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Title: Comparison of DNA methylation profiles between airway epithelium and proxy tissues

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Body: To date, epidemiological studies of DNA methylation and respiratory disease have measured methylation predominantly in blood, or sometimes in buccal samples, because these sources are readily accessible. However, given tissue specificity of DNA methylation, these tissues may not allow reliable inferences about methylation in the lung. We sought to establish which tissue (nasal, buccal, or blood) had the closest methylation profile to that of airway epithelium. Samples of airway epithelial cells (by blind brushing via endotracheal tube), blood, nasal epithelial and buccal cells were obtained from six children undergoing general anaesthetic for elective tonsillectomy. Following bisulphite conversion, CpG site methylation was analysed at 450,000 sites using the Illumina 450k array. Nineteen samples were suitable for analysis. Hierarchical clustering demonstrated that the methylation profile of nasal epithelial cells had the greatest similarity to that of airway epithelial cells; the methylation profile of buccal cells was moderately similar; and that of blood was least similar. When we quantified this by calculating a standard Euclidean distance of the average methylation beta values for each tissue from the average value for airway epithelial cells, the distances for nasal, buccal and blood were, respectively, 46.1, 72.3, and 91.4. DNA methylation in blood poorly reflects methylation in airway epithelium. Given that direct airway sampling is not feasible in epidemiological studies, future population studies of DNA methylation and airway disease should measure methylation either in buccal cells, or preferably in nasal epithelial cells, in order to best capture disease relevant methylation marks.