Dr. Kyrtopoulos and colleagues provided epidemiological analysis to the gender effect on the susceptibility to tobacco smoke-induced cardiovascular diseases. It is an extension research based on his previous study which published on Sci Rep on Feb,2016 (doi: 10.1038). The study was performed rigorously and the findings sound quite interesting. However, I only have some small concerns on the analysis method.

**Major Compulsory Revisions**

1, Line 400-403 checked for the bias from the sample size of male and female, however, the false-positive can be avoid by this single control. I recommend the author to conduct the permutation test to avoid the false positive conclusion.

2, The current result was only derived from beadchip (microarray), as we known, the accuracy of the microarray data is limited and the result should be validated. Is there any possibility to have a validation for the current conclusion? or could the author to collect another independent dataset from GEO to find some supportive evidence to the current manuscript?

**Minor Revisions**

1, Line 80, it is not clear the definition of differentially methylated genes and differentially expressed genes, smoking vs non-smoking or male vs female?

2, Reference should be provided for line 68-70.

3, Detail information for DMR and DGE should be provided as the supplementary Tables between line 80-82.

4, it is a high level analysis/manuscript since all the basic analysis were based on the reference #10, however, this dataset is not public. I recommend the author to upload it to GEO so that all the process could be repeated.

5, Line 95-105 should be re-organized. It is not quite clear since it is the most important content to interpret the statistical method, meanwhile, it is not

6, the subtitle for the result section should be provided.

7, For the methylation part, DMS is quite not stable compared with DMR and majority such kind of different were caused by stochastic noise. I am strongly suspecting whether the result could be repeated by others. DMR based analysis should be conducted to increase the credibility of the conclusion.

8, How did the p-value difference was calculated in Table 2 and Table 3?

**Discretionary Revisions**

1, For line 107-109, Is there any significant probes were identified both in smoking and non-smoking group?

2, Certain effective footnote to the Tables would be helpful.