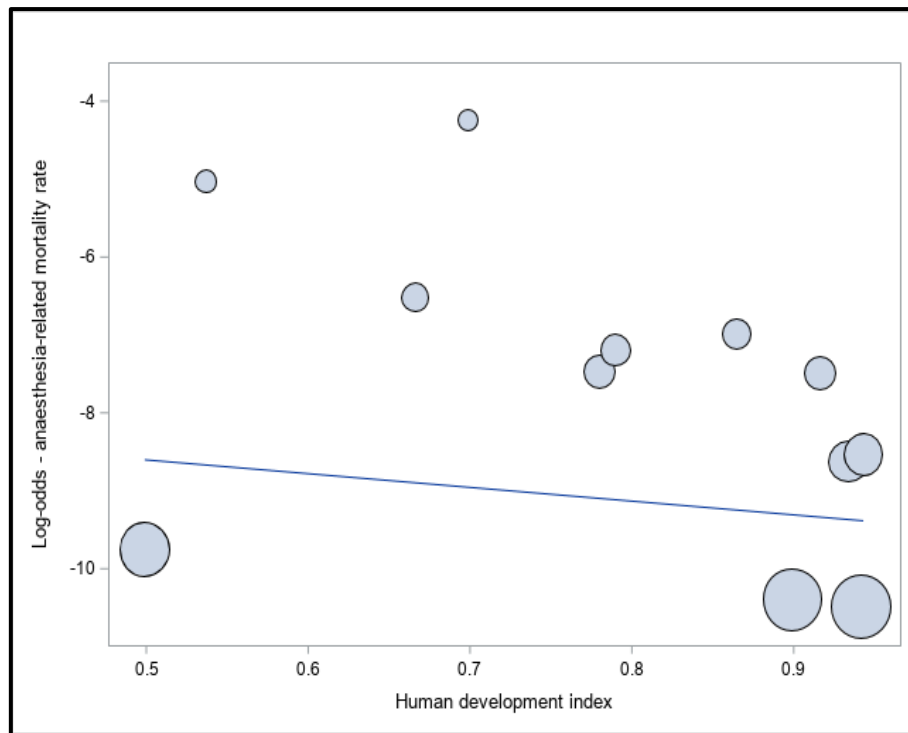
Supplementary Fig. 4. Meta-regression of early-onset anaesthesia-related mortality rates in children one year and older by time (slope: 0.01, 95% CI -0.05 to 0.02; $P=0.48$).



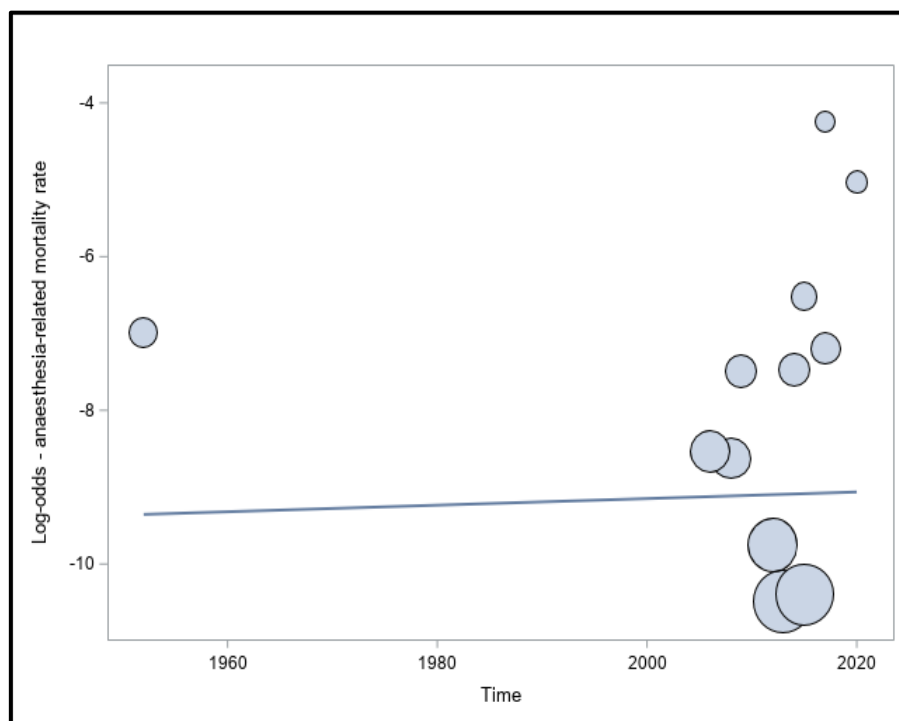
Supplementary Fig. 5. Meta-regression of early-onset anaesthesia-related mortality rates in children younger than one year old by country Human Development Index (slope: -7.07, 95% CI -12.75 to -1.40; $P=0.022$).



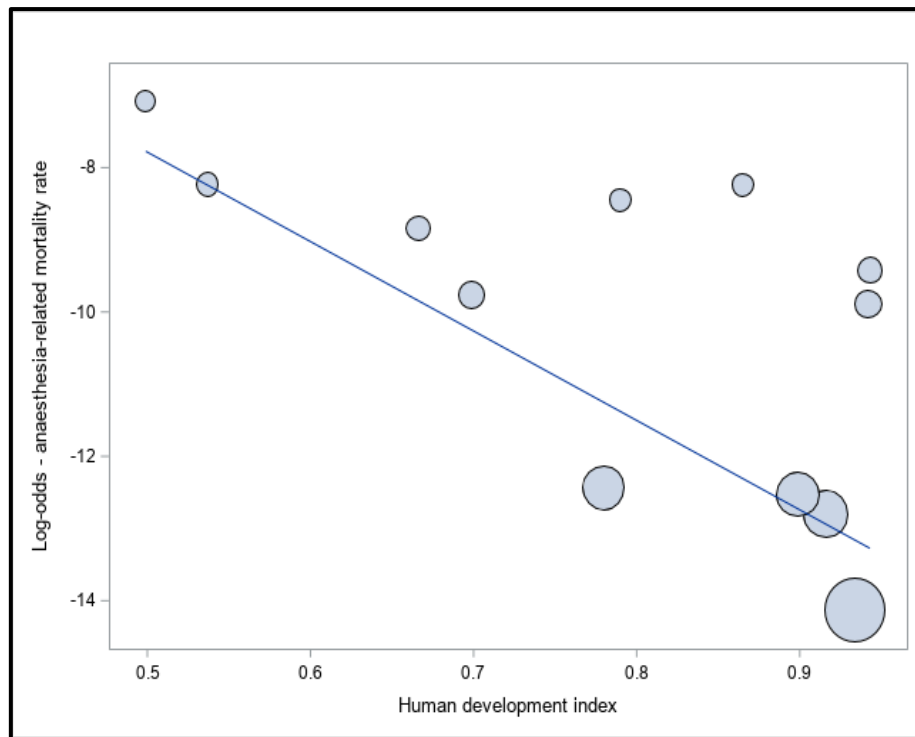
Supplementary Fig. 6. Meta-regression of early-onset anaesthesia-related mortality rates in children one year and older by country Human Development Index (slope: -4.05, 95% CI -8.44 to 0.34; $P=0.083$).



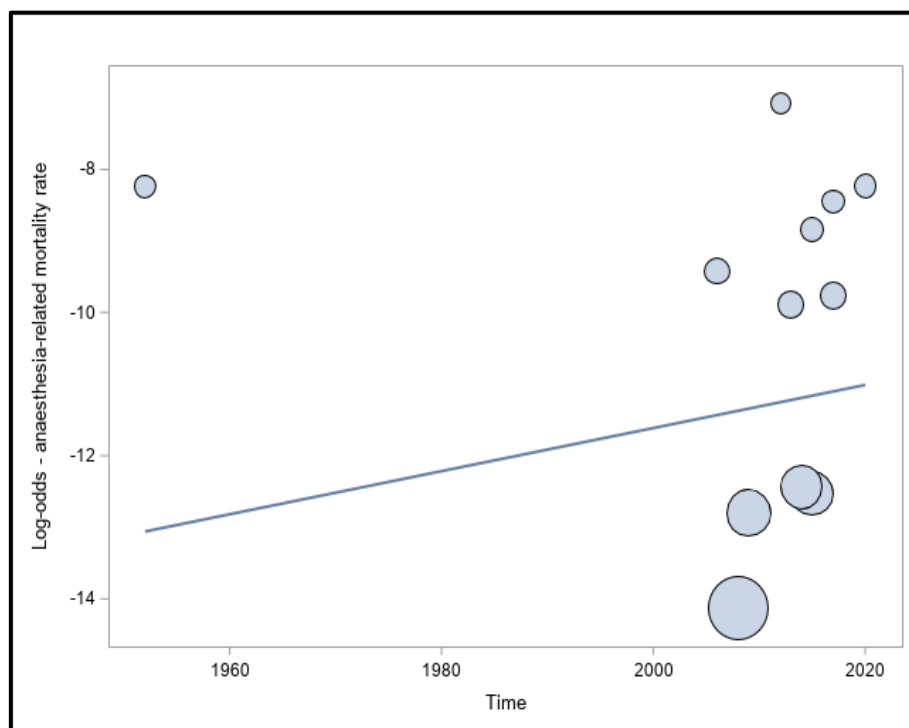
Supplementary Fig. 7. Meta-regression of short-term anaesthesia-related mortality rates in children younger than one year old by country Human Development Index (slope: -1.76, 95% CI -7.35 to 3.82; $P=0.55$).



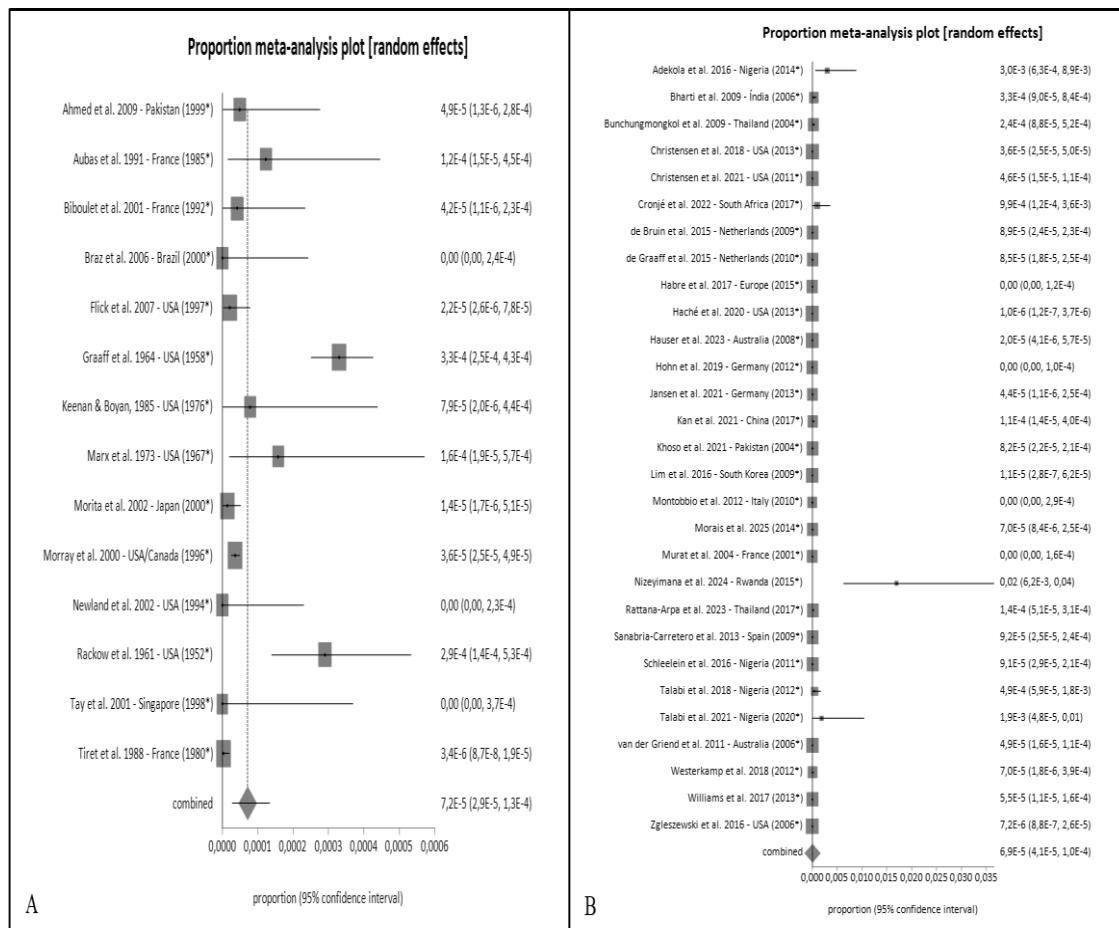
Supplementary Fig. 8. Meta-regression of short-term anaesthesia-related mortality rates in children younger than one year old by time (slope: 0.03, 95% CI -0.10 to 0.03; $P=0.33$).



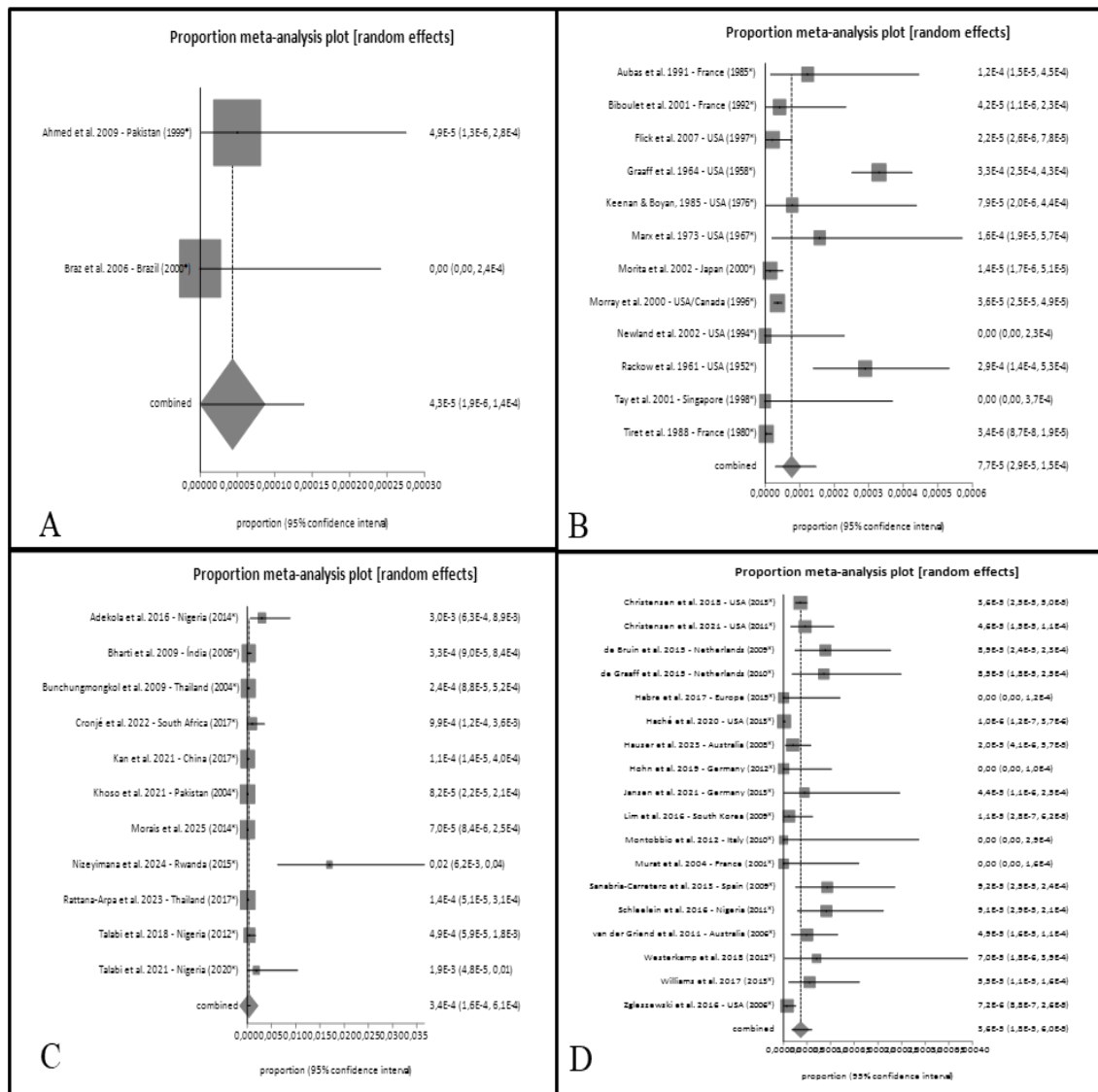
Supplementary Fig. 9. Meta-regression of short-term anaesthesia-related mortality in children one year and older by country Human Development Index (slope: -12.38, 95% CI -21.53 to -3.24; $P=0.024$).



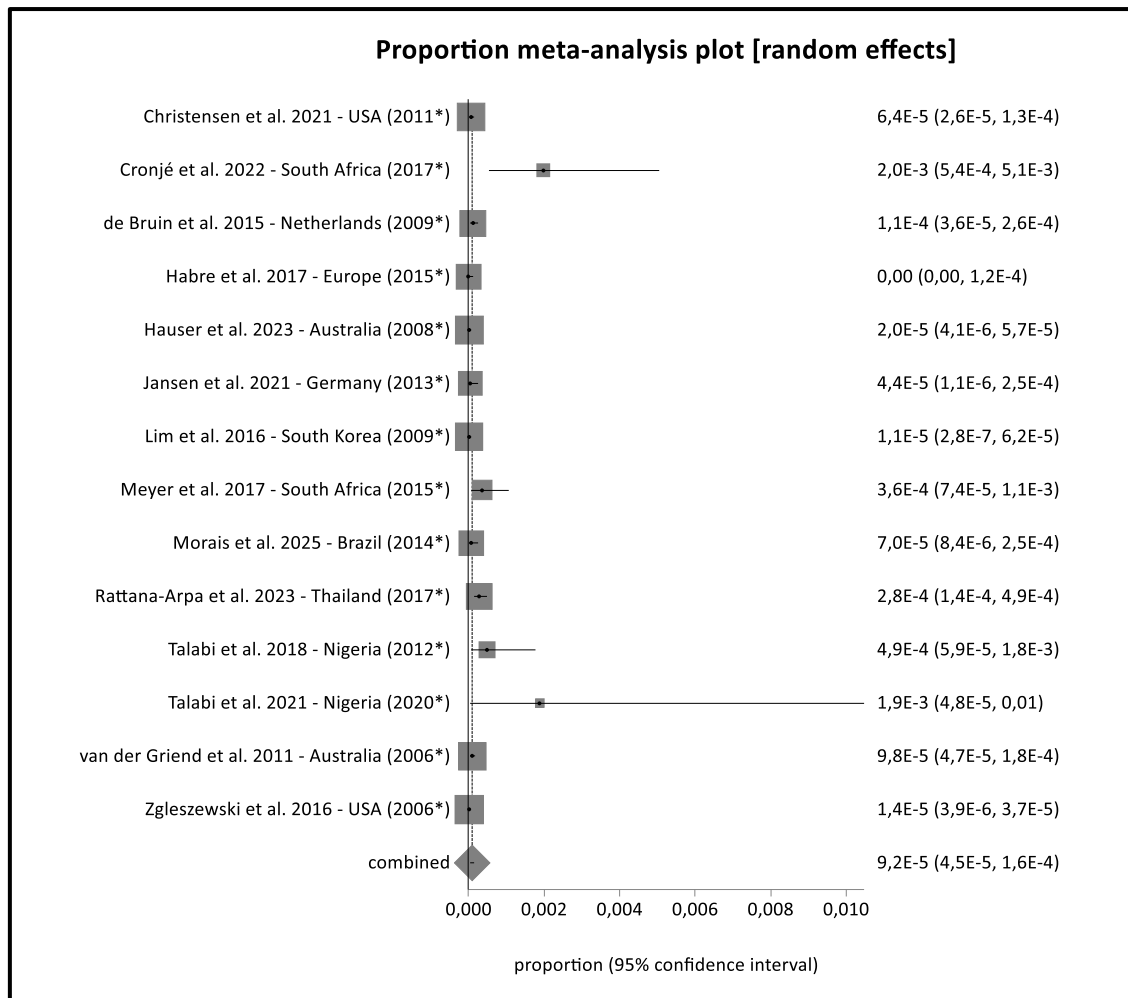
Supplementary Fig. 10. Meta-regression of short-term anaesthesia-related mortality in children one year and older by time (slope: 0.009, 95% CI -0.14 to 0.12; $P=0.88$).



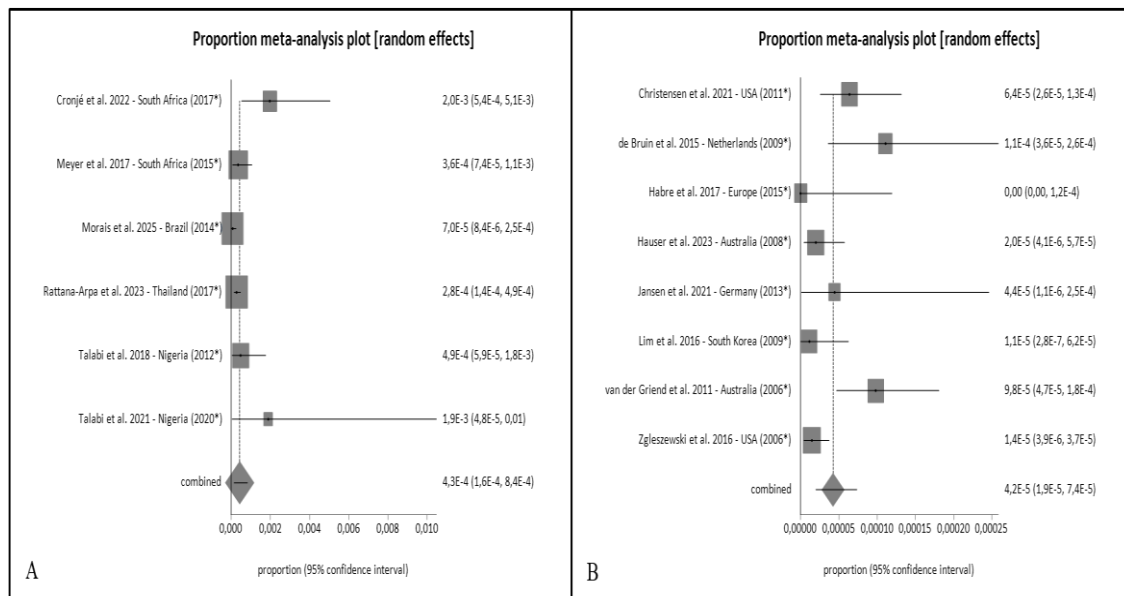
Supplementary Fig. 11. Pooled analysis of proportional random effects from early-onset anaesthesia-related mortality. A. All studies pre-2001: 0.000072 (95% CI 0.000029 to 0.000134); B. All studies 2001-2025 = 0.000069 (95% CI 0.000041 to 0.000104).



Supplementary Fig. 12. Pooled analysis of proportional random effects from early-onset anaesthesia-related mortality. A. Human Development Index (HDI) < 0.800 pre-2001: 0.000043 (95% CI 0.000002 to 0.000139); B. HDI ≥ 0.800 pre-2001: 0.000077 (95% CI 0.000029 to 0.000148); C. HDI < 0.800 2001-2025: 0.000344 (95% CI 0.000157 to 0.000605); D. HDI ≥ 0.800 2001-2025: 0.000036 (95% CI 0.000018 to 0.00006).



Supplementary Fig. 13. Pooled analysis of proportional random effects from short-term anaesthesia-related mortality. All studies 2001-2025 = 0.000092 (95% CI 0.000045 to 0.000156).

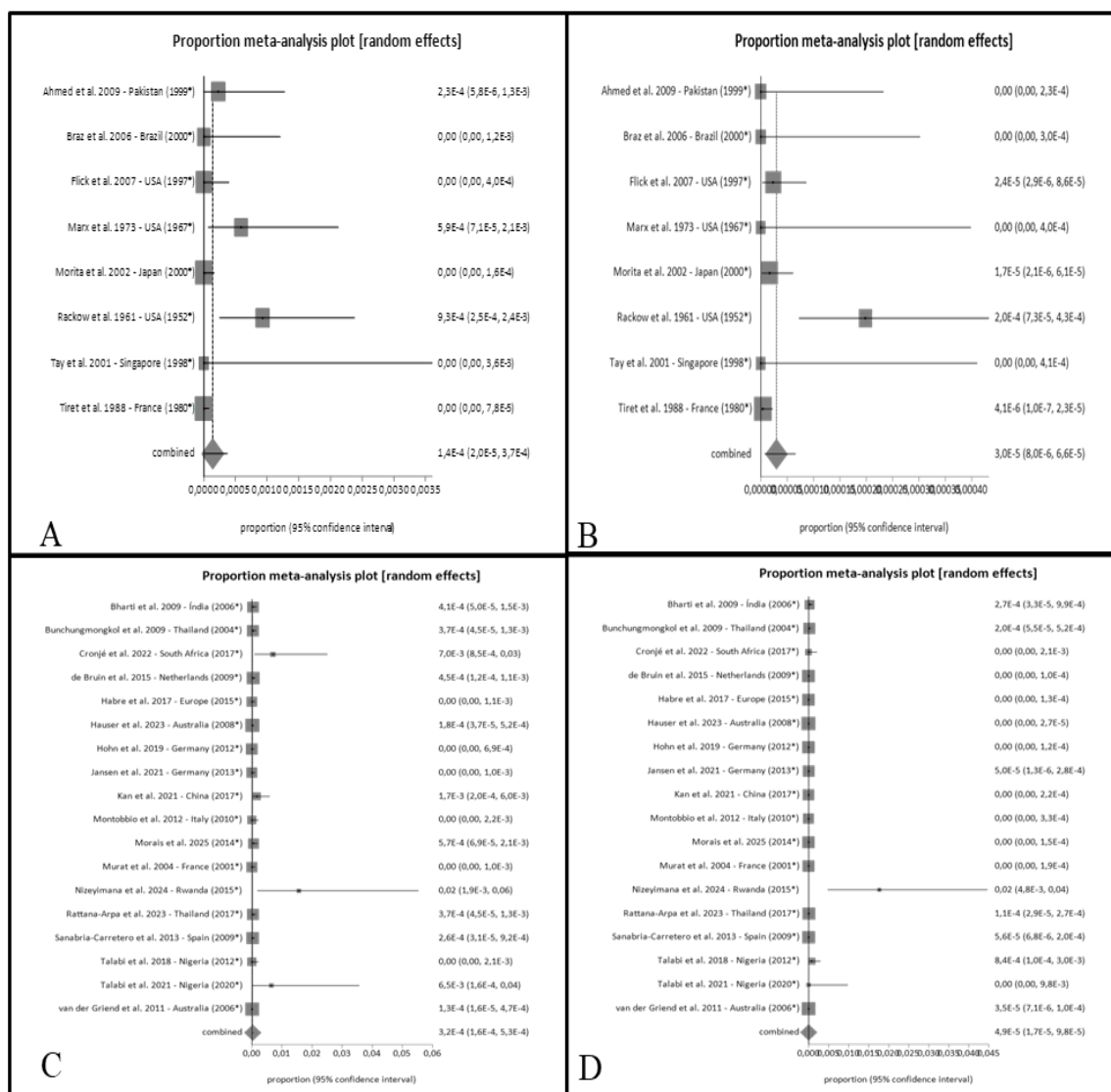


Supplementary Fig. 14. Pooled analysis of proportional random effects from short-term anaesthesia-related mortality. A. HDI <0.800 2001-2025: 0.000435 (95% CI 0.00016 to 0.000844); HDI ≥0.800 2001-2025: 0.000042 (95% CI 0.000019 to 0.000074).

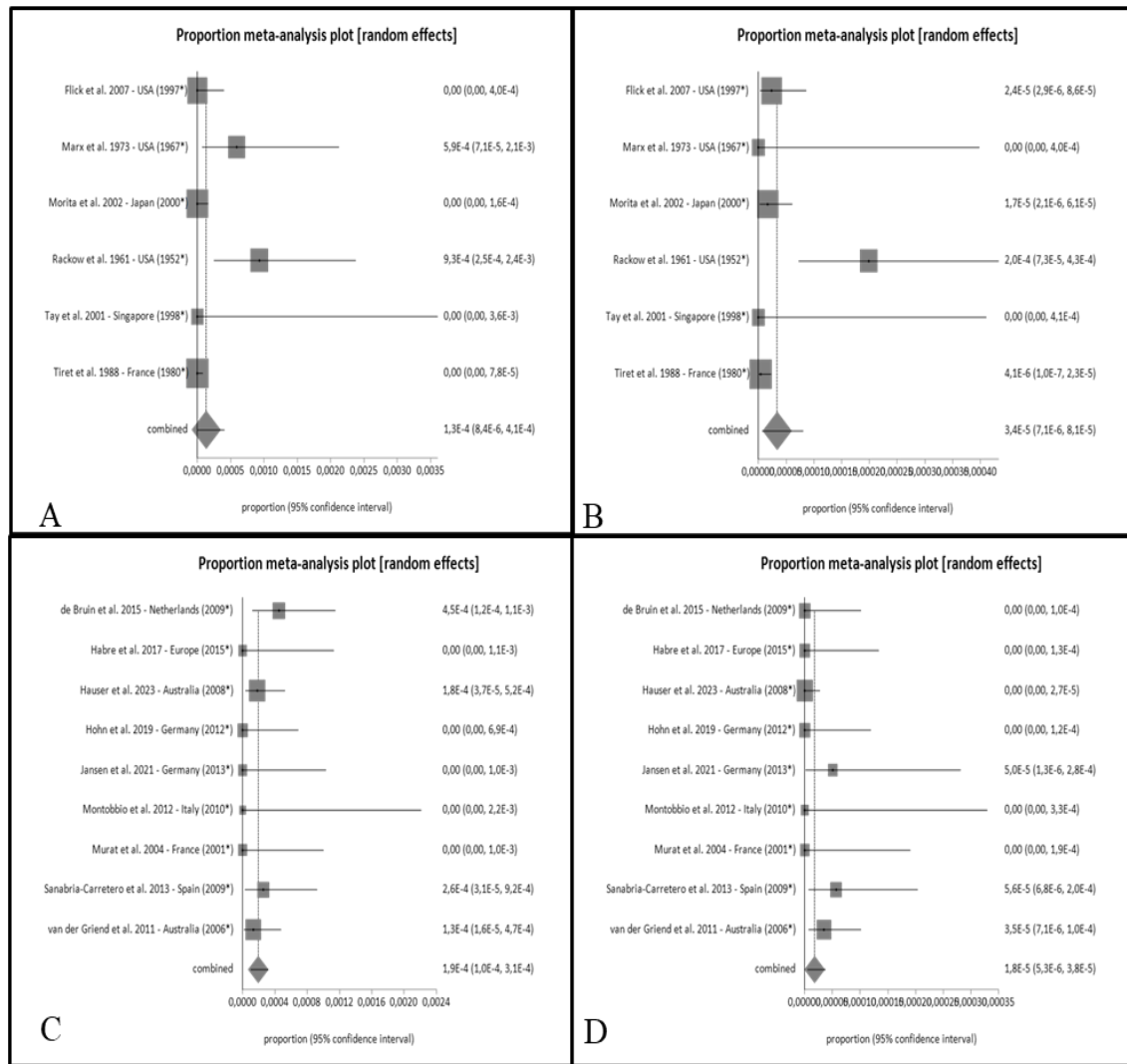
Supplementary Table 4. Anaesthesia-related mortality rates (ARMRs) (per 10,000 anaesthetic procedures) according to age group by period and by country Human Development Index (HDI) (raw event rates provided).

	Events/patients n	Proportional meta-analysis (95% CI)
Early-onset ARMRs		
Pre-2001		
< 1 year	7/95,455	1.41 (0.20-3.70)
≥ 1 year	11/522,488	0.30 (0.08-0.66)
2001-2025		
< 1 year	26/85,579	3.22 (1.64-5.33)
≥ 1 year	22/486,507	0.49 (0.17-0.98)
HDI ≥0.800 Pre-2001		
< 1 year	6/88,014	1.33 (0.08-4.06)
≥ 1 year	11/494,460	0.34 (0.07-0.81)
HDI ≥0.800 2001-2025		
< 1 year	11/62,959	1.93 (1.02-3.13)
≥ 1 year	6/375,438	0.18 (0.05-0.38)
HDI <0.800 Pre-2001		
< 1 year	1/7,441	2.09 (0.10-6.66)
≥ 1 year	0/28,028	0.18 (0.03-1.01)
HDI <0.800 2001-2025		
< 1 year	15/22,620	8.88 (3.26-17.27)
≥ 1 year	16/111,069	1.88 (0.41-4.43)
Short-term ARMRs		
2001-2025		
< 1 year	24/60,085	4.82 (1.92-9.03)
≥ 1 year	19/380,246	0.60 (0.14-1.37)
HDI ≥0.800 2001-2025		
< 1 year	11/47,714	2.47 (1.18-4.24)
≥ 1 year	8/306,129	0.23 (0.09-0.75)
HDI <0.800 2001-2025		
< 1 year	13/12,371	14.82 (3.76-33.17)
≥ 1 year	11/74,117	1.78 (0.30-4.51)

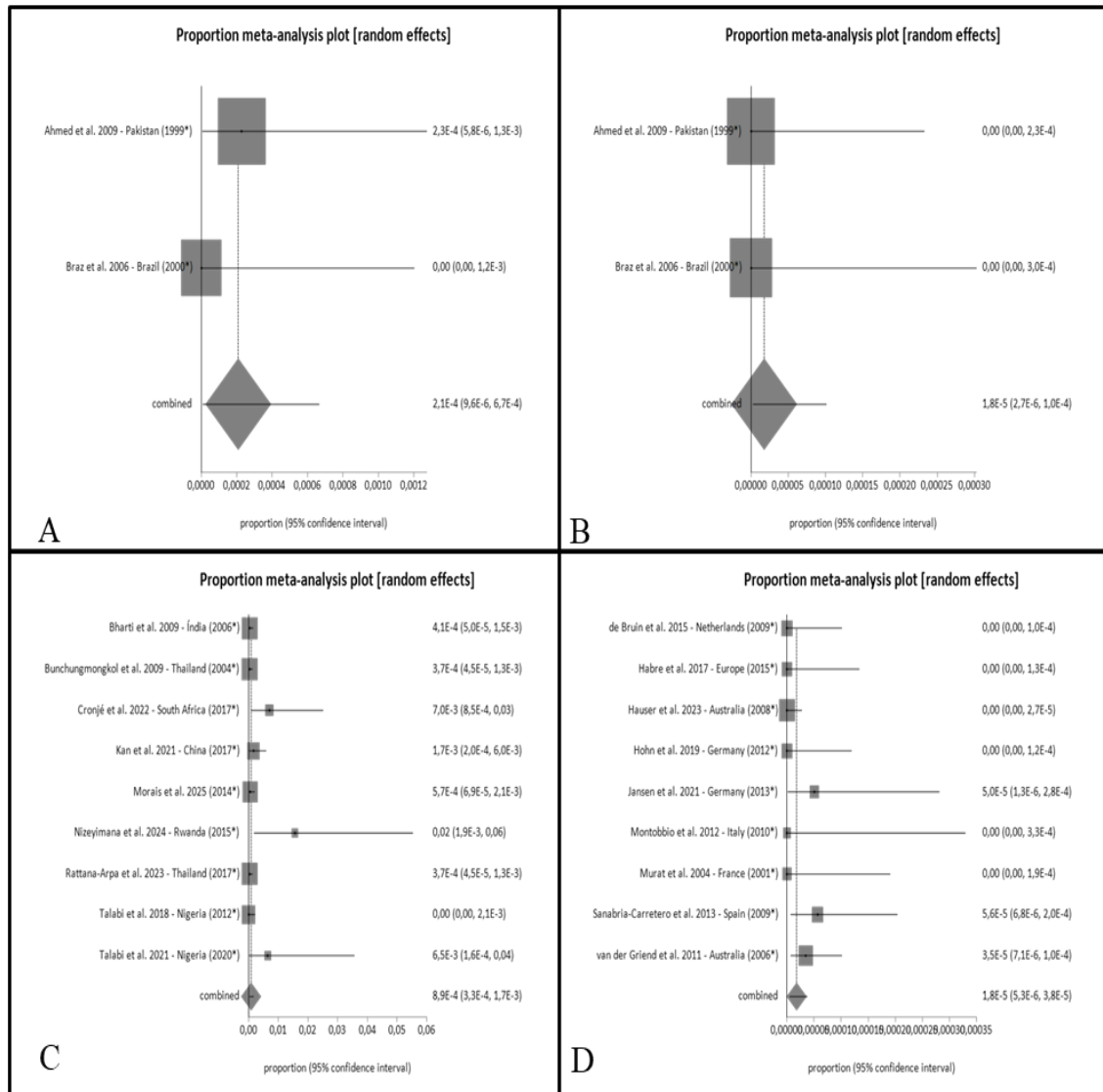
HDI: Human Development Index; CI = confidence interval



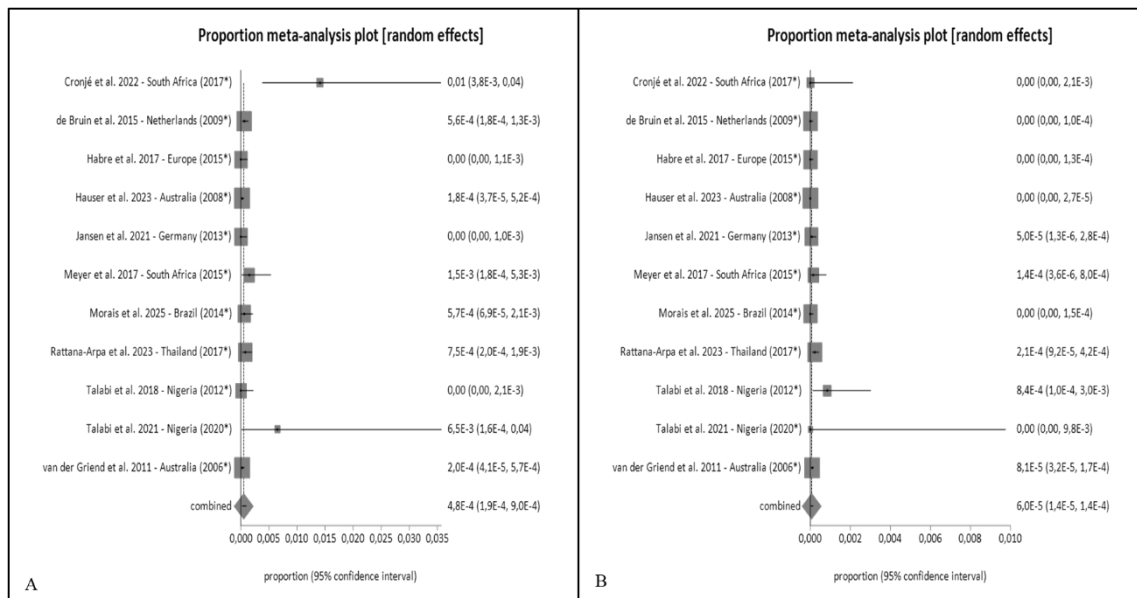
Supplementary Fig. 15. Pooled analysis of proportional random effects from early-onset anaesthesia-related mortality by age group. A. < 1 year pre-2001: 0.000141 (95% CI 0.00002 to 0.00037); B. ≥ 1 year pre-2001: 0.000030 (95% CI 0.000008 to 0.000066); C. < 1 year 2001-2025: 0.000322 (95% CI 0.000164 to 0.000533); D. ≥ 1 year 2001-2025: 0.000049 (95% CI 0.000017 to 0.000098).



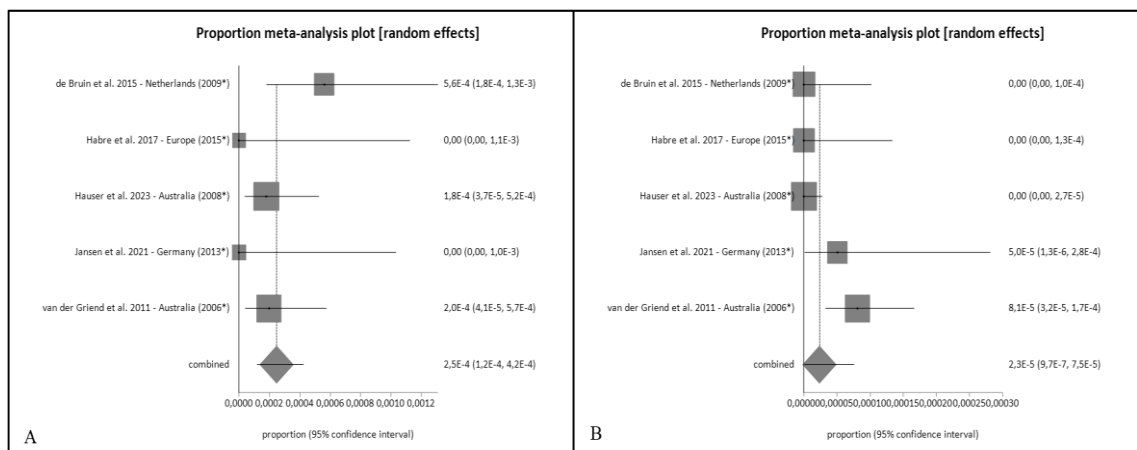
Supplementary Fig. 16. Pooled analysis of proportional random effects from early-onset anaesthesia-related mortality by age group in Human Development Index ≥ 0.800 . A. < 1 year pre-2001: 0.000133 (95% CI 0.000008 to 0.000406); B. ≥ 1 year pre-2001: 0.000034 (95% CI 0.000007 to 0.000081); C. < 1 year 2001-2025: 0.000193 (95% CI 0.000102 to 0.000313); D. ≥ 1 year 2001-2025: 0.000018 (95% CI 0.000005 to 0.000038).



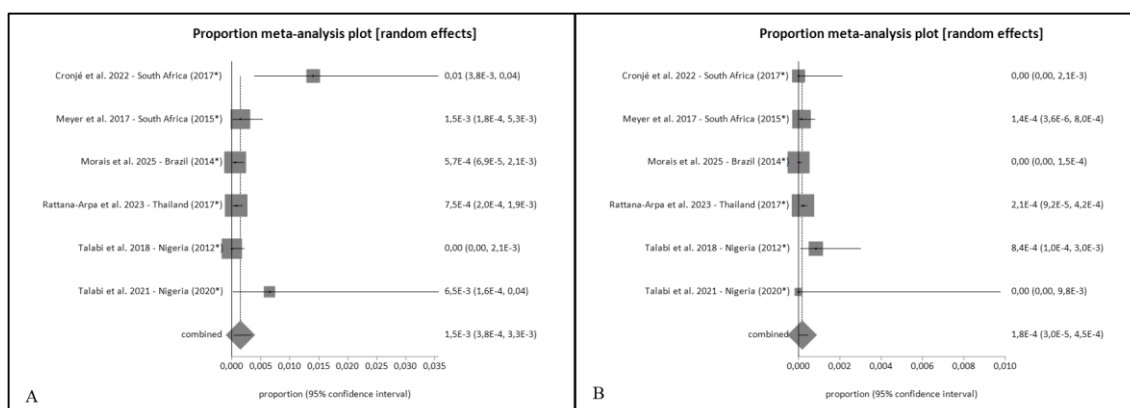
Supplementary Fig. 17. Pooled analysis of proportional random effects from early-onset anaesthesia-related mortality by age group in Human Development Index <0.800. A. < 1 year pre-2001: 0.000209 (95% CI 0.00001 to 0.000666); B. $\geq$ 1 year pre-2001: 0.000018 (95% CI 0.000003 to 0.000101); C. < 1 year 2001-2025: 0.000888 (95% CI 0.000326 to 0.001727); D. $\geq$ 1 year 2001-2025: 0.000188 (95% CI = 0.000041 to 0.000443).



Supplementary Fig. 18. Pooled analysis of proportional random effects from short-term anaesthesia-related mortality by age group. A. < 1 year 2001-2025: 0.000482 (95% CI 0.000192 to 0.000903); B. ≥ 1 year 2001-2025: 0.00006 (95% CI 0.000014 to 0.000137).



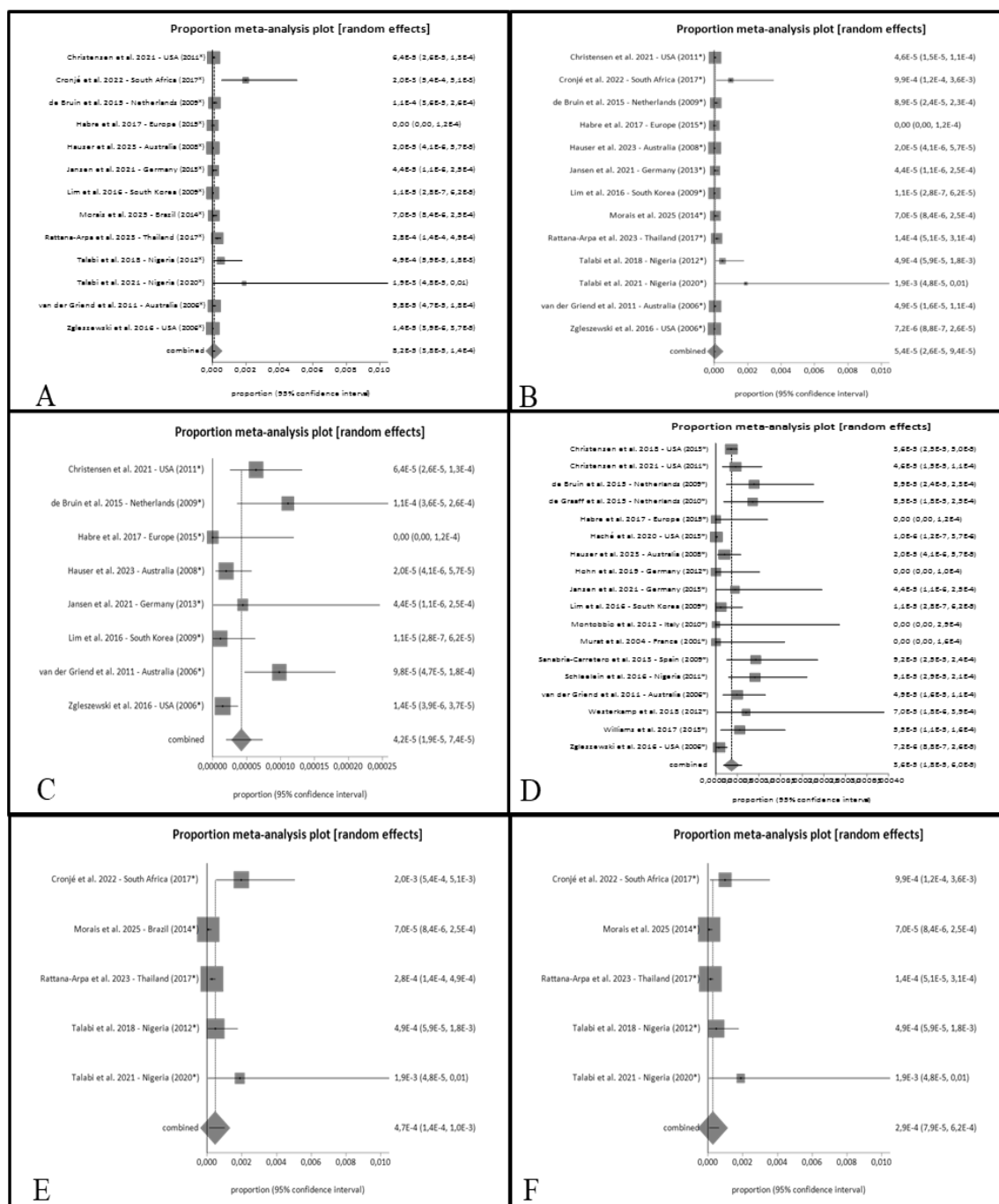
Supplementary Fig. 19. Pooled analysis of proportional random effects from short-term anaesthesia-related mortality by age group in Human Development Index ≥ 0.800. A. < 1 year 2001-2025: 0.000247 (95% CI 0.000118 to 0.000424); B. ≥ 1 year 2001-2025: 0.000023 (95% CI 0.000009 to 0.000075).



Supplementary Fig. 20. Pooled analysis of proportional random effects from short-term anaesthesia-related mortality by age group in Human Development Index <0.800. A. < 1 year 2001-2025: 0.001482 (95% CI 0.000376 to 0.003317); B. ≥ 1 year 2001-2025: 0.000178 (95% CI = 0.00003 to 0.000451).

Supplementary Table 5. Proportional meta-analysis of early-onset *versus* short-term anaesthesia-related mortality rates (per 10,000 anaesthetic procedures) in overall paediatric population and by country Human Development Index (HDI) (raw event rates provided) in 2001-2025 period.

	Events/patients n	Proportional meta- analysis (95% CI)	Odds ratio (95% CI)	P value
2001-2025				
Short-term	52/906,804	0.82 (0.38-1.42)	1.50 (0.99-2.36)	0.052
Early-onset	34/906,804	0.54 (0.26-0.94)	Ref	
HDI ≥0.800 2001-2025				
Short-term	31/828,641	0.42 (0.19-0.74)	1.48 (0.85-2.57)	0.16
Early-onset	21/828,641	0.31 (0.15-0.52)	Ref	
HDI <0.800 2001-2025				
Short-term	21/78,163	4.71 (1.37-10.03)	1.61 (0.91-3.23)	0.17
Early-onset	13/78,163	2.85 (0.79-6.19)	Ref	



Supplementary Fig. 21. Pooled analysis of proportional random effects from short-term and early-onset anaesthesia-related mortality (ARM) in 2001-2025 period. A. short-term ARM overall paediatric population: 0.000082 (95% CI 0.000038 to 0.000142); B. early-onset ARM overall paediatrics population: 0.000054 (95% CI 0.000026 to 0.000094); C. short-term in Human Development Index (HDI) ≥ 0.800 : 0.000042 (95% CI 0.000019 to 0.000074); D. early-onset HDI ≥ 0.800 : 0.000031 (95% CI 0.000015 to 0.000052); E. short-term in HDI < 0.800 : 0.000471 (95% CI 0.000137 to 0.001003); F. early-onset in HDI < 0.800 : 0.000285 (95% CI 0.000079 to 0.000619).

Supplementary Table 6. Short-term anaesthesia-related mortality rates in overall paediatric population by country's HDI and quartile distribution in the 2001-2025 period.

Investigator/year of publication	Country/Continent	Anaesthesia-related mortality rates (per 10,000 anaesthetics)	Quartile
Hohn et al., 2019	Germany	0.00	Q1: 0.16
Habre et al., 2015	33 European countries	0.00	
Lim et al., 2016	South Korea	0.12	
Hauser et al., 2023	Australia	0.20	
Jansen et al., 2021	Germany	0.44	
Christensen et al., 2021	USA	0.64	
Morais et al., 2025	Brazil	0.70	Q2 (median): 0.84
van der Griend et al., 2011	Australia	0.98	
de Bruin et al., 2015	The Netherlands	1.11	
Rattana-Arpa et al., 2023	Thailand	2.80	Q3: 4.23
Meyer et al., 2017	South Africa	3.60	
Talabi et al., 2018	Nigeria	4.86	
Talabi et al., 2021	Nigeria	18.87	
Cronjé et al., 2022	South Africa	19.80	

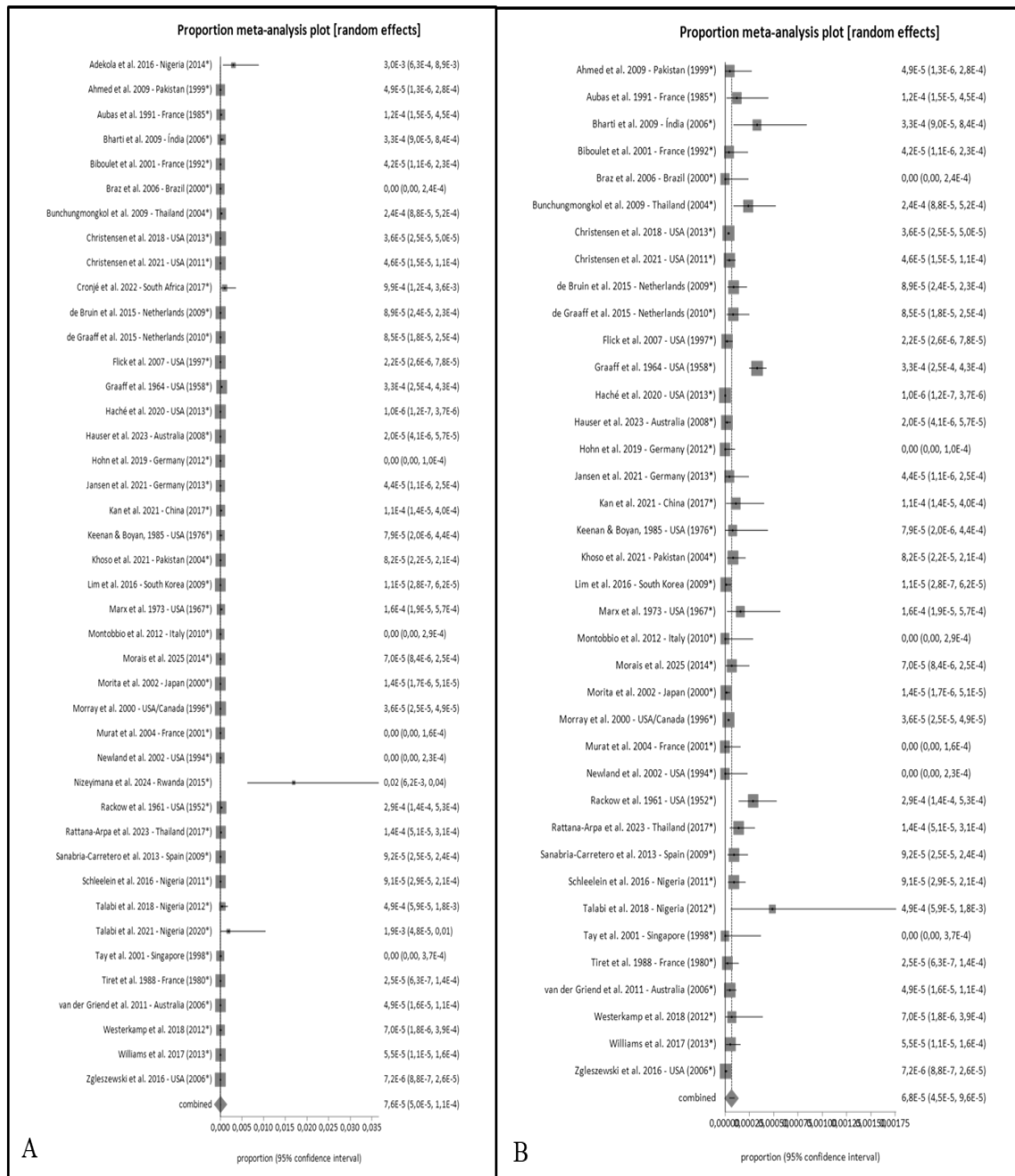
HDI: Human Development Index; Q1, Q2 and Q3: first, second and third quartiles, respectively. Blue highlight indicates HDI ≥ 0.800 country, and yellow highlight indicates HDI < 0.800 country.

Supplementary Table 7. Proportional meta-analysis of aetiology (%) of anaesthesia-related mortality rates in children by country Human Development Index (HDI) status in 2001-2025.

	Cause/mortality n	Proportional meta-analysis (95% CI)	P value for subgroup		
			Cardiovascular vs Respiratory	Cardiovascular vs Medication	Respiratory vs Medication
HDI <0.800					
Cardiovascular- related	21/48	40.28 (23.89-57.87)	0.71	<0.0001	
Respiratory- related	24/48	50.38 (37.19-63.54)			<0.0001
Medication- related	3/48	8.38 (2.51-17.16)			
HDI ≥0.800					
Cardiovascular- related	23/26	84.10 (68.99-94.82)	<0.0001	<0.0001	
Respiratory- related	3/26	15.90 (5.18-31.01)			0.14
Medication- related	0/26	5.08 (0.22-15.72)			

Supplementary Table 8. Anaesthesia-related mortality rates (per 10,000 anaesthetic procedures) in children stratified by ASA 3-5 status and country Human Development Index (HDI) status in 2001-2025.

	Events/patients n	Proportional meta- analysis (95% CI)	Odds ratio (95% CI)	P value
ASA 3-5				
HDI ≥0.800	22/122648	2.32 (0.81-4.61)	Ref	<0.0001
HDI <0.800	23/11793	45.70 (10.49-105.54)	10.24 (9.16-11.44)	



Supplementary Fig. 22. Pooled analysis of proportional random effects from early-onset anaesthesia-related mortality. A. All studies pre-2001 and 2001-2025: 0.000076 (95% CI 0.00005 to 0.000107); B. Exclusion of outlier studies: 0.000068 (95% CI 0.000045 to 0.000096).