In this manuscript, Dr. Kurushima and colleagues conducted comprehensive two-stages epigenetic-based association study to periodontitis based on hm450 array from UK twins cohort. Both gingival bleeding (N=528) and tooth mobility (N=492) were investigated in the study and several positive association were identified, such as *WHAMM, TMCO6. T*he study was performed rigorously and the findings are interesting. I only have several concerns for the authors to think about again and make further response.

**Major Compulsory Revisions**

1. In the self-reported questionnaire section, I am wondering why not asking the earliest time for the tooth mobility? Or why not ask the times of the gingival bleeding in the past several years? I don’t understand why “difference between the time point of dental phenotype collection and DNA extraction” should be taken as a confounder or factors in the linear regression?

2. How to normalize beta-value to normal distribution (N,0,1)? The details should be provided? Did the author removed the probes containing SNPs? For the RNA-seq analysis, how to deal with the splicing reads should be mentioned?

3. In the first result section, cg21245277 was identified to be signficiantly associated with gingival blooding. As the author mentioned, it is obviously a probe containing SNPs. Methylation status in the probes containing SNPs usually shown mis-leading methylation signals since the probe matching and extension, therefore, the epigenetic conclusion here should be double-checked with BS-Seq.

4. In the table 3. Genomic assemble version should be mentioned, hg19 or hg38. Meanwhile, the full variable information (P-value, beta, SE) for all the confounder (age etc) will be helpful to be shown in the supplementary.

5. Buccal DNA methylation was claimed to be

6. In the Figure 1, How to understand only cg21245277 was significantly associated with gingival bleeding while other CpGs in the promoter region of ZNF804A don’t have any significant signals? Another question is that whether the samples in Figure 1B and 1C are same? Can you observe same difference applying same samples?

7. the authors mentioned ‘family structure’ was assigned as one of confounders, I am wondering, how to quantitate this variable? And I didn’t find the information for family structure in Supplementary Tables 1-2.

**Minor Essential Revisions and Discretionary Revisions**

1.The authors mentioned personalized treatments and prevention in both abstract and background, however, nothing further discussion were provided to illustrate how to apply methylation signals in ‘personalized treatments and prevention’.

2.The authors tried to validation the result from whole blood in buccal and adipose tissues, However, as known, the methylation pattern in different tissues usually is different, what’s the meaning to validate the result in different tissue for periodontitis.

3. I want to know why gingival bleeding status and tooth mobility status were obtained from different samples?

4. The author mentioned ‘Informed consent was obtained from all participants before sample and data collection’. As we known, UK twin cohort blood extraction is far before the further study design, a detail relationship about current study design and blood sample, as well questionnaire will be helpful.

5. GSE62992 is not exactly what the authors mentioned in the manuscript. GSE62992 only contains 100 normal whole blood samples, please double check it.