Perioperative and anaesthetic-related mortality in developed and developing countries: a systematic review and meta-analysis

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Summary

Background **The magnitude of risk of death related to surgery and anaesthesia is not well understood. We aimed to assess whether the risk of perioperative and anaesthetic-related mortality has decreased over the past five decades and whether rates of decline have been comparable in developed and developing countries.**

Methods **We did a systematic review to identify all studies published up to February, 2011, in any language, with a sample size of over 3000 that reported perioperative mortality across a mixed surgical population who had undergone general anaesthesia. Using standard forms, two authors independently identified studies for inclusion and extracted information on rates of anaesthetic-related mortality, perioperative mortality, cardiac arrest, American Society of Anesthesiologists (ASA) physical status, geographic location, human development index (HDI), and year. The primary outcome was anaesthetic sole mortality. Secondary outcomes were anaesthetic contributory mortality, total perioperative mortality, and cardiac arrest. Meta-regression was done to ascertain weighted event rates for the outcomes.**

Findings **87 studies met the inclusion criteria, within which there were more than 21·4 million anaesthetic administrations given to patients undergoing general anaesthesia for surgery. Mortality solely attributable to anaesthesia declined over time, from 357 per million (95% CI 324–394) before the 1970s to 52 per million (42–64) in the 1970s–80s, and 34 per million (29–39) in the 1990s–2000s (p<0·00001). Total perioperative mortality decreased over time, from 10 603 per million (95% CI 10 423–10 784) before the 1970s, to 4533 per million (4405–4664) in the 1970s–80s, and 1176 per million (1148–1205) in the 1990s–2000s (p<0·0001). Meta-regression showed a significant relation between risk of perioperative and anaesthetic-related mortality and HDI (all p<0·00001). Baseline risk status of patients who presented for surgery as shown by the ASA score increased over the decades (p<0·0001).**

Interpretation **Despite increasing patient baseline risk, perioperative mortality has declined significantly over the past 50 years, with the greatest decline in developed countries. Global priority should be given to reducing total perioperative and anaesthetic-related mortality by evidence-based best practice in developing countries.**

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Background

Death is one of the most feared complications of surgery, yet the magnitude of risk of death related to surgery and anaesthesia is not well understood. Fortunately, mortality rates in the perioperative period are low.[1] However, this rarity makes quantification of perioperative mortality difficult in individual studies.

More than 230 million major surgical procedures are undertaken annually worldwide.[2] Since fewer than 4% of the major surgical procedures worldwide are done in developing countries,[2,3] there has been a substantial paucity of research to assess whether perioperative-related and anaesthetic-related mortality are greater in developing than in developed countries.[3,4] The recent introduction of the Safe Surgery Checklist has further focused efforts on reducing surgical morbidity and mortality in both developed and developing countries.[5] Although there is a widespread opinion that surgery and general anaesthesia have become safer over time, a comprehensive, systematic global analysis of evidence on this topic has not been done.

In response to a call for action on gaps in surgery safety in low-resource settings,[6] we aimed to synthesise the available global data on anaesthetic and surgery-related deaths in high-income versus low-income settings to assess, through meta-regression, whether the risk of perioperative and anaesthesia-related mortality has decreased progressively over time and whether temporal trends differ for developed versus developing countries.

Methods

Search strategy and selection criteria

We did a systematic review with meta-analysis and meta-regression in accordance with recent methodological guidelines.[7,8] The research question, search strategy, inclusion criteria, and statistical analyses were prespecified. We did a systematic search to identify all observational or randomised studies that reported perioperative mortality, anaesthetic-related mortality, or perioperative cardiac arrest. Two investigators (DB and JM) systematically searched Medline, Cochrane Central, Scopus, and Current Contents databases from the date of inception until April 7, 2009. Routine additional searches of Medline were done thereafter until Feb 3, 2011. Search terms included variants of anesthetic, anaesthetic, anesthesia, anaesthesia, surgery, operation, intra-operative, perioperative, perisurgical, postoperative, post-surgical, death, mortality, survival, and cardiac arrest, using text words and Medical Subject Headings (MeSH) terms (appendix). Tangential electronic exploration of related articles (ie, using links to related references to search for additional articles) and extensive hand searches of bibliographies of relevant reviews and related journals were also done.

See Online for appendix

Studies in any language were included if they reported on a population of at least 3000 patients who underwent general anaesthesia for surgery in the hospital setting. The minimum sample size of 3000 was chosen to reasonably estimate adverse events that occur at a rate of one in 1000 or less in accordance with the rule of three sample size approximation[9] and also to ensure that small studies would not skew the event rate estimates since occurrence of death and cardiac arrest were expected to be lower than one in 1000 in most settings. Because the aim was to ascertain outcomes in allcomers (ie, all reported patients who underwent surgery), studies reporting exclusively on regional or local anaesthesia or those done in a non-hospital setting were excluded. Similarly, to ensure the studies represented a mixed population rather than being confounded by any one particular surgical or patient subtype, studies that focused exclusively on specific age groups (eg, the elderly only or children only) or that reported only one surgical subgroup (eg, cardiac surgery only) were excluded. Studies that reported an estimated rather than actual denominator or that sampled only a portion of adverse events from a larger population and studies that reported only corrected mortality rates on the basis of morbidity scoring systems without providing raw data were also excluded.

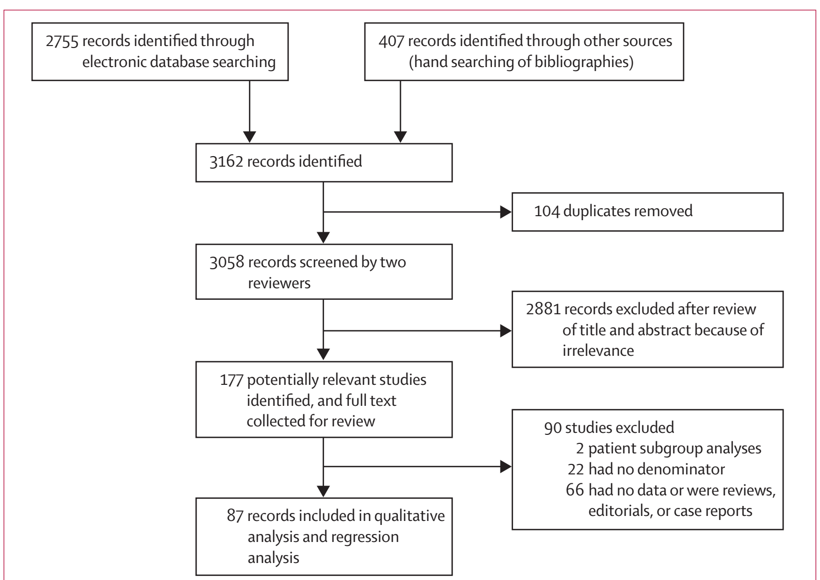

Figure 1: **Flowchart of study identification**

Although most studies were expected to be descriptive cohort studies without a specific intervention or control group, randomised or comparative studies were also eligible. We planned to exclude the intervention arm from randomised trials if the intervention was not standard of care and had shown a differential effect on death in the intervention versus the control group; however, this issue did not arise because there was only one large randomised trial eligible for this analysis, and both arms were eligible for inclusion.

Data extraction and outcome definitions

Using standard forms, two authors independently identified studies for inclusion and extracted information on outcomes, baseline American Society of Anes-thesiologists (ASA) status, year of recruitment, country of origin, and method of data collection. Disagreements were resolved by consensus. The primary outcome was anaesthetic sole mortality, defined as death deemed to be attributable only to anaesthesia. Secondary outcomes were anaesthetic contributory mortality, defined as death deemed to be partially related to anaesthetic conduct; total perioperative mortality, defined as death from any cause; and cardiac arrest.

Country development status was assigned according to the UN Human Development Index (HDI), which is an index based on life expectancy, literacy, enrolment in further education, and per-capita income.[10] Since any country's HDI can change over time, the HDI relevant to the country during the specific time period of the study was assigned. If HDI data were not available for that year, then the HDI at the closest date available was used.

Statistical analysis

For every outcome in every study, event rates, defined as the number of events per million anaesthetic procedures and their corresponding 95% CIs were calculated. The fixed effect model (primary analysis) and the random effects model (secondary analysis to account for heterogeneity) were used to calculate weighted event rates across all studies. Since the results and conclusions were not sensitive to the model used, only data from the fixed effect model are presented here for simplicity. We did meta-regression using the method of moments to assess whether death rates changed significantly over time and by HDI. Since many studies reported data over a time period of several years, the data were assigned as close as possible to the year in which the patients were recruited. When data were provided only in aggregate time intervals, the data were assigned to the median year of the relevant interval of recruitment. Prospective versus retrospective data were collected for sensitivity analyses.

In addition to meta-regression, we subgrouped aggregate event rates per million patients for each double decade and for each HDI category to calculate natural event rates for each time period and by low versus high HDI (<0·8 *vs* ≥0·8, respectively). For subgroup analyses, we did the test for interaction to assess whether effect sizes differed significantly across subgroups. Event rates per million were also measured by baseline ASA physical status subgroups.[11]

Statistical analyses were done using Comprehensive Meta-Analysis version 2.2 (Englewood, NJ, USA, 2008). Statistical significance was defined as a two-sided p<0·01. Heterogeneity was assessed using I^2, which indicates the proportion of variability between studies that cannot be attributable to chance alone.[12] Values of I^2 higher than 50% were deemed to suggest significant heterogeneity between studies.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or decision to publish the results. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

3162 abstracts were reviewed and 177 potentially relevant full text articles were retrieved (figure 1). Of these, 87 studies met the inclusion criteria, within which there were more than 21·4 million anaesthetic administrations given to patients undergoing general anaesthesia for surgery (appendix). The appendix lists the characteristics and designs of the 87 studies. Most studies reported events intraoperatively and within the first 24–48 h postoperatively, whereas only four studies reported 30-day anaesthesia mortality. Exclusion of the latter trials did not substantially affect the mortality estimates. Three trials had no HDI data available, one because multiple countries were studied and two from Taiwan in which HDI data were not collected. Sensitivity analysis by prospective and retrospective data collection did not materially change the results. As expected, statistical heterogeneity (I^2 >50%) was detected for all event rates.

Risk of anaesthetic sole mortality decreased progressively over the decades, from 357 per million (95% CI 324–394) before the 1970s, to 52 per million (42–64) in the 1970s–80s, and 34 per million (29–39) in the 1990s–2000s (table 1; figure 2). In a weighted meta-regression, this reduction over time was significant (p=0·000001; figure 3). When temporal trends were analysed for high-HDI and low-HDI country subgroups separately, only the high-HDI countries had a decline over time (p<0·00001).

Anaesthetic contributory mortality decreased over time, from 650 per million (95% CI 610–693) before the 1970s, to 323 per million (290–360) in the 1970s–80s, and 143 per million (129–157) in the 1990s–2000s (p<0·00001 across subgroups; table 1). This reduction in mortality risk over time was statistically significant in a meta-regression (p<0·00001; appendix). Analysis of temporal trends for high-HDI and low-HDI countries separately showed that only high-HDI countries experienced a decline in

	Events	Weighted event rate per million (95%CI)	p value for subgroup interaction	
			By HDI	By decade
Anaesthetic sole mortality				
Pre-1970s*	403/1 294 158	357 (324–394)	..	<0·00001
High HDI	403/1 294 158	357 (324–394)	NA	..
Low HDI	NR	NR	..	..
1970s–80s	86/2 380 920	52 (42–64)	..	..
High HDI	50/1 761 384	32 (24–42)	<0·00001	..
Low HDI	36/619 536	101 (72–140)	..	..
1990s–2000s	186/8 990 012	34 (29–39)	..	..
High HDI†	151/8 610 720	25 (21–30)	<0·00001	..
Low HDI†	32/274 692	141 (100–199)	..	..
Anaesthetic contributory mortality				
Pre-1970s*	925/1 625 266	650 (610–693)	..	<0·00001
High HDI	867/1 447 338	684 (642–729)	<0·00001	..
Low HDI	58/177 928	326 (252–422)	..	..
1970s–80s	332/1 176 999	323 (290–360)	..	..
High HDI†	150/649 744	234 (200–275)	<0·00001	..
Low HDI†	180/475 127	432 (373–500)	..	..
1990s–2000s	395/5 950 293	143 (129–157)	..	..
High HDI	275/5 641 048	85 (75–96)	<0·00001	..
Low HDI	120/309 245	467 (391–559)	..	..
Total perioperative mortality				
Pre-1970s*	13 253/1 939 879	10 603 (10 423–10 784)	..	<0·0001
High HDI	11 227/1 761 951	10 467 (10 276–10 662)	<0·00001	..
Low HDI	2026/177 928	11 387 (10 904–11 890)	..	..
1970s–80s	4696/1 570 070	4533 (4405–4664)	..	..
High HDI	1723/934 781	1982 (1891–2078)	<0·00001	..
Low HDI	2973/635 289	7336 (7078–7604)	..	..
1990s–2000s	6567/7 047 928	1176 (1148–1205)	..	..
High HDI	5981/6 738 683	1095 (1067–1123)	<0·00001	..
Low HDI	586/309 245	2445 (2255–2651)	..	..
Cardiac arrest				
Pre-1970s*	342/587 906	672 (605–748)	..	<0·0001
High HDI	342/587 906	672 (605–748)	..	..
Low HDI	NR	NR	NA	..
1970s–80s	3045/2 480 112	1872 (1807–1939)	..	..
High HDI†	2799/2 361 710	1798 (1732–1866)	<0·00001	..
Low HDI†	221/66 274	3642 (3193–4155)	..	..
1990s–2000s	4299/6 475 012	719 (698–741)	..	..
High HDI†	3906/6 094 142	659 (638–680)	<0·00001	..
Low HDI†	345/276 270	2068 (1861–2298)	..	..

HDI=human development index. NR=not reported. NA=not available. *Includes studies primarily from the 1950s and 1960s; however, because there were few 1940s studies, they were also included here. Sensitivity analysis revealed no substantial change in event rates when data before the 1950s were excluded from analysis. †HDI subgroup data excludes trials for which no HDI-specific data are available, and therefore addition across subgroups will not always be equal to the overall results.

Table 1: **Anaesthesia mortality and cardiac arrests by decade and by country human development index status**

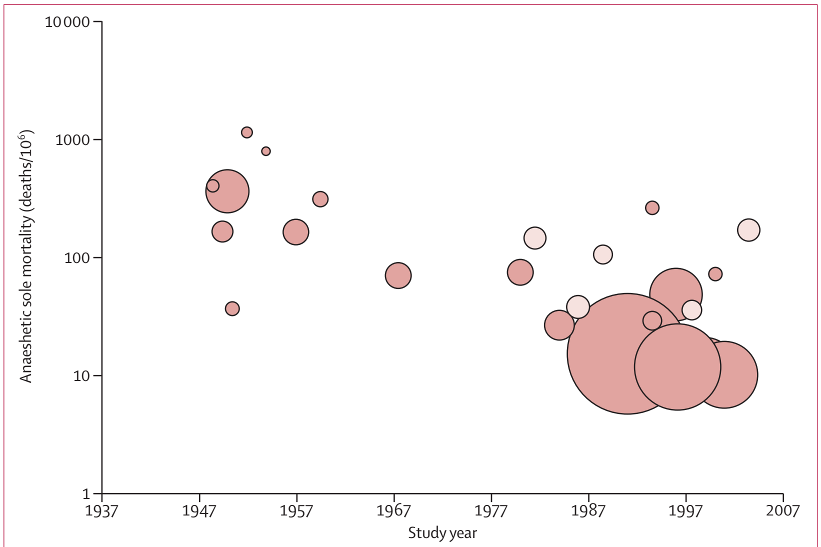

***Figure 2:* Event rates for anaesthetic sole mortality by year**
Every circle represents a study; the circle size is representative of the study's population size. The year represents the median year if the study reported a range of years. Low-income and middle-income countries are shown in light red (human development index [HDI]<0·8) and high-income countries in dark red (HDI≥0·80).

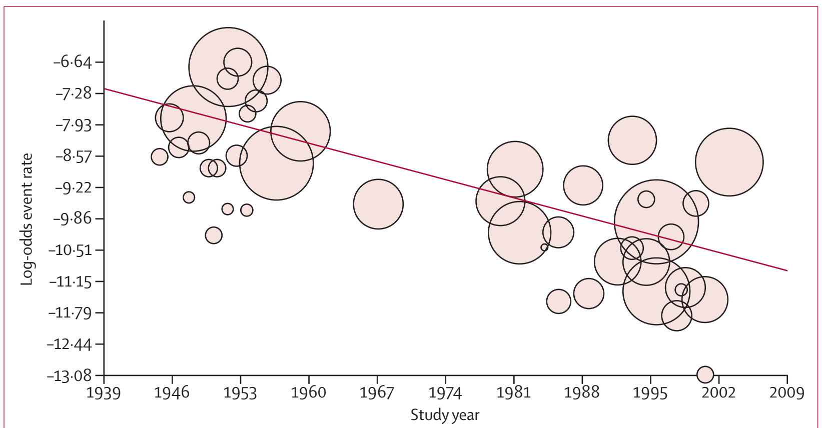

***Figure 3:* Meta-regression for risk of anaesthetic sole mortality by year**
Every circle represents a study; the circle size is representative of the weight of that study in the analysis. The relation between mortality and year of study was significant, with a significant decline over the decades (slope –0·053, 95%CI –0·058 to –0·049; p=0·000001).

mortality risk over time (slope –0·042; p<0·0001), whereas low-HDI countries experienced an increased mortality risk over time (slope +0·019; p=0·0001).

Total perioperative mortality decreased progressively over the decades, from 10 603 per million (95% CI 10 423–10 784) before the 1970s, to 4533 per million (4405–4664) in the 1970s–80s, and 1176 per million (1148–1205) in the 1990s–2000s (p<0·0001 across subgroups; table 1). This reduction in all-cause perioperative mortality was statistically significant in meta-regression over time (p<0·00001; figure 4). When analysed separately, both high-HDI countries (slope –0·050; p<0·0001) and low-HDI countries (slope –0·042; p<0·0001) experienced a significant decline in perioperative mortality over time, although the magnitude of reduction was greatest in high-HDI countries.

The incidence of cardiac arrest varied over the decades, with an overall decline in incidence by time that was statistically significant (p=0·00001; appendix). The event rate in the 1970s–80s was 1872 per million (95% CI 1807–1939), compared with 719 per million (698–741) in the 1990s–2000s (table 1). Although the studies from before the 1970s provided some data for cardiac arrest, the event rate was less reliable for this early subgroup because of the small numbers within each study before 1970 compared with the larger and more numerous studies from the later decades. For this reason, although the event rate for cardiac arrests before the 1970s was calculated to be 672 per million (95% CI 605–748), which is lower than in the later decade subgroups, the meta-regression suggested an overall trend toward a reduction over time because of the weight placed on later years given the study sample sizes (p=0·004).

When data from all countries across all decades were assessed in a weighted meta-regression by HDI, the rate of anaesthetic sole mortality decreased progressively with increasing HDI (p<0·00001; appendix). Table 1 shows that the aggregate event rate for anaesthetic sole mortality was at least three times higher in low-HDI versus high-HDI countries (101 per million [95% CI 72–140] *vs* 32 per million [24–42] in the 1970s–80s, and 141 per million [100–199] *vs* 25 per million [21–30] in the 1990s–2000s). Low-HDI countries were insufficiently represented before the 1970s for sub-analysis to be done.

Meta-regression of anaesthetic contributory mortality by HDI also showed a significant reduction in anaesthetic contributory mortality as HDI increased (p<0·0001; appendix), which is also shown by the higher aggregate event rates for each decade, with the exception of before the 1970s, when low-HDI countries were poorly represented within the subgroup analysis (table 1).

Meta-regression of total perioperative mortality by increasing HDI showed a significant reduction in risk of perioperative death as HDI increased (p<0·00001; appendix), and aggregate event rates by decade group showed significantly greater event rates in low-HDI versus high-HDI countries in every decade group (all p<0·0001; table 1).

Weighted meta-regression showed a significant relation between higher HDI and lower risk of cardiac arrest (p<0·00001; appendix). The incidence of cardiac arrest was at least twice the rate in low-HDI versus high-HDI countries in both the 1970s–80s and 1990s–2000s (table 1).

Perioperative all-cause mortality increased with increasing ASA status at baseline, from a low of 557 per million (95% CI 458–678) for ASA grade 1 to a high of 273 534 per million (253 688–294 320) for ASA grade 5 (table 2). Patients with ASA grade 2 at baseline had more than double the mortality risk of patients with ASA grade 1. Patients in each successive higher category of ASA status at baseline had four to six times the mortality risk when compared with the next lower category of ASA status. The same numeric patterns were noted for cardiac arrest when examined by baseline ASA status. Incidence of cardiac arrest ranged from 193 per million (95% CI 149–249) for patients with ASA grade 1 up to 234 121 per million (186 231–289 939) in those with ASA grade 5.

When subgroup analysis was done to dichotomously compare patients with ASA grade 1–3 with those with ASA grade 4–5, the relative risk of all-cause perioperative mortality in the high-ASA status group compared with the low-ASA status group was 48 (95% CI 42–53; table 3). Similarly, the relative risk of cardiac arrest was 61 (50–72). When meta-regression by ASA status was done for death or cardiac arrest, there was a significant increasing relation between higher ASA at baseline and death or cardiac arrest ($p<0 \cdot 00001$).

Meta-regression by time period showed that the baseline ASA status of patients increased significantly over the decades, confirming the widespread opinion that the baseline risk and complexity of patients presenting for surgery increased over the decades ($p<0 \cdot 0001$).

Discussion

This comprehensive systematic review with meta-regression quantifies the global risk of anaesthetic-related and total perioperative mortality and shows the rates of change in these risks by time, country HDI, and baseline ASA status. The results show a clear reduction in anaesthetic-related and perioperative mortality over the past 50 years, despite the increasing baseline ASA risk status of patients and patient complexity. Cardiac arrests in the perioperative setting have also declined over time. The rate of decline in anaesthetic-related mortality and perioperative mortality over the decades has been greatest and most consistent in countries with a high HDI compared with those with a low HDI.

Despite the widespread emphasis on patient safety in anaesthesia since the early 1980s, and with more concentrated efforts toward patient safety since the 1990s, this aggregate analysis of all published worldwide data suggests a steady improvement in anaesthetic-related and perioperative mortality even preceding these efforts, particularly in high-HDI countries. This finding might have been as a result of early advancement in anaesthesia and surgical practices (training, certification, drugs, and techniques); improved selection of patients for surgery (better matching of patient risk to procedure benefit); increasing advances in aseptic techniques and equipment sterilisation; increased use of antibiotics; improvements in physiological monitoring, and fluid and blood management protocols; improved post-operative critical care; and improvements in teamwork and education of the expanded perioperative health-care team. Unfortunately, the studies did not provide sufficient details to test these hypotheses specifically. The continued reduction in anaesthetic and perioperative mortality in recent years is encouraging and suggests that the recent heightened efforts toward standardisation and patient optimisation (eg, treatment of disorders such as high cholesterol, hypertension, and angina before surgery); higher levels of experience, improved surgical technologies and techniques; and optimum timing of antibiotics, timeouts, safe surgery checklists, and related protocols might be translating collectively into continued improvements in patient outcomes.[1,5,13–15] The results of this global meta-analysis are particularly noteworthy since anaesthetic-related and perioperative mortality are sufficiently rare that individual studies are generally insufficient in size to detect measurable differences, and cannot rule out the possibility that important differences might exist because of any single intervention or accumulation of efforts.[13] Although these results lend support to an overall improvement in patient care

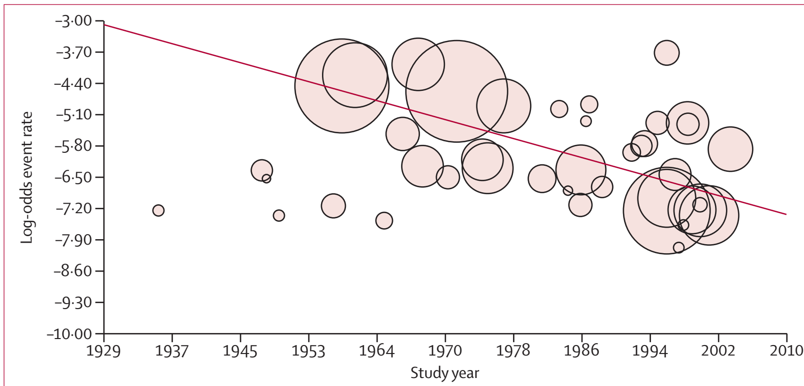

Figure 4: **Meta-regression for total perioperative mortality by year**
Every circle represents a study; the circle size is representative of the weight of that study in the analysis. The relation between mortality and year was significant, with a significant decline over the decades (slope –0·053, 95% CI –0·054 to –0·052; p<0·00001).

	Mortality event rate per million (95% CI)	Cardiac arrest event rate per million (95% CI)	Mortality or cardiac arrest event rate per million (95% CI)
ASA grade 1	557 (458–678)	193 (149–249)	379 (324–442)
ASA grade 2	1408 (1254–1582)	1112 (944–1310)	1301 (1184–1431)
ASA grade 3	9369 (8761–10 018)	5936 (5208–6764)	8515 (8022–9039)
ASA grade 4	61 797 (58 412–65 365)	75 193 (68 146–82 904)	64 823 (61 730–68 058)
ASA grade 5	273 534 (253 688–294 320)	234 121 (186 231–289 939)	268 963 (250 430–288 340)

ASA=American Society of Anesthesiologists. See also the appendix for details of raw event rates.

Table 2: **Mortality or cardiac arrest by American Society of Anesthesiologists status**

	Event rate per million (95%CI)		RR (95%CI)	p for subgroup interaction
	ASA grade 1–3	ASA grade 4–5		
Mortality	4793 (4533–5068)	93 268 (88 986–97 735)	48 (42–53)	<0·00001
Cardiac arrest	2114 (1925–2328)	86 830 (79 255–95 054)	61 (50–72)	<0·00001
Mortality or cardiac arrest	3887 (3704–4078)	91 865 (88 108–95 766)	50 (47–53)	<0·00001

ASA=American Society of Anesthesiologists. RR=relative risk of adverse outcome for patients with ASA grade 4–5 *vs* ASA grade 1–3.

Table 3: **Mortality or cardiac arrest by high versus low American Society of Anesthesiologists subgroup**

contributing to better patient outcomes at present, subsequent updates of this dataset should be done over time to provide a continued global measure of the patterns in anaesthetic-related and perioperative mortality as an aggregate representation of the translation of the aforementioned patient safety efforts into tangible outcomes over time in the real-world setting, both in the developed and developing world.

The rate of improvement in perioperative mortality over time is significantly related to HDI, and this might be a result of the ability of wealthier countries to increase health-care investment in the technologies, techniques, and training necessary to improve patient safety. Conversely, this finding might also be a result of a difference in case mix, with less developed countries tending to have higher rates of surgery for traumatic injury and advanced diseases and fewer elective surgical procedures for chronic stable conditions or minor diseases.[3,4] Since the studies identified in this analysis reported insufficient details to allow greater exploration of outcomes by patient characteristics, the latter hypothesis remains unproven, but should be pursued in future research.

Although anaesthetic mortality remains low compared with traffic fatalities or suicide,[16] it still remains high compared with death caused by air travel, which is a commonly used yardstick to benchmark the risk of anaesthesia.[17–20] Quantification of acceptable risk for individuals is often difficult since a surgical procedure is associated with potential benefits that need to be weighed against potential risks when deciding whether to undergo surgery. Using updated quantified risks from this analysis might help facilitate informed decision making, in particular when placed in perspective against other everyday risks, and might be especially important for patients undergoing procedures for which benefits might be small or uncertain and need to be closely balanced against risks.

The global burden of disease and disability-adjusted life-years[3] that could potentially be improved through surgical intervention, if surgery was more accessible in the developed world,[4] highlights the importance of ensuring that improved safety measures will accompany all efforts to improve access to surgery in low-HDI countries. The two to four times increased risk of anaesthesia-related and perioperative mortality in low-HDI compared with high-HDI countries shows the gap that has existed between health-care systems, and this inequity remains despite recent efforts to improve global perioperative safety regardless of country and social status. Targeted initiatives involving collaboration between lower and higher HDI countries should be developed to reduce this gap between actual anaesthesia-related and perioperative mortality in low-HDI countries and achievable perioperative mortality in high-HDI countries. Closing this gap is an important achievable global health improvement and would probably exceed the payback on other potential improvements that compete for our time and resources in the developed world—for example, new and expensive surgical technologies, which generally offer smaller marginal benefits in the developed world than the lives that could be saved by closing the global perioperative mortality inequity gap in the developing world.

These results need to be interpreted in light of the limitations of the data available. Since most studies failed to report sufficient risk factor data to allow for adequate risk stratification, we used crude death rates, without adjustment for specific comorbidities or type of surgical procedure. Therefore, biases and confounders that may differ over time might have affected the results, particularly with respect to patient risk factors and type of surgery. We aimed to minimise selection bias by using large studies (>3000) of allcomers undergoing anaesthesia for all decades, and measured trends over time by HDI and by baseline ASA score to minimise the effect of different surgical procedures and patient risk, which are probably of greatest difference in countries of different HDI (and thus include patients of different ages and with different comorbidities). We calculated rates of change over time within high-HDI and low-HDI country settings separately to minimise the effect of confounders between countries. Ideally, global registries would provide more complete data with more detailed patient and procedural information to allow for more informative analyses in the future with adjustment for confounding. Nevertheless, the consistency in reductions over time for all outcomes measured in this analysis, considered together with the fact that baseline ASA risk status significantly increased over time, suggests that the trends might be further improved if more specific risk adjustment could be done.

Although substantial effort was made to ensure that all relevant studies were included in this analysis, some studies from the 1940s and 1950s could not be retrieved. Also, other existing studies, particularly from the developing world, were probably not identified (eg, because they were not available in English or were not published in an indexed journal). Publication bias might have contributed to inadequate power to detect mortality trends from the developing world because few studies were available from the developing world in the earlier decades. Readers are encouraged to notify the authors if additional relevant studies exist so that new data can be incorporated into subsequent updates of this analysis. In particular, studies in languages other than English and from the developing world would further improve the estimates by HDI status.

Future studies on perioperative mortality should aim to be more thorough in the reporting of information, including outcomes by surgical subtypes, by anaesthetic subtype, and by patient risk groups. Furthermore, the likely cause of perioperative death should be provided more consistently. Definitions of anaesthetic-related mortality and perioperative mortality remain disparate across studies (eg, subjective judgment is often needed to class mortality as related to anaesthesia, and even the timeframe for perioperative death varies, such as death within 24 h *vs* within 7 days after surgery), and calls for standardisation of definitions seem to be mostly unheeded so far.[19,21–23]

Despite an increase in patient baseline risk, perioperative and anaesthetic-related mortality rates have steadily declined over the past 50 years, and this might be an indicator of the cumulative effect of efforts to improve patient safety in the perioperative setting over the decades. However, the decline was greatest and most consistent in developed countries, and overall rates of perioperative and anaesthetic-related mortality remain two to three times higher in developing countries. Global priority should be given to reducing total perioperative and anaesthetic-related mortality with evidence-based best practice in developing countries to reduce the disparity in mortality compared with developed countries.

Contributors

DB extracted data, reviewed the results, and wrote the manuscript. JM did the statistical analyses, reviewed the results, and wrote the manuscript. MA extracted data, reviewed the results, and edited the manuscript. DC reviewed the results and edited the manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

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