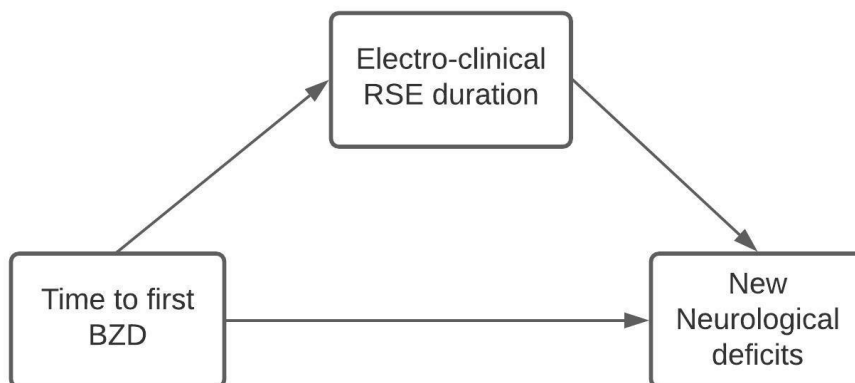


## **Appendix e2. Causal mediation analysis: electro-clinical refractory status epilepticus duration as a mediator between time to first benzodiazepine and the development of new neurological deficits.**

Delayed time to administration of first benzodiazepine (BZD) treatment affects short-term outcomes of status epilepticus (SE) (p.e. duration of SE), but the relationship with long-term outcomes such as the development of new neurological deficits is unclear.<sup>1-3</sup> We hypothesize that there may be an association of time to first BZD and the presence of new neurological deficits during follow-up, and that the causality might be mediated by the electro-clinical duration of the refractory status epilepticus (RSE). We conducted a causal mediation analysis to further investigate the mediating effect of RSE duration between the time to first BZD treatment and the development of new neurological deficits. We followed the conventional approach to conduct the causal mediation analysis,<sup>4, 5</sup> with the time to first BZD treatment as a continuous treatment variable, the appearance of new neurological deficits as a binary outcome variable, and RSE duration as a continuous mediator. We performed a logistic regression model to evaluate the association of the outcome variable with the time to first BZD treatment alone, and then, with the time to first BZD treatment and the RSE duration jointly. We used linear regression to analyze the association of seizure duration with the time to first BZD treatment. Then the causal mediation analysis was conducted based upon results from the regression models. In such a setting, the analysis results showed that the time to first BZD treatment was neither a predictor of new neurological deficits ( $p = 0.620$ ) nor a predictor of electro-clinical RSE duration ( $p = 0.473$ ). Therefore, the RSE duration was not expected to be a mediator here. The final causal mediation analysis validated this, giving insignificant indirect, direct, and total effects.

### **Path diagram of the mediation analysis.**



## References

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