Tidal Volume and Mortality in Mechanically Ventilated Children: A Systematic Review and Meta-Analysis of Observational Studies

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Objective: To determine whether tidal volume is associated with mortality in critically ill, mechanically ventilated children.

Data Sources: MEDLINE, EMBASE, and CINAHL databases from inception until July 2013 and bibliographies of included studies without language restrictions.

Study Selection: Randomized clinical trials and observational studies reporting mortality in mechanically ventilated PICU patients.

Data Extraction: Two authors independently selected studies and extracted data on study methodology, quality, and patient outcomes. Meta-analyses were performed using the Mantel-Haenszel random-effects model. Heterogeneity was quantified using I^2. Study quality was assessed using the Newcastle-Ottawa Score for cohort studies.

Data Synthesis: Out of 142 citations, seven studies met the inclusion criteria, and additional two articles were identified from references of the found articles. One was excluded. These eight studies included 1,756 patients. Mortality rates ranged from 13% to 42%. There was no association between tidal volume and mortality when tidal volume was dichotomized at 7, 8, 10, or 12 mL/kg. Comparing patients ventilated with tidal volume less than 7 mL/kg and greater than 10 mL/kg or greater than 12 mL/kg and tidal volume less than 8 mL/kg and greater than 10 mL/kg or greater than 12 mL/kg also showed no association between tidal volume and mortality. Limiting the analysis to patients with acute lung injury/acute respiratory distress syndrome did not change these results. Heterogeneity was observed in all pooled analyses.

Conclusions: A relationship between tidal volume and mortality in mechanically ventilated children could not be identified, irrespective of the severity of disease. The significant heterogeneity observed in the pooled analyses necessitates future studies in well-defined patient populations to understand the effects of tidal volume on patient outcome. (*Crit Care Med* 2014; XX:00–00)

Key Words: children; mechanical ventilation; mortality; tidal volume

Mechanical ventilation (MV) is one of the most practiced interventions in the PICU. Up to 64% of all admitted children are mechanically ventilated for at least 24 hours (1, 2). MV has added significantly to patient survival, but it is also irrefutably linked to the initiation or even aggravation of lung injury, termed "ventilator-induced lung injury" (VILI) (3, 4). Volutrauma (i.e., the delivery of too large tidal volumes [V_ts]) has been identified as one of the causative mechanisms of VILI (4). Its pathophysiologic contribution was confirmed by the outcome of two major clinical studies performed in critically ill adults, including the "prospective, randomized, multicenter trial of 12 mL/kg versus 6 mL/kg tidal volume positive pressure ventilation for treatment of acute lung injury and acute respiratory distress syndrome" trial (Prospective, Randomized, Multi-Center Trial of 12ml/kg Tidal Volume Positive Pressure Ventilation for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome trial) by the acute respiratory distress syndrome (ARDS) Network (5, 6). In these studies, MV with low V_t (i.e., 6 mL/kg predicted body weight) and a plateau pressure (P_{plat}) less than 30 cm H_2O instead of 12 mL/kg and P_{plat} less than 50 cm H_2O resulted in a significant decrease in mortality and development of multiple system organ failure.

Much of the current clinical practice of MV in children is based on data originating from adult studies. This especially applies to the targeting of the V_t. The outcome of the two adult studies has led to practice changes in pediatric critical care favoring the use of low V_t (7, 8). It has been recommended

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The authors have disclosed that they do not have any potential conflicts of interest.

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DOI: 10.1097/CCM.0000000000000546

to use a V_t of 4–6 mL/kg in the routine management of children with acute lung injury (ALI) and ARDS (8). However, the Pediatric Acute Lung Injury Mechanical Ventilation (PALIVE) study and others showed that children with ALI were actually ventilated with a mean V_t of approximately 8 mL/kg (7, 9, 10). This signifies that the "optimal" V_t remains subject of debate, especially since three other trials in mechanically ventilated adults could not confirm the benefits of a low V_t strategy (11–13). Furthermore, animal work suggests that children might be less susceptible to VILI than adults, thereby challenging the recommendations and questioning whether experiences with adult patients can be directly translated into pediatric critical care (14, 15).

At present, the effect of low V_t MV on the outcome of mechanically ventilated children was only explored in a number of observational studies. The aim of this study, therefore, was to evaluate if V_t was associated with mortality in mechanically ventilated critically ill children using various cutoff values through a systematic review and meta-analysis of published observational studies.

METHODS

Data Sources

MEDLINE, EMBASE, and CINAHL were electronically searched from inception until July 2013 for randomized clinical trials (RCTs) and observational studies using the following key words: mechanical ventilation, tidal volume, mortality, acute lung injury, acute respiratory distress syndrome, critical care, and intensive care unit (**Appendix 1**). Terms were exploded and combined using Boolean operators where appropriate. Searches were limited to children (< 18 yr). Language restrictions were not applied.

The study was exempt from approval by our institutional review board.

Study Selection

Two investigators (P.d.J., M.C.J.K.) unblinded to the authors or author's institution independently reviewed the retrieved citations. Full articles were retrieved when either the title or the abstract indicated that the study reported on the effect of V_t on mortality in mechanically ventilated children. In addition, references in these articles were scanned for additional eligible studies that were not identified by the electronic search. Articles were subsequently included when it was confirmed that the study addressed the association between V_t and mortality. Studies were excluded if they did not meet this criterion or if they had included prematurely born infants or adult patients. Disagreement regarding inclusion was reconciled by consensus.

Data Extraction and Quality Assessment

A standardized data abstraction form was constructed before the literature search. Two unblinded reviewers (P.d.J., M.C.J.K.) independently extracted the following data from the included studies: publication year, study design (prospective/retrospective, single center/multicenter, and study period), patient characteristics (age, percentage of patients ALI/ARDS, and discharge diagnosis), ventilator characteristics (overall V_t, overall peak inspiratory pressure [PIP], and overall positive end-expiratory pressure), and mortality. The authors of the included studies were contacted if data could not be extracted from the article or were unclear and required clarification. Study quality was assessed using the Newcastle-Ottawa Score (NOS) for cohort studies (16, 17).

Data Analysis

Mortality (either PICU or hospital) was designated as measure of outcome for this systematic review. All analyses were performed using Review Manager (RevMan version 5.1, Cochrane Collaboration, Oxford, United Kingdom). We used a random-effects Mantel-Haenszel model to calculate pooled odds ratios (ORs) and 95% CIs. I^2 statistics were used to assess statistical heterogeneity among the studies. These statistics characterize the percentage of total variability across studies that can be attributed to heterogeneity rather than chance. Heterogeneity was defined in agreement with the Cochrane Handbook for Systematic Reviews, v 5.1.0, as low if I^2 less than 40%, moderate if I^2 is between 30% and 60%, substantial if I^2 is between 50% and 90%, and considerable if I^2 greater than 90% (18). Pooled ORs and 95% CI were calculated using cutoff points of V_t at 7, 8, 10, and 12 mL/kg. p Values less than 0.05 were considered statistically significant. A funnel plot was visually examined to assess the presence of publication bias.

RESULTS

Study Selection

The initial search strategy yielded 142 individual citations (**Fig. 1**). Seven (4.9%) of them met the inclusion criteria. The

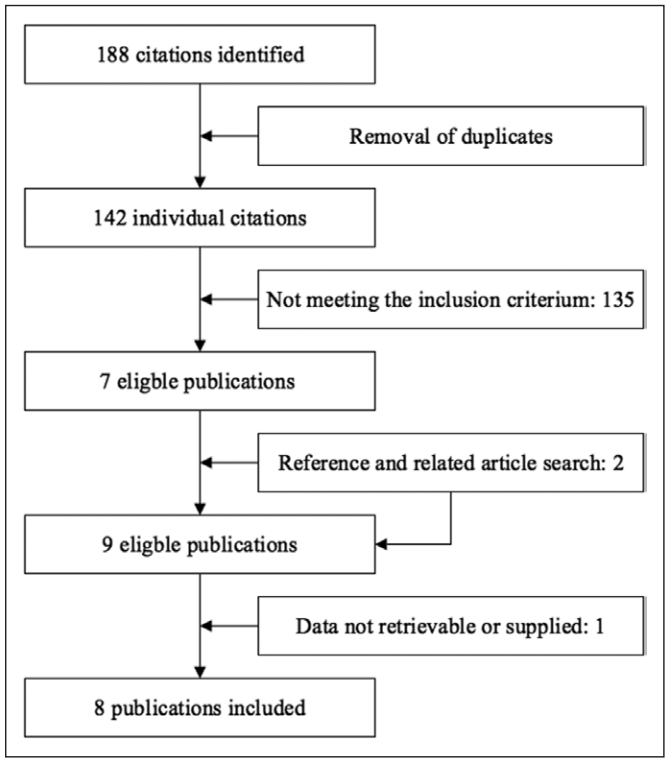

Figure 1. Flowchart of study selection for the systematic review.

TABLE 1. Characteristics of Included Studies for Meta-Analysis

Author (Reference)	Albuali et al (9)	Erickson et al (10)	Flori et al (19)	Halbertsma et al (20)	Hu et al (21)	Khemani et al (22)	Khilnani et al (23)	Silva et al (24)
Study characteristics								
Prospective	No	Yes	Yes	No	Yes	No	No	Yes
Multicenter	No	Yes	Yes	No	Yes	No	No	No
Period	1988–1992; 2000–2004	2004–2005	1996–2000	2003–2004	2004–2005	2000–2007	1998–2000; 2000–2004	2005–2006
Sample size	164	117	328	96	461	398	143	49
Lung-protective ventilation strategy	Yes[a]	No	No	No	Yes	Yes	Yes[a]	No
Mean age (yr)[b]	1.3 ± 3.4; 2.6 ± 7.7[a]	Unknown	3.4 (0–18)	2.1 (0–16.1)	0.9 (0.3–3.3)	4.3 (1–11.5)	2.7 (0.2–5.2)	Unknown
Acute lung injury/acute respiratory distress syndrome (%)	100	100	100	41	78	48	100	84
Quality according to the Newcastle-Ottawa Scale								
Selection	****	****	****	****	****	****	****	****
Comparability	*		*		*	*		
Exposure	***	***	***	***	***	***	***	***
Ventilator characteristics								
Timing	3d Average	Admission	Admission	Admission	Average	Day 1	Unknown	Admission
Ventilator mode (%)	PC52–55; VC 47-37; HFO 1–8[a]	PRVC 20; synchronized intermittent mandatory ventilation 51; HFO 12	VC 76, PC 20, HFO 3	Unknown	VC 5, PC 93	PC > 90	PRVC 100	PC
V_t used for analysis	Expiratory	Calculated	Calculated	Unknown	Expiratory	Calculated	Expiratory	Expiratory
V_t (mL/kg)[b]	10.2 ± 1.7; 8.1 ± 1.4[a]	9.3 (7.8–11.6)	10.0 ± 4.9	10.1 ± 2.5	8.8 (6.7–10.4)	7.5 (6.1–9.0)	10–15; 6–8	10 (9–11)
Peak inspiratory pressure (cm H_2O)[b]	31.5 ± 7.3; 27.8 ± 4.2[a]	28 (25–31)	30.6 ± 9.8	Unknown	25 (20.9–30)	26.5 (22.8–31.7)	Unknown	24 (20.4–27.6)
Positive end-expiratory pressure (cm H_2O)[b]	6.1 ± 2.7; 7.1 ± 2.4[a]	8.5 (7–11)	5.3 ± 2.6	Unknown	5 (3–7)	7.4 (5–10)	7–16; 7–16[a]	8 (6–10)
Outcome								
Type	PICU	28 day	PICU	Unknown	In-hospital	PICU	PICU	28 d
Mortality (%)	35; 21[a]	35	22	14	42	20	23; 37[a]	35

PC = pressure controlled, VC = volume controlled, HFO = high-frequency oscillatory ventilation, PRVC = pressure regulated volume controlled, V_t = tidal volume.
[a]Study was designed to compare between ventilated before and during the use of a lung-protective ventilation strategy.
[b]Data are depicted as mean ± SD or median and 25–75 interquartile range.

great majority of articles were excluded because the association between V_t and mortality was not studied or prematurely born infants or adult patients were included. Additional two articles were identified from references of the initial search. No RCTs were identified. Thus, a total of nine observational studies were eligible for analysis (9, 10, 19–25). One study was excluded because the investigators declined to provide the study data (25). Seven other study groups consented following the request for data information (9, 10, 19–22, 24). Thus, a total of eight studies were included for analysis. Data of patients not published by any means or evaluated prior in the original publications were not added to the analysis.

Description of the Included Studies

The characteristics of the studies included are summarized in **Table 1**. There were no RCTs identified; all retrieved studies were designed as cohort studies. Four studies were designed as prospective, of which three were multicenter studies. One study also included nonventilated patients; the first author of this study was contacted and provided data after censoring the patients (19). All but two studies exclusively included patients with acute hypoxemic respiratory failure (9, 10, 19, 21–23, 25), including patients with ALI/ARDS (9, 10, 19, 23). Six studies were cohort studies; in two studies, comparisons were made between a period before and a period after publication of the ARMA trial (9, 23). The use of a lung-protective ventilation strategy was reported by four studies (9, 21–23, 25). Two studies compared their ventilation practice before and after the publication of the ARMA trial (9, 23). All studies scored well on "selection" and "exposure" according to the NOS, but poor on comparability.

All studies included patients less than 18 years old; in general, the mean age was less than 5 years old. Two studies excluded neonatal patients (i.e., < 1 mo old) (21, 23). The majority of patients had primary respiratory failure, whereas one study included 45% postoperative surgical patients (20). Two studies reported the inclusion of patients with (acquired) immunodeficiency (9, 23). Data on length of PICU stay or ventilator-free days could not accurately been retrieved. Causes of death were not specified in the included studies.

There was a considerable variation in V_t measurement used for analysis in the individual studies. The reported V_t was measured at admission or day 1 in five studies (10, 19, 20, 22, 24), whereas others have used the daily mean V_t during the first 3 days of admission (9) or for the total duration of ventilation for analysis (21). The V_t delivered varied significantly between the individual studies. Except for one study, the expired V_t was used for analysis. Three groups of investigators calculated the V_t used for analysis taking the compressible volume into account (10, 19, 22). It could not be determined whether the V_t was measured in the ventilator or near the endotracheal tube at the Y-piece. There was no information on the use of cuffed endotracheal tubes. Also, it could not be determined if actual or ideal body weight was used.

The main mode of ventilation in all studies except for one was pressure-controlled (PC) ventilation. In one study, volume-controlled (VC) ventilation was the primary mode of ventilation, whereas in another study, PC with preset V_t (pressure regulated volume controlled, PRVC) was used exclusively (19, 23).

Table 2 summarizes the mortality rates for various thresholds of V_t. A significant decline in mortality was found in one study (10). In two studies, there was an increase in mortality (9, 19).

Effect of V_t on Mortality–All Patients

Mortality rates ranged from 13% to 42%. Studies were pooled for various cutoff values of V_t. There was no association between V_t and mortality when dichotomized at 7 mL/kg (n = 6 studies, 1,122 patients) (9, 10, 19, 21, 22, 24), 8 mL/kg (n = 7 studies, 1,265 patients) (9, 10, 19, 21–24), 10 mL/kg (n = 6 studies, 1,054 patients) (9, 10, 19, 22–24), or 12 mL/kg (n = 6 studies, 1,007 patients) (9, 10, 19, 20, 22, 24) (**Fig. 2 *A–D***). A moderate degree of heterogeneity was observed as the I^2 was between 30% and 60%. Visual inspection of the funnel plot showed asymmetry in the analyses using 10 and 12 mL/kg as cutoff value (**Fig. 3, *C* and *D***). Similar findings

TABLE 2. Effect of Tidal Volume Threshold on Mortality

Author (Reference)	< 7 mL/kg		7–8 mL/kg		8–10 mL/kg		10–12 mL/kg		> 12 mL/kg	
	n	Mortality	*n*	Mortality	*n*	Mortality	*n*	Mortality	*n*	Mortality
Albuali et al (9)[a]	8	12.5	12	16.7	53	28.3	67	29.9	19	57.9
Erickson et al (10)[b]	30	43.3	7	42.3	26	27.0	16	25	12	0
Flori (19)[c]	43	16.3	19	21.1	60	18.3	47	25.5	45	35.6
Khemani (22)	168	23.2	68	17.7	97	18.6	35	20	30	13.3
Silva (24)	4	50	6	33.3	14	28.6	24	37.5	1	0
Total	253	24.5	112	20.5	250	22	189	27.5	107	29.0

[a]$p = 0.011$.
[b]$p = 0.006$.
[c]$p = 0.025$.
n = total sample size for that threshold. Data are depicted as absolute number (n) or percentage of total (mortality). Data were analyzed using the Cochran-Armitage Trend test.

were made when we included only studies in which V_t was measured at admission and/or day 1 (data not shown).

We then compared studies in which patients were ventilated with V_t less than 7 mL/kg and greater than 10 mL/kg ($n = 5$ studies, 549 patients) (9, 10, 19, 22, 24) or 12 mL/kg ($n = 5$ studies, 360 patients) (9, 10, 19, 22, 24) (**Fig. 2, *E* and *F***). Similar findings were made when V_t less than 8 mL/kg was compared with greater than 10 mL/kg ($n = 6$ studies, 804 patients) (9, 10, 19, 22–24) or greater than 12 mL/kg ($n = 5$ studies, 472 patients) (9, 10, 19, 22, 24) (**Fig. 1, *G* and *H***). Importantly, the degree of heterogeneity was substantial in these pooled analyses.

The findings of our study were similar when we compared studies in which greater than 90% of patients were managed in a PC mode of ventilation or when we compared studies by nature (retrospective vs prospective).

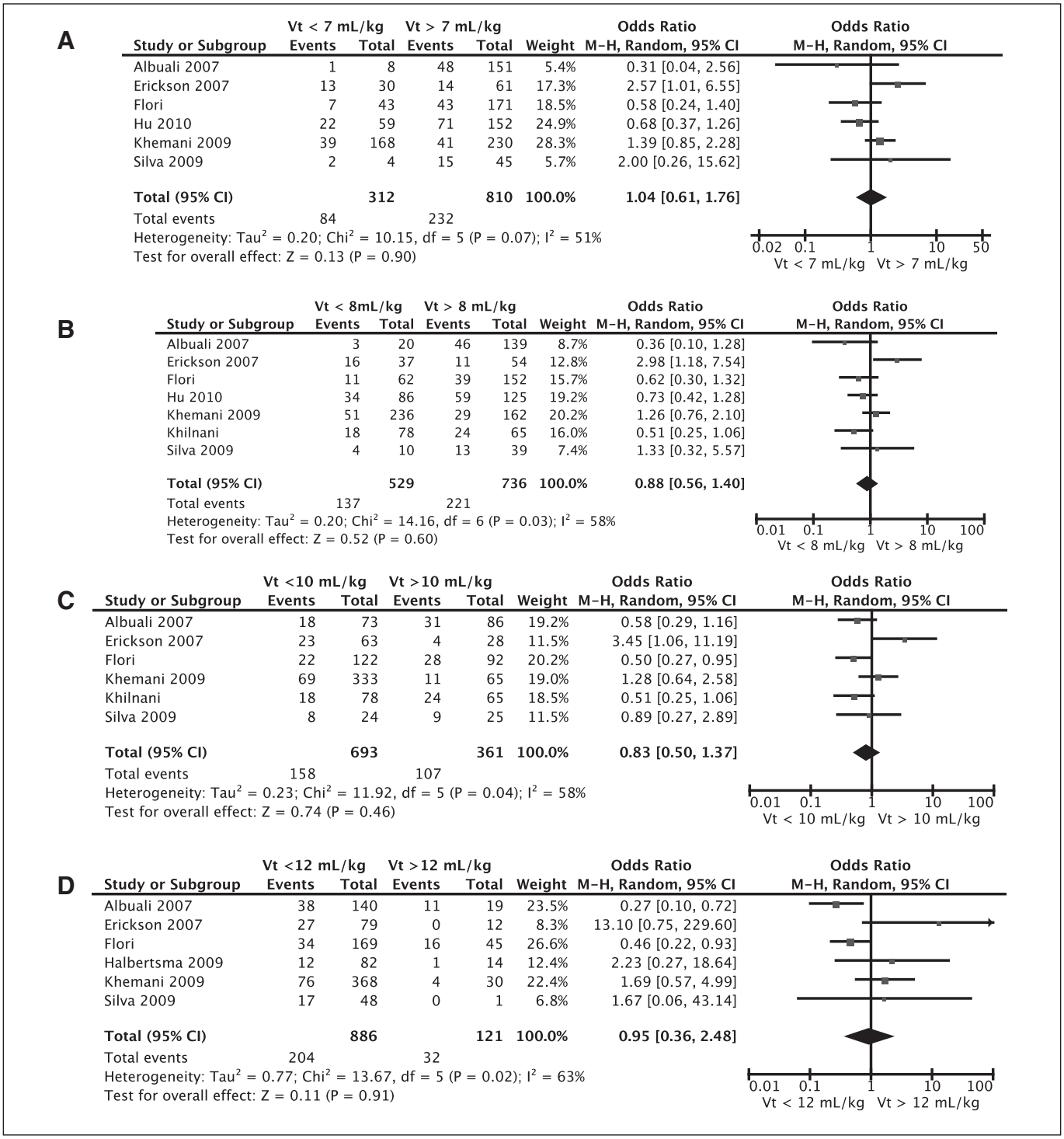

Figure 2. (*Continued*)

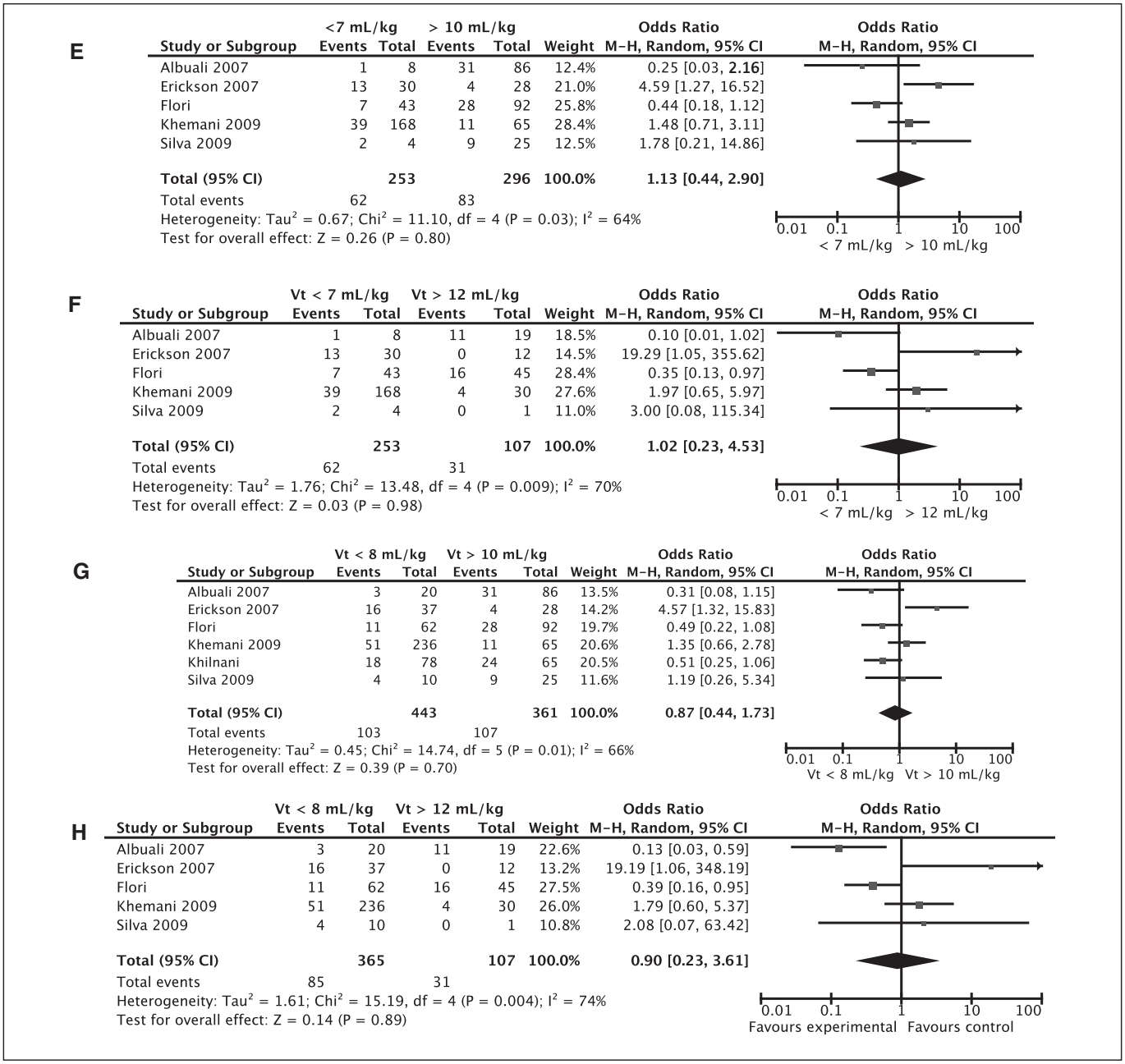

Figure 2. (*Continued*) Attributable PICU mortality associated with tidal volume (V_t) dichotomized at 7 mL/kg body weight (**A**), 8 mL/kg (**B**), 10 mL/kg (**C**), 12 mL/kg (**D**), and comparison between 7 and 10 mL/kg (**E**), 7 and 12 mL/kg (**F**), 8 and 10 mL/kg (**G**), and between 8 and 12 mL/kg (**H**). The pooled odds ratio and 95% CI were calculated using a random-effects model. Weight refers to the contribution of each study to the overall pooled estimate. M-H = Mantel-Haenszel.

Effect of V_t on Mortality–Patients With ALI/ARDS

Five studies had included patients with ALI/ARDS (n = 799 patients) (9, 10, 19, 22, 23). There was no association between V_t and mortality when dichotomized at 7 mL/kg (n = 4 studies, 656 patients) (9, 10, 19, 22), 8 mL/kg (n = 5 studies, 799 patients) (9, 10, 19, 22, 23), 10 mL/kg (n = 5 studies, 799 patients) (9, 10, 19, 22, 23), or 12 mL/kg (n = 4 studies, 656 patients) (9, 10, 19, 22) (**Fig. 4** ***A–D***). Visual inspection of the funnel plot suggested asymmetry for all analyses except the one with 10 mL/kg as cutoff value (**Fig. 5** ***A–D***). A moderate-to-substantial degree of heterogeneity was observed. In addition, there was also no association between V_t and mortality when low V_t (< 7 or 8 mL/kg) was compared with high V_t (> 10 or 12 mL/kg) (**Fig. 4** ***E–H***).

The findings of our study were similar when we compared studies in which more than 90% of patients were managed in a PC mode of ventilation or when we compared studies by nature (retrospective vs prospective).

DISCUSSION

We could not confirm a relationship between V_t and mortality in this systematic review and meta-analysis of observational studies, irrespective of the level of V_t or the presence of ALI/

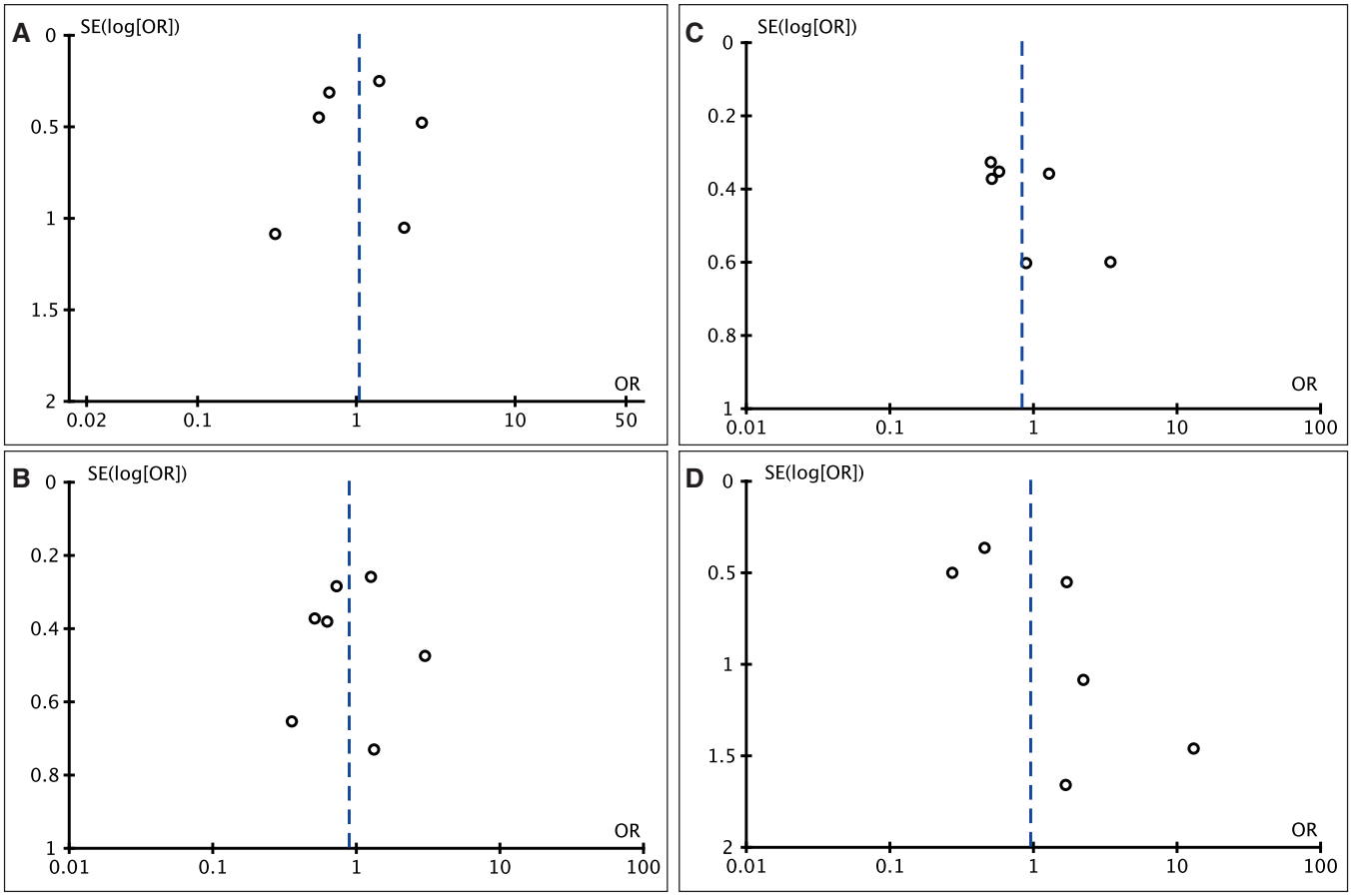

Figure 3. Funnel plot for pooled analysis of mortality with tidal volume (V_t) dichotomized at 7 mL/kg body weight (**A**), 8 mL/kg (**B**), 10 mL/kg (**C**), and 12 mL/kg (**D**). OR = odds ratio.

ARDS. However, we also observed significant heterogeneity when studies were pooled. To the best of our knowledge, this is the first meta-analysis addressing the issue of V_t in mechanically ventilated children.

Much of the current clinical practice related to pediatric MV is based on anecdotal experience in combination with data originating from studies in critically ill adults (26). For instance, lung-protective ventilation including the use of low V_t has become mainstay in daily pediatric critical care following the results of the ARDSNetwork low V_t trial (5). However, only a few studies have prospectively looked into the question of an optimal lung-protective V_t in children so far. The findings of this meta-analysis do not provide an answer to the question whether low V_t is beneficial in mechanically ventilated children. By contrast, we could not confirm an association between V_t and mortality for any given cutoff value. The results of our meta-analysis are in line with a meta-analysis pooling the results from the adult trials (27). In this analysis also no association between V_t and mortality could be confirmed.

It is challenging to explain why we could not ascertain an association between V_t and mortality. Whereas two individual studies did observe a positive association between V_t and mortality (9, 23), another group of investigators found the opposite—that is, a negative relationship between V_t and mortality (10) (Table 2). This opposing direction of the signals in the individual studies may thus explain why we could not demonstrate an association between V_t and mortality. It probably originates from a number of reasons. First, there are well-recognized limitations of V_t measurement in mechanically ventilated children (28). Erroneous V_t measurement occurs frequently due to, among others, tube leakage and inability to measure at the Y-piece near the endotracheal tube, thus overestimating the V_t delivered (29). Only two studies in our pooled analysis adjusted for this (19, 22), so this factor cannot be ruled out. Second, there were inconsistencies between the individual studies regarding study population (not all studies exclusively focused on patients with ALI/ARDS), and the timing of V_t measurement was not uniform. We therefore have performed two additional analyses: one including only patients with ALI/ARDS and one including studies that have used similar moments of V_t measurement. These analyses did not provide new information. Third, all studies have included patients up to the age of 18 years. However, animal work suggested that the PICU population might be less susceptible to the detrimental effects of MV compared with adults, especially since the inflammatory response to injury is age-dependent (15, 30, 31). This possible age-related susceptibility could not be explored in the individual studies. Fourth, it may be questioned if mortality is a good outcome measure, especially since mortality rates in pediatric ALI/ARDS are considerable lower than in adults (32). Mortality rates have dropped

to about 18–27% over the last decade. Remarkably, the reported mortality in the included studies was considerably higher. Also, although many patients met the criteria for ALI/ARDS, we could not determine the spectrum of disease severity of the included patients. Next to this, also included were patients with a priori a low probability of death, such as infants with viral bronchiolitis. The latter signifies that alternative endpoints, such as functional outcome, need to be considered (33). Also, we choose hospital mortality as endpoint, but it cannot be ruled out that a number of patients died after hospital discharge, mandating the need for follow-up studies of pediatric ARDS survivors. Fifth, there was no uniformity in the ventilation mode used among the included studies. This is in line with daily clinical practice in pediatric critical care, where—in general—there is no uniformity in ventilator modes used (7). With PC, the delivered V_t is determined by the respiratory system compliance (C_{rs}) (i.e., the better the lung compliance, the higher the allowable V_t would be). The use of PC may thus have led to confounding, as patients with better lung compliance and a better outcome would be more likely to have been ventilated with higher V_t. This assumption is supported by a retrospective analysis on patient individual data from the ARMA trial showing that the level of C_{rs} prerandomization affected patient outcome (34). Furthermore, in the studies by Erickson et al (10) and Khemani et al (22), there was also a positive relationship between PIP and mortality, suggesting that the lung compliance may have affected patient outcome rather than V_t itself. One group of investigators tried to overcome this confounding by adjusting for ventilator mode in multivariate

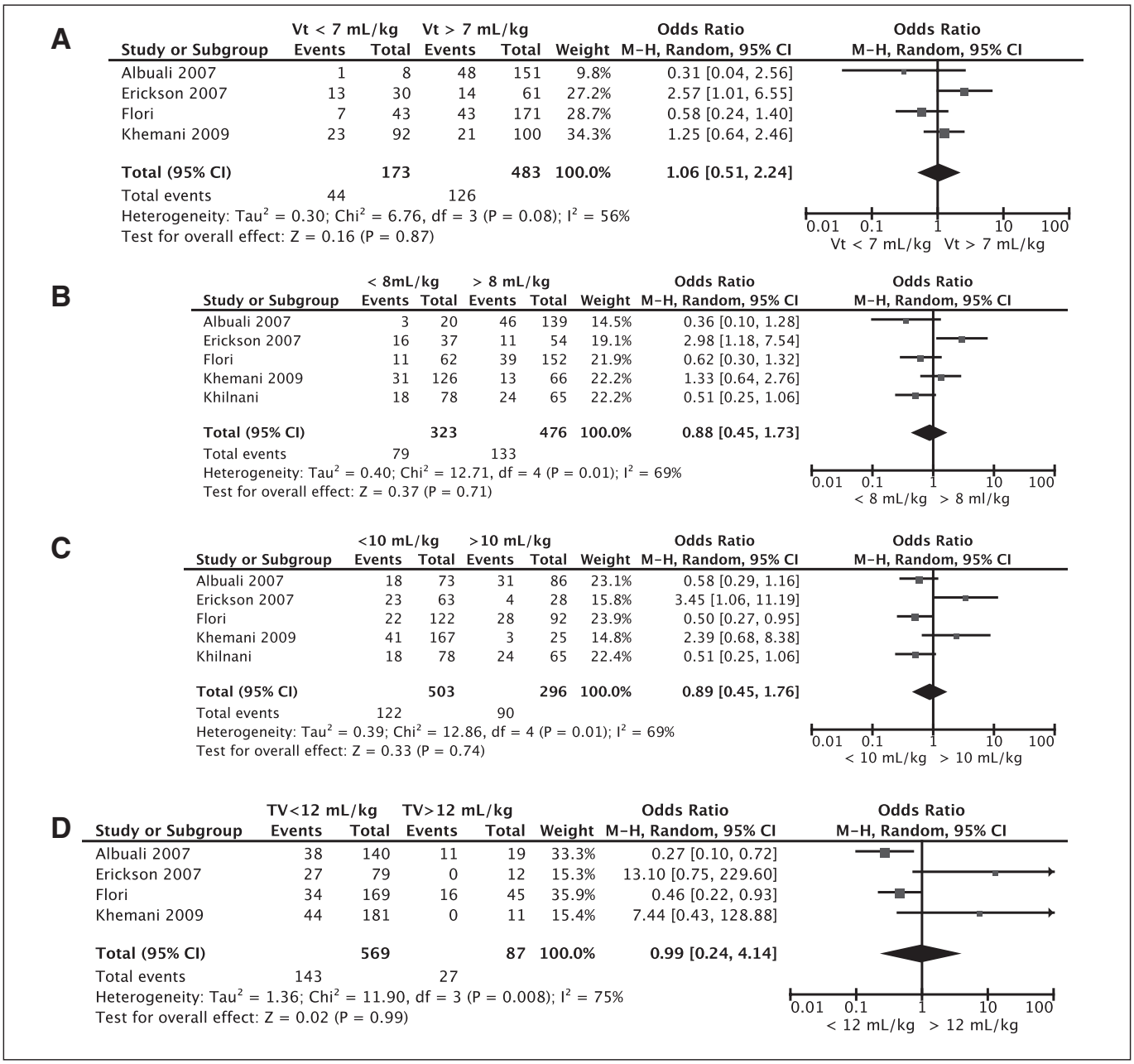

Figure 4. (*Continued*)

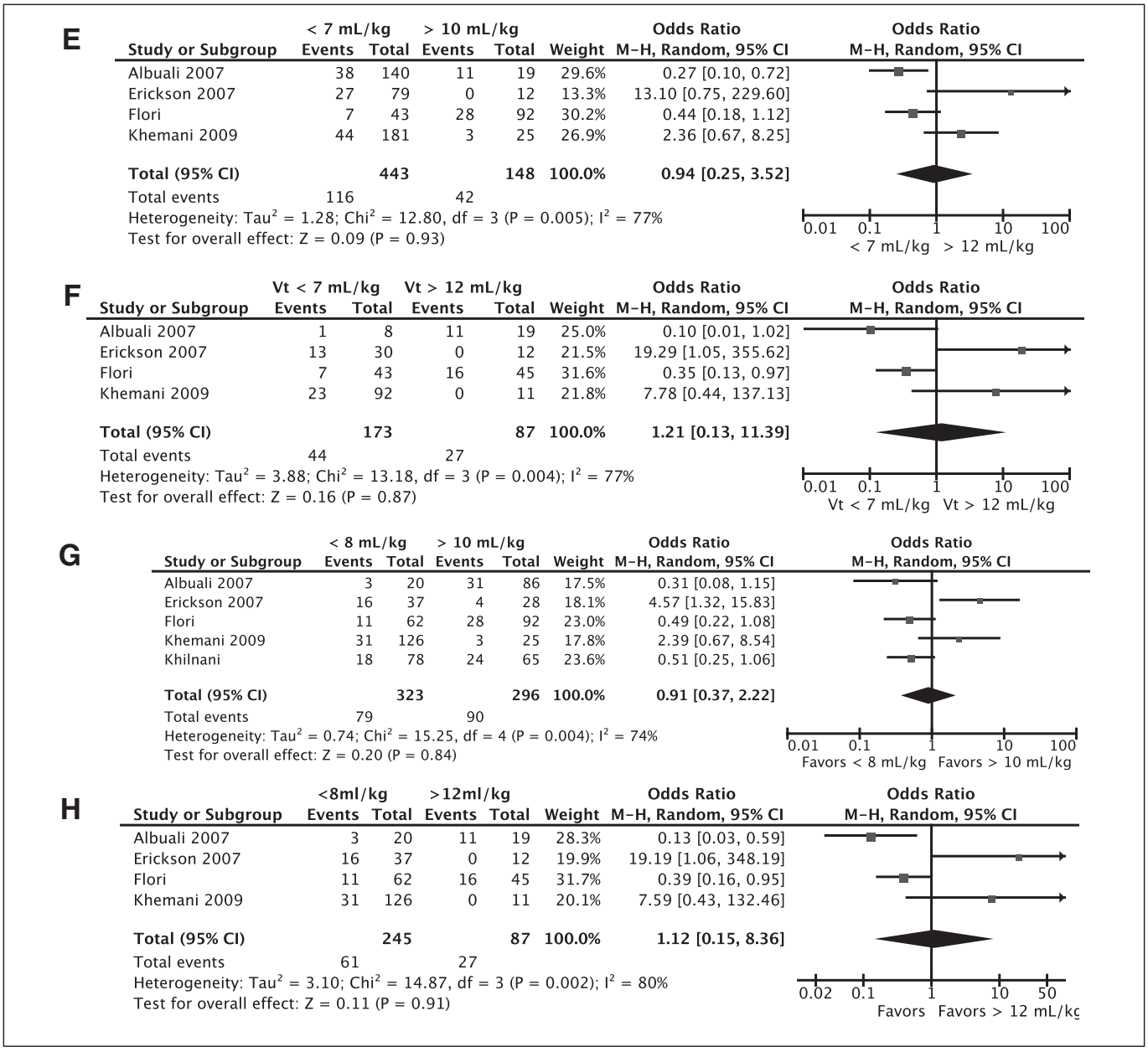

Figure 4. (*Continued*) Attributable PICU mortality in patients with acute lung injury/acute respiratory distress syndrome associated with tidal volume (V_t) dichotomized at 7 mL/kg body weight (**A**), 8 mL/kg (**B**), 10 mL/kg (**C**), 12 mL/kg (**D**), and comparison between 7 and 10 mL/kg (**E**), 7 and 12 mL/kg (**F**), 8 and 10 mL/kg (**G**), and 8 and 12 mL/kg (**H**). The pooled odds ratio and 95% CI were calculated using a random-effects model. Weight refers to the contribution of each study to the overall pooled estimate. M-H = Mantel-Haenszel.

analysis (9). High V_t remained independently associated with increased mortality after this analysis. Likewise, the use of VC or PRVC may also have led to confounding; with such an approach, the physician empirically sets the V_t, usually between 6 and 10 mL/kg and thereby neglecting lung compliance (35).

Translating our findings to the bedside is difficult. No recommendations related to an optimal V_t can be supported by scientific evidence, and this meta-analysis does not provide any definitive answers. The physiological V_t in children is in the range of 4–7 mL/kg body weight (36). The difficulty in finding the optimal V_t may be overcome by ventilating the patient dependent upon the disease characteristics and respiratory system mechanics (i.e., a "physiologic" approach). The delivered V_t would then be smaller in sicker lungs and higher in less sick or improving lungs, taking the underlying disease and severity of lung disease into account in the individual patient (37). However, this approach needs to be tested in future trials, albeit that ventilating with V_t greater than 10 mL/kg is not accepted as standard-of-care nowadays (8).

Our findings may also have implications for the possible design of pediatric V_t trials. A pediatric ARMA trial only seems feasible in a well-described patient population with a limited age range while also excluding mild-to-moderate pediatric ARDS (38). However, a recent survey among pediatric intensivists showed that they would prefer to copy the design of the ARMA trial for a pediatric counterpart (39). However, such a design

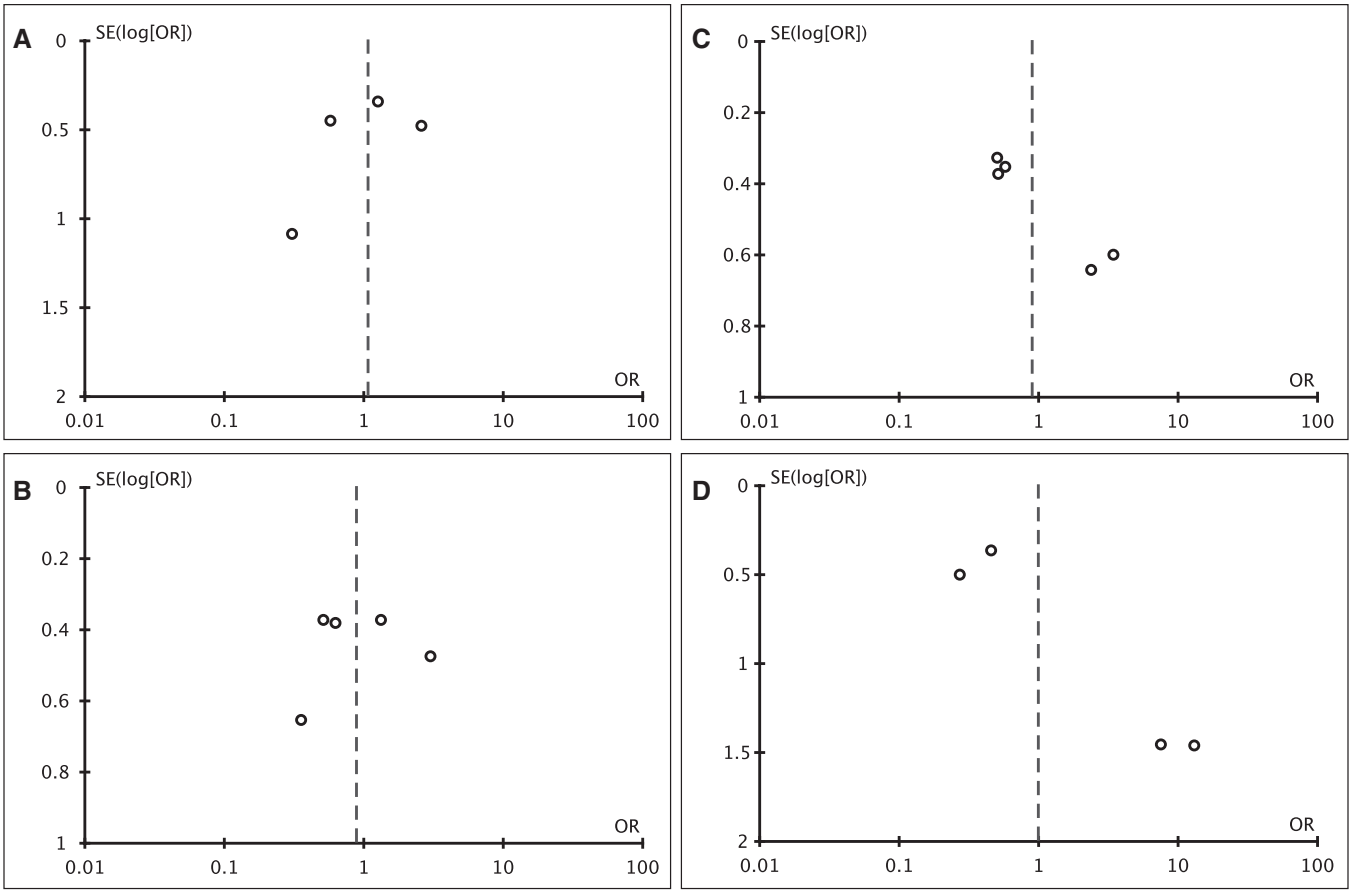

Figure 5. Funnel plot for pooled analysis of mortality in patients with acute lung injury/acute respiratory distress syndrome with tidal volume dichotomized at 7 mL/kg body weight (**A**), 8 mL/kg (**B**), 10 mL/kg (**C**), and 12 mL/kg (**D**). OR = odds ratio.

seems unrealistic, given the many criticisms in design of the ARMA trial (39). Furthermore, the results of this meta-analysis add to the uncertainty of such a trial. For instance, we choose a lowest cutoff of 7 mL/kg as no data could be retrieved from the identified publications to study the effect of 6 mL/kg on mortality. Nonetheless, RCTs have been pushed forward as the highest level of evidence, but also suffer from a number of drawbacks including among others the effectiveness and timing of the intervention, as well as the identification of the right patient for the trial (40). Beforehand, well-balanced prospective observational studies like the PALIVE study are necessary as they provide valuable information on the current practice of MV in critically ill children (7). At present, there is insufficient knowledge on how children with moderate-to-severe ARDS are managed, and how ventilator settings in these patients may affect outcome. A prerequisite for observational studies in pediatric ARDS is identification of the right patient. However, the recognition of ARDS in critically ill children is challenging, but recent efforts have been undertaken to define pediatric ARDS (41). Furthermore, this meta-analysis also indicates that standardization of data collection, ventilation measurements, and analysis are required to obtain meaningful results that can optimize patient care.

The strength of this meta-analysis includes obtaining data from individual investigators and the use of a rigorous systematic review in accordance with recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement and the Strengthening the Reporting of Observational Studies in Epidemiology statement (16, 42). But our study also has limitations. The most prominent one is the significant degree of heterogeneity observed in the pooled analyses. This suggests that there may be many (methodological) differences between the included studies other than discussed above, including among others variation in respiratory and supportive care practice in the diverse study sites (7). Although all studies scored high on "selection" and "exposure" according to the Newcastle-Ottawa Scale for cohort studies, none of them did well regarding comparability. To name but a few, the use of neuromuscular blockade or (early) high-frequency oscillatory ventilation may have significantly affected the results from the individual studies (43, 44). Next to this, a number of included studies were retrospectively designed with their inherent limitations. This may explain the differences in direction of each effect. Many funnel plots showed an asymmetrical profile. This may be interpreted as publication bias and may thus pose a severe limitation of our analysis. However, asymmetry in funnel plots may also originate from poor methodological quality of the included studies or true heterogeneity between the included studies as already outlined above (45, 46). In addition to this, many of the included studies did not report a clinical algorithm describing the practice of MV. Lastly, although no

language restrictions were applied, we did not search nontraditional data sources.

CONCLUSIONS

Our systematic review and meta-analysis of observational studies did not identify a relationship between V_t and mortality in mechanically ventilated children, irrespective of the severity of disease. However, significant heterogeneity was observed in the pooled analysis. This means that future studies are necessitated in well-defined patient populations to truly understand the effects of V_t on patient outcome.

ACKNOWLEDGMENTS

We greatly acknowledge Dr. Dafne Bourguignon, Dr. Simon Erickson, Dr. Heidi Flori, Dr. Feiko Halbertsma, Dr. Robinder Khemani, Dr. Alik Kornecki, and Dr. Bo Sun for providing additional data for their studies. We also thank Dr. Khemani for his critical appraisal of our article.

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APPENDIX 1: Search Strategy for Medline (Inception–July 2013)

1. "mechanical ventilation" [mesh]
2. "tidal volume" [mesh]
3. "mortality" [mesh]
4. "acute lung injury" [mesh]
5. "acute respiratory distress syndrome" [mesh]
6. "critical care" [mesh]
7. "intensive care" [mesh]
8. 1 AND 2 AND 3
9. 8 AND 4
10. 8 AND 5
11. 8 AND (4 OR 5)
12. 8 AND (6 OR 7)
13. 2 AND 3
14. 2 AND 3 AND 4
15. 2 AND 4 AND 5
16. 3 AND 4
17. 3 AND 5