Published in final edited form as:

Diabetes Obes Metab. 2018 August ; 20(8): 2039–2040. doi:10.1111/dom.13323.

Unaccounted for Regression to the Mean Renders Conclusion of Article Titled “Uric acid lowering in relation to HbA1c reductions with the SGLT2 inhibitor Tofogliflozin” Unsubstantiated

Chanaka N. Kahathuduwa^{1,2}, Diana M. Thomas³, Cynthia Siu⁴, and David B. Allison⁵

¹Department of Human Development and Family Studies, Texas Tech University, Lubbock, TX, USA

²Department of Physiology, Faculty of Medicine, University of Peradeniya, Sri Lanka

³Department of Mathematics, US Military Academy, West Point, NY, USA

⁴COS & Associates Ltd., Central, Hong Kong

⁵Department of Epidemiology and Biostatistics, School of Public Health – Bloomington, Indiana University, Bloomington, IN, USA

Ouchi et al. [1] reported aggregated outcomes of four clinical trials that examined the effects of the SGLT2 inhibitor tofogliflozin (vs. placebo) on HbA1c and serum uric acid levels. The authors reported that the individuals with highest levels of HbA1c experienced greater reductions in HbA1c than did persons with lower baseline HbA1c levels within the tofogliflozin arm. The authors concluded SGLT2 inhibitor tofogliflozin *caused* greater reductions in HbA1c among individuals with highest levels of HbA1c than it did among individuals with lower baseline levels. Furthermore, the authors reported *effects* of SGLT2 inhibitor on changes in serum uric acid (UA) levels being greater among those with high baseline UA levels. While these conclusions may appear appealing, these observations are plausibly due to a statistical phenomenon known as regression to the mean (RTM) [2–5] and the conclusions about causal effects of the SGLT2 inhibitor tofogliflozin on changes in UA and HbA1c levels in patients with particularly high or low baseline values therefore unwarranted. It is important to distinguish genuine reductions due to SGLT2 inhibitor tofogliflozin treatment from the effect of regression to the mean by using the placebo group and testing significance of statistical interaction effect for baseline HbA1c by tofogliflozin (vs. placebo) on the reduction in HbA1c and UA levels.

RTM, was initially described by Sir Francis Galton in relation to repeated measures of height [2]. Specifically, Galton found that the children of taller than average parents were taller than average, but not as much above average in stature as were their parents. The conclusion is not that tall parents have shorter than average children. Rather, when an initial measurement deviates from the true population mean (for example, when the height of a

Correspondence: Dr. David B. Allison, Department of Epidemiology and Biostatistics, School of Public Health–Bloomington, Indiana University, Bloomington, IN 47405. allison@iu.edu.

Conflict of Interest

The authors have no potential conflicts of interest pertinent to this manuscript.

parent exceeds the population mean), measurements on other variables (e.g., children's stature) which are positively correlated, but correlated less than 1.0, tend to 'regress' from the initial measurement's deviation from the mean to be closer to the population mean [3, 6]. The fact that RTM can 'masquerade' as treatment effect is one of the reasons why control groups are needed in studies evaluating the effects of interventions [3–5, 7]. If the effects of RTM are not accounted for, RTM may lead to unjustified conclusions [3–12].

Additionally, the inappropriate conclusions resulting from RTM can be aggravated when study samples are segregated based on extreme¹ criteria (e.g. HbA1c $\geq 7.0\%$) and when repeated measurements (e.g. post- vs. pre-intervention) of such extreme samples are compared [3–5, 7, 13]. Ouchi et al. [1] stratified their sample into four quartile-defined categories based on the pre-intervention HbA1c levels and compared the effects of intake of tofogliflozin on the post- vs. pre-intervention changes of HbA1c without taking RTM into consideration. Moreover, in this sample, HbA1c quartiles and the serum UA levels had a significant inverse association at prior to the intervention (i.e. the group with highest level of HbA1c had the lowest level of serum UA and vice versa). In an ANCOVA that did not consider a control group, the authors made the observation that the group with the lowest mean HbA1c (i.e. the group with the highest mean serum UA level) experienced the greatest reduction of serum UA with tofogliflozin treatment. Both of these findings could simply be misleading illusions observed due to neglecting RTM, rather than due to treatment with tofogliflozin. While not ideal due to the differences in the combinations of medications used in some of the pooled studies, use of the placebo group from the Kaku et al. [14] study as controls in the analyses could have alleviated the effects of RTM on the above observations at least to an extent.

In conclusion, the data presented by Ouchi et al. [1] are insufficient to arrive at the conclusion that treatment with tofogliflozin *causes* greater reductions in serum UA or HbA1c among persons with higher baseline levels of serum UA or HbA1c. Careful consideration of the effects of RTM as well as potential pitfalls in the study design and statistical methods are warranted in conducting clinical studies and also in the peer review process. We encourage the authors to adjust their published conclusions.

Acknowledgments

Supported in part by NIH grants R25DK099080 and R25HL124208. The opinions expressed are those of the authors and do not necessarily represent those of the NIH or any other organization.

References

1. Ouchi M, Oba K, Kaku K, et al. Uric acid lowering in relation to HbA1c reductions with the SGLT2 inhibitor tofogliflozin. *Diabetes Obes Metab*. 2017
2. Galton F. Regression towards mediocrity in hereditary stature. *The Journal of the Anthropological Institute of Great Britain and Ireland*. 1886; 15:246–263.
3. George BJ, Beasley TM, Brown AW, et al. Common scientific and statistical errors in obesity research. *Obesity (Silver Spring)*. 2016; 24:781–790. [PubMed: 27028280]

¹Here by 'extreme' we merely mean 'deviating from the population mean'.

4. Cockrell Skinner A, Goldsby TU, Allison DB. Regression to the Mean: A Commonly Overlooked and Misunderstood Factor Leading to Unjustified Conclusions in Pediatric Obesity Research. *Child Obes.* 2016; 12:155–158. [PubMed: 26974388]
5. Skinner AC, Heymsfield SB, Pietrobelli A, Faith MS, Allison DB. Ignoring regression to the mean leads to unsupported conclusion about obesity. *Int J Behav Nutr Phys Act.* 2015; 12:56. [PubMed: 25948534]
6. Bland JM, Altman DG. Some examples of regression towards the mean. *BMJ.* 1994; 309:780. [PubMed: 7950567]
7. Bland JM, Altman DG. Best (but oft forgotten) practices: testing for treatment effects in randomized trials by separate analyses of changes from baseline in each group is a misleading approach. *The American journal of clinical nutrition.* 2015; 102:991–994. [PubMed: 26354536]
8. Smith DL, Thomas DM, Siu CO, Verhulst S, Allison DB. Regression to the mean, apparent data errors and biologically extraordinary results: letter regarding ‘changes in telomere length 3–5 years after gastric bypass surgery’. *Int J Obes (Lond).* 2017
9. Allison DB, Loebel AD, Lombardo I, Romano SJ, Siu CO. Understanding the relationship between baseline BMI and subsequent weight change in antipsychotic trials: effect modification or regression to the mean? *Psychiatry Res.* 2009; 170:172–176. [PubMed: 19897253]
10. Halliday TM, Thomas DM, Siu CO, Allison DB. Letter to the editor. *J Women Aging.* 2018; 30:2–5. [PubMed: 29220635]
11. Kroeger CM, Thomas DM, Siu CO, Allison DB. Overlooking Regression to the Mean Leads to Unwarranted Interpretations: Letter Concerning, “Do Obese and Extremely Obese Patients Lose Weight after Lumbar Spine Fusions? Analysis of a Cohort of 7303 Patients from the Kaiser National Spine Registry. *Spine.* 2018
12. Yeh Y, Hartlieb KB, Danford C, Jen K-LC. Correction to: Effectiveness of Nutrition Intervention in a Selected Group of Overweight and Obese African-American Preschoolers. *Journal of Racial and Ethnic Health Disparities.* 2017
13. Senn S. Francis Galton and regression to the mean. *Significance.* 2011; 8:124–126.
14. Kaku K, Watada H, Iwamoto Y, et al. Efficacy and safety of monotherapy with the novel sodium/glucose cotransporter-2 inhibitor tofogliflozin in Japanese patients with type 2 diabetes mellitus: a combined Phase 2 and 3 randomized, placebo-controlled, double-blind, parallel-group comparative study. *Cardiovasc Diabetol.* 2014; 13:65. [PubMed: 24678906]