drugs affecting metabolic inflammation in individuals with evidence of metabolic dysfunction and asthma, not simply increased BMI and asthma, are needed.

Whatever the limitations of one study in leading to definitive conclusions regarding mediators of severe asthma, the study by Peters and colleagues is important. It should drive future studies to phenotype metabolic dysfunction, not simply measure BMI in patients with asthma. This strategy might require the measurement of various mediators and measures more typically used in studies of diabetes than in studies of asthma. It also shows that while many exciting new drugs targeting type 2 pathways are available, such drugs will probably be of limited use in patients with disease metabolic factors outside the lung might be causing disease in the airway.

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1 Dixon AE, Holguin F, Sood A, et al. An official American Thoracic Society Workshop report: obesity and asthma. *Proc Am Thorac Soc* 2010; **7:** 325–35.
2 Peters MC, McGrath KW, Hawkins GA, et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. *Lancet Respir Med* 2016; published online June 6. http://dx.doi.org/10.1016/S2213-2600(16)30048-0.
3 Kloting N, Bluher M. Adipocyte dysfunction, inflammation and metabolic syndrome. *Rev Endocr Metab Disord* 2014; **15:** 277–87.
4 Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. *Nat Immunol* 2015; **16:** 448–57.
5 Aurora RN, Punjabi NM. Obstructive sleep apnoea and type 2 diabetes mellitus: a bidirectional association. *Lancet Respir Med* 2013; **1:** 329–38.
6 Shore SA, Terry RD, Flynt L, Xu A, Hug C. Adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in mice. *J Allergy Clin Immunol* 2006; **118:** 389–95.
7 Hawkins GA, Robinson MB, Hastie AT, et al. The IL-6R variation Asp(358) Ala is a potential modifier of lung function in subjects with asthma. *J Allergy Clin Immunol* 2012; **130:** 510–15.
8 Shore SA, Williams ES, Zhu M. No effect of metformin on the innate airway hyperresponsiveness and increased responses to ozone observed in obese mice. *J Appl Physiol* 2008; **105:** 1127–33.
9 Dixon AE, Subramanian M, DeSarno M, Black K, Lane L, Holguin F. A pilot randomized controlled trial of pioglitazone for the treatment of poorly controlled asthma in obesity. *Respiratory Research* 2015; **16**: 143.

Statistical methods for evaluating delirium in the ICU

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Recently, several studies have evaluated the effectiveness of statins and other interventions in reducing delirium in critically ill patients.[1-4] Studying the effectiveness of interventions on delirium in the intensive care unit (ICU) setting is challenging for several reasons: delirium state can change over the course of hours or days; it occurs along a continuum of acute brain dysfunction and cannot be assessed when patients are more severely impaired (ie, during a comatose state); and delirium evaluation is often stopped at ICU discharge, inhibiting researchers' ability to know its full duration. Moreover, death is a common outcome in the critically ill, with deceased patients no longer able to experience delirium. These characteristics of delirium evaluation in the ICU offer important statistical challenges.

In a Comment in *The Lancet Respiratory Medicine*,[5] Sharshar and colleagues suggested that delirium-free days until 28 days after randomisation could be used as an outcome measure in trials of delirium treatments. This endpoint is similar to another common critical care endpoint, ventilator-free days that was proposed back in 2002,[6] and is calculated by counting the days free of delirium up to day 28, with days after ICU discharge typically counted as delirium-free. We recommend against the use of this endpoint in favour of a joint modelling approach proposed[7] in 2007 and implemented in the *R* statistical package frailty pack in 2012.[8] Instead of representing delirium over 28 days with a single value, the joint modelling approach combines two survival models: one for the repeated (recurrent) daily indicator of delirium and another for the terminating event (ie, an event after which patients can no longer be assessed for the outcome) of ICU discharge or death. A random effect (also referred to as a "frailty") is included in the survival model for daily delirium, linking an individual patient's delirium events, and enters the terminating event model as a main effect linking the delirium events and the terminating event. The effect of a randomised intervention in a trial is evaluated by inclusion of a main effect of treatment in the survival model for daily delirium. The hazard ratio (HR) for the randomised intervention compares the daily hazard of delirium in the intervention group with that in the control group. A HR lower than 1 would indicate a

lower daily hazard of delirium in participants assigned to the intervention, implying a shorter average duration of delirium among days at risk for delirium (ie, ICU days in a non-comatose state).

The figure illustrates the differences between delirium-free days and the joint modelling approach by considering five hypothetical ICU patients randomised at day 0 and followed up until the earliest of discharge from the ICU, death, or 28 days. Patient 1 remains alive in the ICU for the entire 28 days and contributes the same information to the joint modelling approach and the analysis of delirium-free days. Patient 2 experiences death at the end of day 4 after experiencing delirium for 3 days. The delirium-free days approach assigns this patient one delirium-free day. Alternatively, patients who die during follow-up may be assigned 0 delirium-free days (indicating that death is the worst possible outcome), creating a composite endpoint. The interpretability of this composite endpoint that combines mortality and delirium could be questioned when the intervention being evaluated is not expected to affect mortality. In the joint modelling approach, Patient 2 contributes 4 days of exposure and three recurrent delirium events.

Patients 3 and 4 are both discharged alive from the ICU after day 6, with 2 delirium-free days. Patient 4 continues to have delirium until day 28; however, both patients would be assigned 24 delirium-free days with the delirium-free days approach given that they are not followed up beyond ICU discharge. As is the case with Patient 4, delirium often continues after ICU discharge (eg, 16–49% of patients with acute respiratory distress syndrome have been reported to have delirium on their final assessment in the ICU[1,9]). This situation creates a problem with either counting zero for days of delirium after discharge or the feasibility of continuing delirium assessments on the ward, given the added time and resources required and the low sensitivity of validated ICU-based delirium screening tools outside the ICU.[10] The joint modelling approach makes no assumption about delirium for patients discharged from the ICU, such that Patients 3 and 4 contribute the same information to the analysis.

Days with coma are common and can further complicate the calculation of delirium-free days. Patient 5 experiences coma for the first 2 days followed by 3 days of delirium, and by death at the end of day 5.

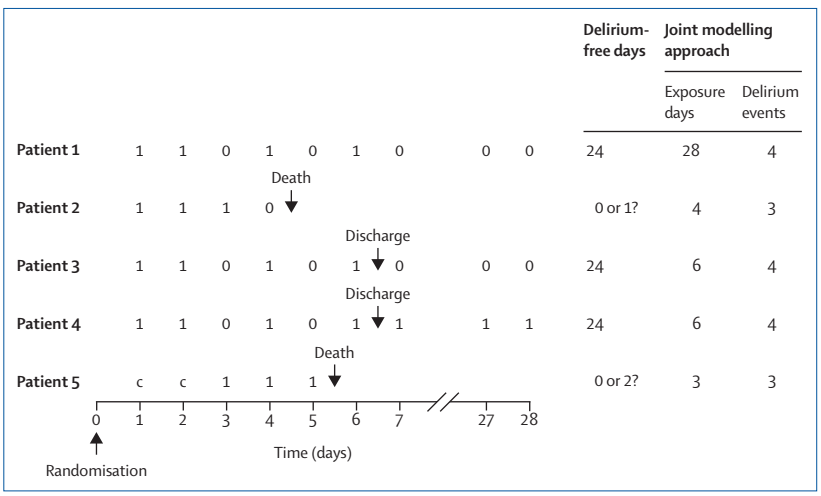

Figure: **Hypothetical patients from a clinical trial in which patients are randomised at day 0 and followed until the earliest of discharge from the intensive care unit, death, or 28 days**
For each patient, delirium-free days to day 28 is calculated along with days of exposure and delirium for the joint modelling approach. 1, 0, and c denote a day with delirium, a delirium-free day, and a day in coma, respectively.

This patient has 2 delirium-free days. Days with coma could be included in a modified endpoint of delirium-free and coma-free days that would yield a value of 0 for Patient 5. In the joint modelling approach, Patient 5 contributes 3 days of exposure and three recurrent delirium events to the analysis; this approach only evaluates days when patients are at risk for delirium (ie, does not include days when the patient is comatose).

Notably, the joint modelling approach has a limitation of incorporating only a single terminating event model. The single terminating event model is flexible to allow for the possible intervention effect to be defined separately for each terminating event type via a statistical interaction term, as was done in our example. However, the correlation between the recurrent event (ie, delirium) and the hazard of both terminating events is assumed to be the same. In ICU studies, these two terminating events are likely to be correlated with delirium in opposite directions. In our study,[1] 230 (90%) of the 256 terminating events were ICU discharge, minimising the effect that multiple terminating event models would have on our results. Research into expanding the joint modelling approach to accommodate multiple terminating event models is needed.

Given the many problems with delirium-free days as an endpoint and the recent availability of appropriate and flexible statistical methodology and software, we recommend the use of a joint modelling approach to evaluate the effect of interventions on delirium in the ICU.

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1 Needham DM, Colantuoni E, Dinglas VD, et al. Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial. *Lancet Respir Med* 2016; **4:** 203–12.
2 Billings FT, IV, Hendricks PA, Schildcrout JS, et al. High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery: a randomized clinical trial. *JAMA* 2016; **315:** 877–88.
3 Simons KS, Laheijj RJF, van den Boogaard M, et al. Dynamic light application therapy to reduce the incidence and duration of delirium in intensive-care patients: a randomised controlled trial. *Lancet Respir Med* 2016; **4:** 194–202.
4 Casarin A, McAuley DF, Alce, TM, et al. Evaluating early administration of the hydroxymethylglutaryl-CoA reductase inhibitor simvastatin in the prevention and treatment of delirium in critically ill ventilated patients (MoDUS trial): study protocol for a randomized controlled. *Trials* 2016; **16:** 218.
5 Sharshar T, Polito A, Bozza F, et al. Statins and brain dysfunction in intensive care. *Lancet Respir Med* 2016; **4:** 169–70.
6 Schoenfeld DA, Bernard GR, ARDS Network. Statistical evaluation of ventilator-free days as an efficacy measure in clinical trials of treatments for acute respiratory distress syndrome. *Crit Care Med* 2002; **30:** 1772–77.
7 Rondeau V, Mathoulin-Pellissier S, Jacqmin-Gadda H, et al. Joint frailty models for recurring events and death using maximum penalized likelihood estimation: application on cancer events. *Biostatistics* 2007; **8:** 708–21.
8 Rondeau V, Mazroui Y, Gonzalez JR. Frailtypack: an R package for the analysis of correlated survival data with frailty models using penalized likelihood estimation or parametric estimation. *J Stat Soft* 2012; **47:** 1–28.
9 Fan E, Shahid S, Kondreddi VP, et al. Informed consent in the critically ill: a two-step approach incorporating delirium screening. *Crit Care Med* 2008; **36:** 94–99.
10 Neufeld K, Hayat MJ, Coughlin JM, et al. Evaluation of two intensive care delirium screening tools for non-critically ill hospitalized patients. *Psychosomatics* 2011; **52:** 133–40.