Review Report

*Multiproxy analysis exploring patterns of diet and disease in dental calculus and skeletal remains from a 19th century Dutch population*

The manuscript brought forth by Bartholdy et al. represents an important step forward in the study of secondary metabolite residues in archaeological human remains. Building on their own team’s recent advances as well as research published by other scholarly groups, the authors address new questions – the correlation between the detection of different compounds, or the correlation between pathological conditions and residue signals – while at the same time increasing the time depth for the application of a protocol previously only tested on contemporary samples. While contamination remains an issue to be aware of, Bartholdy et al. also provide suggestions as to how to distinguish diagenetic impacts and lab contaminants from metabolomic signals related to human substance consumption.

**Specific suggestions for improvements:**

- It might be worthwhile to include King et al. (2017) in the discussion on the proportions of caffeine, theophylline, and theobromine.


- As the authors mention the need to account for soil-calculus contamination, I would appreciate an indication as to the plans for control in upcoming analysis. Personal experience has shown this to be of utmost importance not only with regard to potential false positives for salicylic acid but also methylxanthines.

- While quantitation of detected compounds is expressly not a focus of this study – and I agree with the authors regarding the taphonomic complexity – I believe a comparison of nicotine/cotinine peak area values between positive individuals with pipe notches and those without this dental pathology would further augment the value of the authors’ protocol accuracy statement.