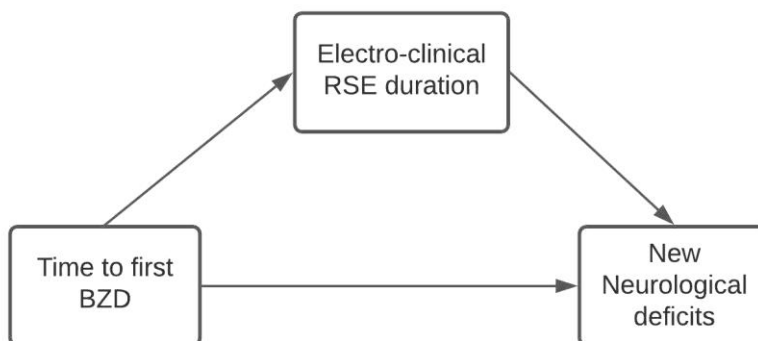


Appendix e2. Causal mediation analysis: electro-clinical refractory status epilepticus duration as a mediator between time to first benzodiazepine and the development of new neurological deficits.

It has been shown that 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 has not been investigated.¹⁻³ 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). Causal mediation analysis was conducted 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,^{4, 5} 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. Logistic regression was performed for the outcome variable on the time to first BZD treatment alone, and then on the time to first BZD treatment and the RSE duration. Linear regression was performed for seizure duration on the time to first BZD treatment. Then the causal mediation analysis was conducted based upon results from the regression models. In such a setting, unfortunately, the analysis results show that the time to first BZD treatment is 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 is not expected to be a mediator here. Final causal mediation analysis validated this, giving an insignificant indirect effect ($p = 0.54$) and an insignificant total effect ($p = 0.52$). The direct effect is also insignificant ($p = 0.73$).

Path diagram of the mediation analysis.



References

1. Gaínza-Lein M, Sanchez Fernandez I, Jackson M, et al. Association of Time to Treatment With Short-term Outcomes for Pediatric Patients With Refractory Convulsive Status Epilepticus. *JAMA Neurol* 2018.
2. Sanchez Fernandez I, Abend NS, Agadi S, et al. Time from convulsive status epilepticus onset to anticonvulsant administration in children. *Neurology* 2015;84:2304-2311.
3. Cohen NT, Chamberlain JM, Gaillard WD. Timing and selection of first antiseizure medication in patients with pediatric status epilepticus. *Epilepsy Res* 2019;149:21-25.
4. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods* 2010;15:309-334.
5. Ten Have TR, Joffe MM. A review of causal estimation of effects in mediation analyses. *Stat Methods Med Res* 2012;21:77-107.