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CORRESPONDENCE

Reply to "Efficacy and safety of hydrolyzed formulas for cow's milk allergy management: A systematic review of randomized controlled trials"

Dear Editor,

We read with interest the systematic review "Efficacy and safety of hydrolyzed formulas for cow's milk allergy management: A systematic review of randomized controlled trials" performed by Stróżyk et al.[1] Being strong supporters of Open Science, we were pleased to provide, under the request of Dr Stróżyk, the complete data sets of two published randomized controlled trials (RCTs) performed by our group.[2,3] We found some inaccuracies, including calculation errors, in the new analysis of one of our RCT[3] performed by Stróżyk et al. Our RCT,[3] newly analysed by Stróżyk et al, was aimed at testing whether an extensively hydrolysed casein formula with *L rhamnosus* GG (E = experimental treatment) was more effective than an extensively hydrolysed casein formula without *L rhamnosus* GG (C = control treatment). The main outcome of the RCT was the incidence of any allergic event at 36 months of follow-up. The allergic events making the main outcome were eczema, urticaria, asthma and rhinoconjunctivitis. Reaching just one of these outcomes within 36 months meant reaching the main outcome. Our secondary outcome was the time-dependent acquisition of cow's milk tolerance. We performed *repeated measures* of the outcomes at 12, 24 and 36 months, and took them into account in a secondary analysis of the main outcome and in the main analysis of the secondary outcome.[3]

The following are our specific comments about the systematic review of Stróżyk et al:

1. Stróżyk et al chose to calculate risk ratios (RR) instead of risk differences. This is somewhat surprising because, for RCTs, risk differences are much more informative than RR.[4] We, however, followed Stróżyk et al and calculated RR from our data. Table 1 compares the RR computed by us with those reported by Stróżyk et al. These RR are not corrected for repeated measures, but this is not important for our present aim.
2. Stróżyk et al tested 17 null hypotheses (#1 to #17), while we tested just one of these hypotheses (#17) (Table 1). The hypothesis we tested was, of course, the main study hypothesis (see above), which was designed with the aim of detecting a *clinically relevant difference*.[3] In our paper,[3] we reported the components of the main outcome just because, whenever there is a composite outcome, the reader could judge whether its single components are reasonably combined[5] (Table 1).
3. It is surprising that Stróżyk et al tested whether the number of *new cases* was the same for C *vs*. E in a given *time interval* when the metric of interest is cumulative incidence and not incidence inside a given time interval. Take eczema, for instance (Table 1). It is perhaps reasonable to calculate the RR of eczema from 0 to 12 months, even if we were not interested in it. But what about calculating the same RR from 12 to 24 months? And from 24 to 36 months? The fact is that the numbers here do sum so that the number of incident cases at 12 months, 12 + 24 months and 12 + 24+36 months is the only methodologically reasonable option. This choice is even more surprising in view of the fact that the authors correctly performed the 12, 12 + 24 and 12 + 24+36 comparisons when they analysed the outcome "tolerance acquisition" using data from our two RCTs.[2,3]
4. We found that two RRs were miscalculated. They are marked in bold in Table 1. We calculated exact (Pearson-Clopper) 95% confidence intervals (CI) only for completeness. We repeat that, had we chosen to test these hypotheses, which we did not do for the reasons stated above, we would have taken the repeated measures into account. 95% CI would otherwise be incorrect, and also *our* exact 95% CI are not correct on that ground. We also do not know how Stróżyk et al calculated 95% CI so that a direct comparison of the 95% CI is difficult.
5. The 95% CI (0.80 to 0.84) of the RR for urticaria from 0 to 36 months does not contain the point estimate (0.39).
6. Only by trial and error, we understood how "0 cells" were handled, *that is* by adding 0.5 to 0 cells[6]: (a) RR for eczema from 12 to 24 months = (0.5/98)/(3.5/95) = 0.14; (b) RR for urticaria from 12 to 24 months = (2.5/98)/(0.5/95) = 4.85.
7. A metanalysis for repeated measures could have been easily performed using the patient-level data that we provided to Stróżyk et al.[7] Of course, this will not change the fact that the main study hypothesis was #17 and that we were not focused into the remaining 16 hypotheses tested by Stróżyk et al (Table 1).

This is a correspondence letter referring to Stróżyk A, Horvath A, Meyer R, Szajewska H. Efficacy and safety of hydrolyzed formulas for cow's milk allergy management: A systematic review of randomized controlled trials. Clin Exp Allergy. 2020;50:766-779

TABLE 1 Risk ratio calculation in the two studies

						Risk ratio (nC/NC)/(nE/NE)					
						Our calculation[a]			Stróżyk		
H#	New cases of	nE	NE	nC	NC	PE	95 LB	95 UB	PE	95 LB	95 UB
1	Eczema from 0 to 12 months	17	95	14	98	**0.80**	0.36	1.72	**0.88**	0.42	1.53
2	Eczema from 12 to 24 months	3	95	0	98	See text	-	-	0.14	0.01	2.65
3	Eczema from 24 to 36 months	6	95	1	98	0.16	0.00	1.33	0.16	0.02	1.32
4	Eczema from 0 to 36 months (*sum of the above*)	26	95	15	98	0.56	0.28	1.10	0.56	0.32	0.99
5	Urticaria from 0 to 12 months	18	95	4	98	0.22	0.05	0.65	0.22	0.08	0.61
6	Urticaria from 12 to 24 months	0	95	2	98	See text	-	-	4.85	0.24	99.70
7	Urticaria from 24 to 36 months	2	95	2	98	0.97	0.07	13.37	0.97	0.14	6.74
8	Urticaria from 0 to 36 months (*sum of the above*)	20	95	8	98	0.39	0.15	0.92	0.39	**0.80**	**0.84**
9	Asthma from 0 to 12 months	2	95	6	98	2.91	0.52	29.46	2.90	0.60	14.00
10	Asthma from 12 to 24 months	8	95	2	98	0.24	0.03	1.21	0.24	0.05	1.10
11	Asthma from 24 to 36 months	8	95	1	98	0.12	0.00	0.90	0.12	0.02	0.95
12	Asthma from 0 to 36 months (*sum of the above*)	18	95	9	98	0.48	0.19	1.14	0.48	0.23	1.02
13	Rhinoconjunctivitis from 0 to 12 months	5	95	5	98	0.97	0.22	4.21	0.97	0.29	3.24
14	Rhinoconjunctivitis from 12 to 24 months	3	95	1	98	**0.32**	0.01	4.02	**0.24**	0.05	1.10
15	Rhinoconjunctivitis from 24 to 36 months	16	95	2	98	0.12	0.01	0.52	0.12	0.03	0.51
16	Rhinoconjunctivitis from 0 to 36 months (*sum of the above*)	24	95	8	98	0.32	0.13	0.74	0.32	0.15	0.68
17	At least one allergic event over 36 months (*main outcome*)	44	95	23	98	0.51	0.29	0.86	0.51	0.33	0.77

Abbreviations:: H#, hypothesis number #; nE, number of events in the experimental group; NE, number of subjects in the experimental group; nC, number of events in the control group; NC, number of subjects in the control group; PE, point estimate of the risk ratio; 95LB, lower bound of 95% exact confidence interval of the risk ratio; 95 UB, upper bound of 95% exact confidence interval of the risk ratio.

[a]Rounding to 2 decimal places.

8. Whatever the sophistication of the metanalysis, however, we wonder what is the added value of performing a metanalysis pooling data from just two studies from the same research group and using RRs when risk differences would be greatly preferable. We are the first to believe that *external* validation of the finding is central to the scientific enterprise.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

RBC, GB and RN conceived the letter and wrote the manuscript. MDC, AA, LC, CDS and VG read, revised and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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