the interpretation of the results. We would really appreciate it if the investigators could provide information on this issue.

Declaration of interest

None declared.

References

1. Wesselink EM, Kappen TH, van Klei WA, Dieleman JM, van Dijk D, Slooter AJ, *et al*. Intraoperative hypotension and delirium after on-pump cardiac surgery. *Br J Anaesth* 2015; **115**: 427–33
2. Acharya NK, Goldwaser EL, Forsberg MM, *et al*. Sevoflurane and Isoflurane induce structural changes in brain vascular endothelial cells and increase blood–brain barrier permeability: possible link to postoperative delirium and cognitive decline. *Brain Res* 2015; **1620**: 29–41
3. Chan MT, Cheng BC, Lee TM, Gin T, *et al*. CODA Trial Group BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol* 2013; **25**: 33–42
4. Radtke FM, Franck M, Lendner J, Krüger S, Wernecke KD, Spies CD, *et al*. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. *Br J Anaesth* 2013; **110**(Suppl 1): i98–105
5. Ruiz Bajo B, Roche Bueno JC, Seral Moral M, Martí Martínez J, *et al*. Incidence and predictive factors of delirium in hospitalised neurological patients. *Neurologia* 2013; **28**: 356–60
6. Fakin R, Zimpfer D, Sodeck GH, *et al*. Influence of temperature management on neurocognitive function in biological aortic valve replacement. A prospective randomized trial. *J Cardiovasc Surg (Torino)* 2012; **53**: 107–12
7. Cook RC, Gao M, Macnab AJ, Fedoruk LM, Day N, Janusz MT, *et al*. Aortic arch reconstruction: safety of moderate hypothermia and antegrade cerebral perfusion during systemic circulatory arrest. *J Card Surg* 2006; **21**: 158–64
8. Joshi B, Brady K, Lee J, *et al*. Impaired autoregulation of cerebral blood flow during rewarming from hypothermic cardiopulmonary bypass and its potential association with stroke. *Anesth Analg* 2010; **110**: 321–8

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Reply from the authors

Intraoperative hypotension and postoperative delirium: no confusion on confounding

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Editor—We would like to thank Zhang and colleagues for their interest in our study. The authors raise concerns about the possibility of residual confounding in our study on the relation between intraoperative hypotension (IOH) and delirium after on-pump cardiac surgery.[1] The authors of the letter suggest three possible mechanisms for residual confounding.

First, the depth of anaesthesia and the dose of inhalational anaesthetics were suggested as possible confounders. The relation with depth of anaesthesia and IOH is complicated, because these are part of the same causal chain; deeper levels of anaesthesia cause more IOH. Including two independent variables that share the same causal pathway in a statistical analysis is not very rational.

Nonetheless, the authors also suggest that there is a direct effect of the depth of anaesthesia on postoperative delirium, through an increase in blood–brain barrier permeability. As the literature on the direct effects of anaesthetics on postoperative delirium is still very limited, we cannot simply assume that the direct effect of the depth anaesthesia is larger than the indirect effect through IOH. Consequently, an analysis that includes depth of anaesthesia as a confounder may be difficult to understand.

However, as the authors requested, we performed a sensitivity analysis that included the average concentration of inhalational anaesthesia (bispectral index monitoring was not routinely performed). This sensitivity analysis did not change the odds ratios for different IOH definitions (Table 1, second analysis compared with first analysis).

Second, a history of stroke is indeed a risk factor for postoperative delirium. In addition, stroke is also likely to be associated with IOH, because a stroke is an expression of arteriopathy. Preoperative cognitive impairment, another established risk factor for delirium, may have a similar relation to IOH. However, extracardiac arteriopathy (e.g. carotid occlusion) is one of the risk factors included in the EuroSCORE.[2] Adjusting the analysis for the EuroSCORE is likely to suffice as adjustment for the relation between IOH, stroke, and postoperative delirium.

Moreover, while the difference in history of stroke [35 (5%) *vs* 6 (6%)] between non-delirious and delirious patients was statistically significant, the effect is of dubious clinical relevance. The rounded difference between the groups is 1%, yet the real difference is only 0.55%. The clinical irrelevance of this difference is confirmed by our sensitivity analysis, because additional adjustment for stroke did not change the results of the original analysis (Table 1, third analysis compared with first analysis).

Third, the authors of the letter suggest temperature management during CPB to be a confounder. The authors present three articles to support this claim, yet none of the articles confirms hypothermia to be an established risk factor for postoperative delirium.[3–5] Even when we assume an established relation between hypothermia during CPB and postoperative delirium, this does not mean that there is a strong relation between hypothermia and IOH. The sensitivity analysis indeed confirms that hypothermia during CPB was not a residual confounder in the original analysis (Table 1, fourth analysis compared with first analysis).

Table 1 Adjusted odds ratios for the association between the area under the curve of intraoperative hypotension during cardiac surgery and occurrence of postoperative delirium. *Results were adjusted for EuroSCORE, duration of surgery and CPB, total intraoperative fluid, cumulative duration of vasopressors, and inotropes. †Restrictive cubic splines were used to include the additional variable in the regression model. ‡Estimates per 1000 mm Hg^2 min^2 AUC^2 increase of intraoperative hypotension depth or duration, or both. AUC, area under the curve; CI, confidence interval; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; OR, odds ratio

Definition of intraoperative hypotension	Original adjusted analysis*		Additionally adjusted for depth of anaesthesia*†		Additionally adjusted for history of stroke*		Additionally adjusted for lowest temperature on CBP*†	
	OR‡	99% CI	OR‡	99% CI	OR‡	99% CI	OR‡	99% CI
MAP <60 mm Hg	1.04	0.99–1.10	1.04	0.97–1.12	1.04	0.99–1.10	1.04	0.99–1.11
MAP <50 mm Hg	1.14	0.98–1.52	1.22	0.88–2.04	1.14	0.97–1.51	1.16	0.98–1.59
MAP decrease >30% relative to baseline	1.00	0.99–1.01	1.00	0.98–1.01	1.00	0.99–1.01	1.00	0.99–1.02
MAP decrease >40% relative to baseline	1.01	0.97–1.04	1.00	0.96–1.04	1.01	0.97–1.04	1.01	0.98–1.06

In conclusion, the concerns about the interpretation of the study results do not seem to be justified. From a conceptual standpoint, none of the three factors should be considered as a confounder; depth of anaesthesia and dose of anaesthetics are part of the same causal chain as the determinant (i.e. IOH), whereas a history of stroke or cognitive impairment and hypothermia are not related to the determinant. This conceptual standpoint is backed up by the sensitivity analysis, because additional adjustment for these variables did not change the study results.

Declaration of interest

None declared.

References

1. Wesselink EM, Kappen TH, van Klei WA, Dieleman JM, van Dijk D, Slooter AJ. Intraoperative hypotension and delirium after on-pump cardiac surgery. *Br J Anaesth* 2015; **115**: 427–33
2. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999; **16**: 9–13
3. Fakin R, Zimpfer D, Sodeck GH, *et al*. Influence of temperature management on neurocognitive function in biological aortic valve replacement. A prospective randomized trial. *J Cardiovasc Surg (Torino)* 2012; **53**: 107–12
4. Cook RC, Gao M, Macnab AJ, Fedoruk LM, Day N, Janusz MT. Aortic arch reconstruction: safety of moderate hypothermia and antegrade cerebral perfusion during systemic circulatory arrest. *J Card Surg* 2002; **21**: 158–64
5. Joshi B, Brady K, Lee J, *et al*. Impaired autoregulation of cerebral blood flow during rewarming from hypothermic cardiopulmonary bypass and its potential association with stroke. *Anesth Analg* 2010; **110**: 321–8

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Reliable critical care: how knowledge translation can result in patient harm

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Editor—I read with interest the editorial by Sundaram and Rooney[1] discussing the translation of evidence into routine clinical practice with reference to lung-protective ventilation. This is one of the few therapies in critical care that has stood the test of time and clearly should be implemented in clinical practice. However, I believe that knowledge translation in critical care should be discussed in the broader context of the trend towards reversal of evidence over the last decade.

A review of 2044 articles published between 2001 and 2010 in *The New England Journal of Medicine* found that 'of the 363 articles testing standard of care, 146 (40.2%) reversed that practice'.[2] Even before trial results are reversed, positive trials are often not as robust as they seem. Walsh and colleagues[3] measured the Fragility Index of 399 papers from five major medical journals. This index is a measure of 'the number of events required to change statistically significant results to non-significant results'. It was found that the number of patients lost to follow-up exceeded the Fragility Index in 52.9% of trials. In recent years, interventions such as intensive insulin therapy, activated protein C, steroids in sepsis, and glutamine have been shown to be ineffective or indeed harmful. This is despite initial evidence appearing robust. It is easy to see why critical care physicians are slow to translate knowledge into practice.