



Correspondence

Reply to: "Methodological issues regarding "Decline in ankle-brachial index is stronger in poorly than in well controlled diabetes: Results from the Heinz Nixdorf Recall cohort study""


To the Editor,

We are thankful to Dr. Yarandi et al. for their critical view on our manuscript [1]. They address several methodical issues, and we would like to give our position on these issues.

1. We analyzed observational data from a cohort study with 5-year and 10-year follow-up. Yarandi et al. objected that we did not do a sample size calculation and, thus, cannot detect significant associations when the sample size is too small. Thus, in the view of Yarandi et al., finding statistically significant associations is the aim of statistical analyses. However, we stated in the Methods section that our aim was estimation and not significance testing. Significance testing has met a lot of criticism. The American Statistical Association, for example, advises against significance testing [2], and Nature has recently published a comment titled "Retire Statistical Significance" [3].
2. Yarandi et al. suppose that we used "enter mode" to select variables for our multivariable model. This is not the case, and we did not state this in the Methods section. Instead, we used a direct acyclic diagram (causal diagram) to identify a minimally sufficient adjustment set.
3. Yarandi et al. advise us to have at least 10 events per variable included in the model. To have at least 10 events per variable (EPV) (or, to be more precise, per degree of freedom) is a rule of thumb for which there is some support in the literature. However, no consensus has been reached on this issue. Courvoisier et al. stated that problems may arise even if EPV is > 10 [4]. Peduzzi et al. did a simulation study and suggested at least 10 EPVs [5]. Vittinghoff and McCulloch, however, claimed that severe problems only arise for $EPV < 5$ [6]. In our logistic regression models for 10-year follow-up, we included the exposure variable (HbA1c categories) plus 2 covariates in the first and plus 12 variables in the second model. There were 149 incident events of $ABI < 0.9$, and, thus, the number of events per degree of freedom was 24.8 in the first, and 8.8 in the second model. So EPV is slightly smaller than 10 in model 2.
4. Yarandi et al. criticize that the confidence intervals are rather wide in Table 3 [1]. This is true, and, of course, the estimates they picked out from the Table (0.6 (95% CI: 0.1–2.3) and 0.4 (95% CI: 0.1–1.7)) for newly detected diabetes are very imprecise and are compatible with an increase as well as a decrease of the odds to develop $ABI < 0.9$. The crucial information from Table 3 is the increased odds for poorly controlled diabetes compared to no diabetes ($OR = 4.6$ (95% CI: 2.2–9.7), and 3.1 (95% CI: 1.3–7.0),

respectively). With regard to well controlled known diabetes, and newly detected diabetes, results from the linear regression models shown in Table 2 and results from the mixed linear models (cf. Results section) are more informative than the estimates from the logistic regression models [1].

We clearly communicated that the number of subjects with diabetes was rather small at baseline (288, in total). Please note that evidence synthesis (e.g. meta-analysis) makes no difference between statistically significant and non-significant study results. Instead, the inverse of the variance of the estimates are used for weighted pooling. Further studies on diabetes control and atherosclerosis are necessary.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

References

- [1] B. Kowall, R. Erbel, S. Moebus, N. Lehmann, K. Kröger, A. Stang, Decline in ankle-brachial index is stronger in poorly than in well controlled diabetes: results from the Heinz Nixdorf Recall Cohort Study, *Atherosclerosis* 284 (2019) 37–43.
- [2] R.L. Wasserstein, A.L. Schirm, N.A. Lazar, Moving to a world beyond „ $p < 0.05$ “, *Am. Stat.* (2019), <https://doi.org/10.1080/00031305.2019.1583913>.
- [3] V. Amrhein, S. Greenland, B. McShane, Retire statistical significance, *Nature* 567 (2019) 305–307.
- [4] D.S. Courvoisier, C. Combescure, T. Agoritsas, A. Gayet-Ageron, T.V. Perneger, Performance of logistic regression modeling: beyond the number of events per variable, the role of data structure, *J. Clin. Epidemiol.* 64 (2011) 993–1000.
- [5] P. Peduzzi, J. Concato, E. Kemper, T.R. Holford, A.R. Feinstein, A simulation study of the number of events per variable in logistic regression analysis, *J. Clin. Epidemiol.* 49 (1996) 1373–1379.
- [6] E. Vittinghoff, C.E. McCulloch, Relaxing the rule of ten events per variable in logistic and Cox regression, *Am. J. Epidemiol.* 165 (2007) 710–718.

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