

## EDITORIAL



# Statistical challenges in haematopoietic cell transplantation

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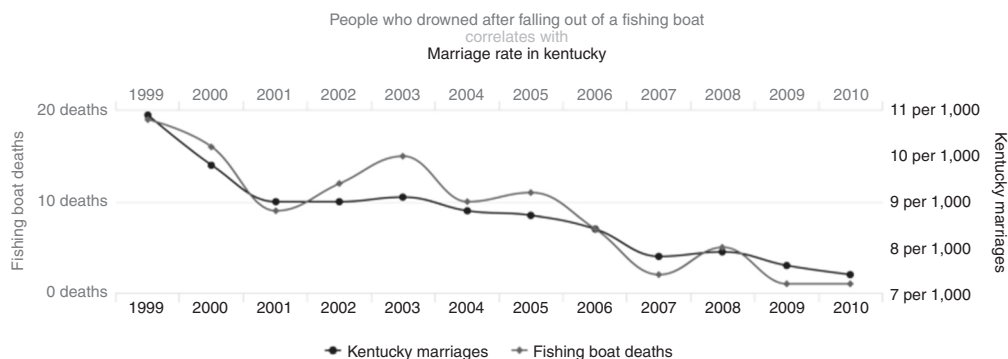
With the publication of a 11th article we complete our series of hopefully informative articles on statistical issues in haematopoietic cells transplant studies [1]. With the help of experts from many centers we tried to cover a range of topics of interest to clinical scientists and especially clinical trialists. The series, begun in December, 2018, was a 3 year effort. When we introduced the series we identified several challenges in interpreting data from clinical trials (Fig. 1), included in the Introduction, showed the correlation between people drowning after falling out of a fishing boat and marriage rate in Kentucky. We now add Fig. 2 correlating per capita cheese consumption and numbers of people who died by becoming entangled in their bedsheets. Correlations are not cause-and-effect! Although eating too much epoisses in bed (especially with cognac) might make you lightheaded and

therefore more likely to get entangled in your bedsheets this seems an unlikely explanation. This issue is discussed elsewhere in a more mathematical context [2] (<https://web.archive.org/web/20190925212058/http://www.burns.com/wcbpspurcorl.htm>).

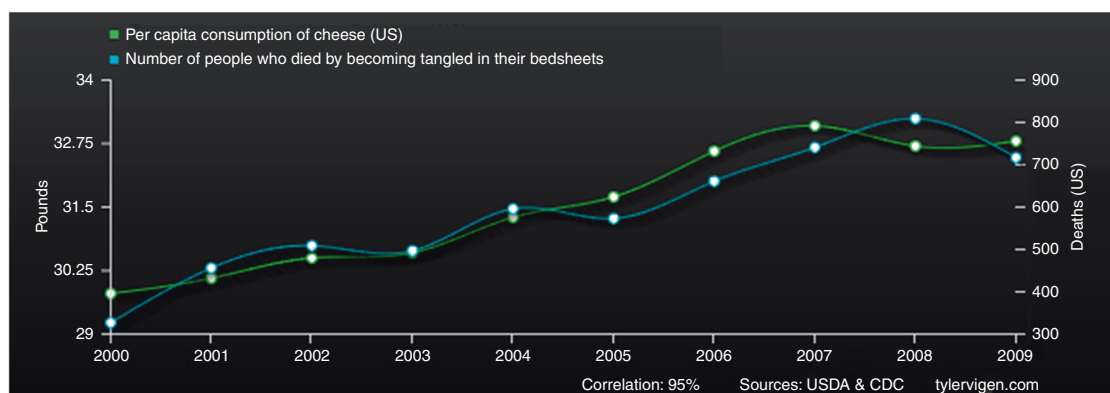
Table 1 Articles all of which are or will soon be available as a NATURE Collection at <https://www.nature.com/collections/ejhigdbeeh>.

Several articles explain complexities of survival and cumulative incidence analyses including those by (Hu, Gale and Zhang/Othus, Zhang and Gale and/de Wreede, Schetelig and Putter/Wei and Peng). Another article provides a SAS macro readers can use to estimate direct adjusted survival functions for time-to-event data with or without left truncation (see the correction at [3]).

There are also articles on when and how to use spline plots (Gauthier, Wu and Gooley), on precision medicine (Moodie and Krakow) and on case control study design (Cai, Kim). Another article deals with the complexities of analyzing and interpreting results of measurable residual disease-testing (Othus, Gale, Hourigan and Walter).



**Fig. 1** Marriage rate in Kentucky and drowning deaths from falling out of a fishing boat ([https://tylervigen.com/view\\_correlation?id=598](https://tylervigen.com/view_correlation?id=598)).



**Fig. 2** Cheese consumption and strangulation death from bedsheets ([https://tylervigen.com/view\\_correlation?id=7](https://tylervigen.com/view_correlation?id=7)).

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**Table 1.** A list .... (as shown in text).

1. Fraser R. Inappropriate use of statistical power. (in press).
2. De Wreede LC, Scheteling J, Putter H. Analysis of survival outcomes in haematopoietic cell transplant studies: pitfalls and solutions. (in press).
3. Othus M, Zhang MJ, Gale RP. Clinical trials: design, endpoints and interpretation of outcomes. <i>Bone Marrow Transplant.</i> 2022;7:1–5.
4. Cai J, Kim S. Case-cohort design in hematopoietic cell transplant studies. <i>Bone Marrow Transplant.</i> 2021;16:1–5.
5. Hu ZH, Wang HL, Gale RP, Zhang MJ. A SAS macro for estimating direct adjusted survival functions for time-to-event data with or without left truncation. <i>Bone Marrow Transplant.</i> 2021;19:1–5.
6. Moodie EE, Krakow EF. Precision medicine: Statistical methods for estimating adaptive treatment strategies. <i>Bone Marrow Transplant.</i> 2020;55:1890–6.
7. Othus M, Gale RP, Hourigan CS, Walter RB. Statistics and measurable residual disease (MRD) testing: uses and abuses in hematopoietic cell transplantation. <i>Bone Marrow Transplant.</i> 2020;55:843–50.
8. Gauthier J, Wu QV, Gooley TA. Cubic splines to model relationships between continuous variables and outcomes: a guide for clinicians. <i>Bone Marrow Transplant.</i> 2020;55:675–80.
9. Hu ZH, Gale RP, Zhang MJ. Direct adjusted survival and cumulative incidence curves for observational studies. <i>Bone Marrow Transplant.</i> 2020;55:538–43.
10. Zheng C, Dai R, Gale RP, Zhang MJ. Causal inference in randomized clinical trials. <i>Bone Marrow Transplant.</i> 2020;55:4–8.
11. Gale RP, Zhang MJ. Statistical analyses of clinical trials in haematopoietic cell transplantation or why there is a strong correlation between people drowning after falling out of a fishing boat and marriage rate in Kentucky. <i>Bone Marrow Transplant.</i> 2020;55:1–3.

There is considerable confusion regarding the correct interpretation of statistical power explained in the article by Fraser. For example, it is improper to calculate a study's power retrospectively. A last article with what some might consider a philosophical bent deals with the fundamental issue of causal inference (Zheng, Dai, Gale and Zhang). It shows, for example, limitations in implying causation even from results of a randomized controlled trial. Readers may also be interested in two other relevant articles, one by us entitled What is a *p* value anyway [4] and a second on the role of observational databases in analyses of transplant outcomes [5].

We hope this collection of articles will be of interest to readers of *Bone Marrow Transplantation* and encourage you to read them carefully. Each article is preceded by a Note from us explaining the relevance of the content to clinician scientists. You may want to share some with statistical colleagues at your center. We have intentionally gone light on equations and the like, so you need not fear.

As we wrote in the series Introduction: We can be reached on Twitter at #BMTStats. Our operators are standing by.



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## REFERENCES

1. Gale RP, Zhang MJ. Statistical analyses of clinical trials in haematopoietic cell transplantation or why there is a strong correlation between people drowning after falling out of a fishing boat and marriage rate in Kentucky. *Bone Marrow Transpl.* 2020;55:1–3.

2. Hrabac P, Trkulja V. Of cheese and bedsheets—some notes on correlation. *Croat Med J.* 2020;61:293–95.
3. Hu ZH, Wang HL, Gale RP, Zhang MJ. SAS macro for estimating direct adjusted survival functions for time-to-event data with or without left truncation. *Bone Marrow Transplant* 2022;57:6–10. <https://doi.org/10.1038/s41409-021-01435-2>.
4. Gale RP, Zhang MJ. What is the P-value anyway? *Bone Marrow Transpl.* 2016;51:1439–40.
5. Gale RP, Eapen M, Logan B, Zhang MJ, Lazarus HM. Are there roles for observational database studies and structured quantification of expert opinion to answer therapy controversies in transplants? *Bone Marrow Transpl.* 2009;43:435–46.

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## COMPETING INTERESTS

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## ADDITIONAL INFORMATION

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