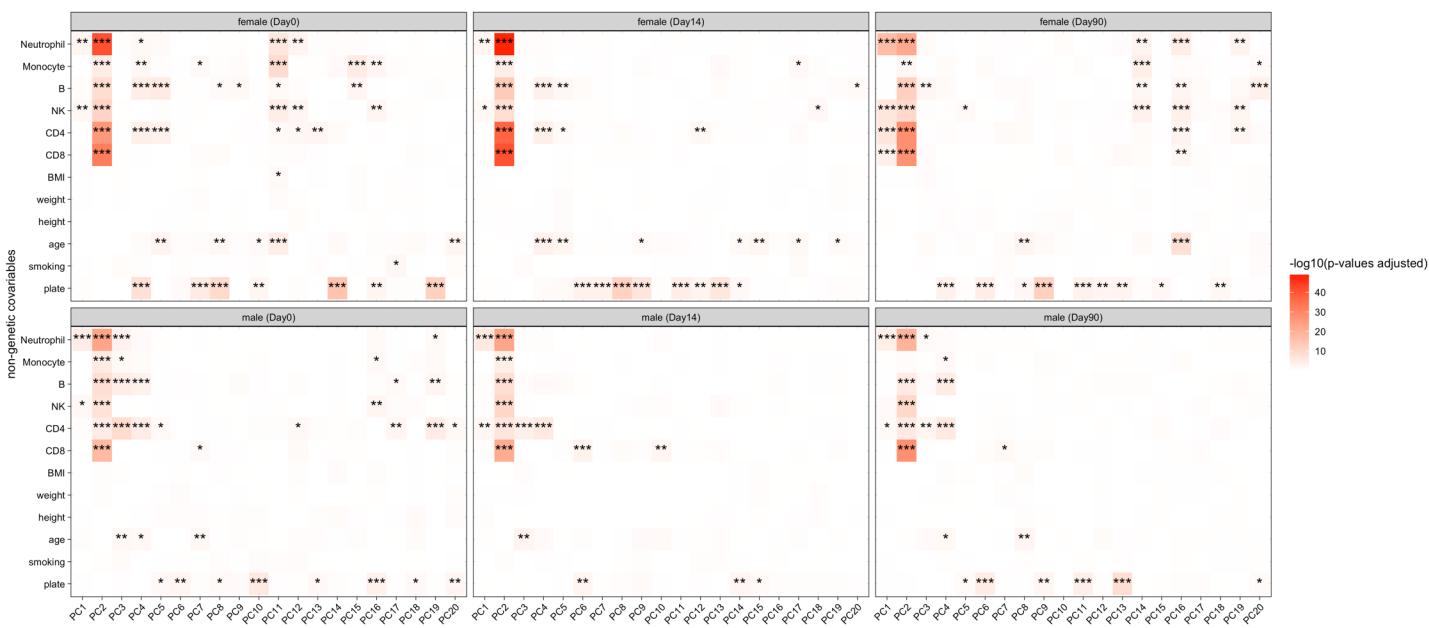


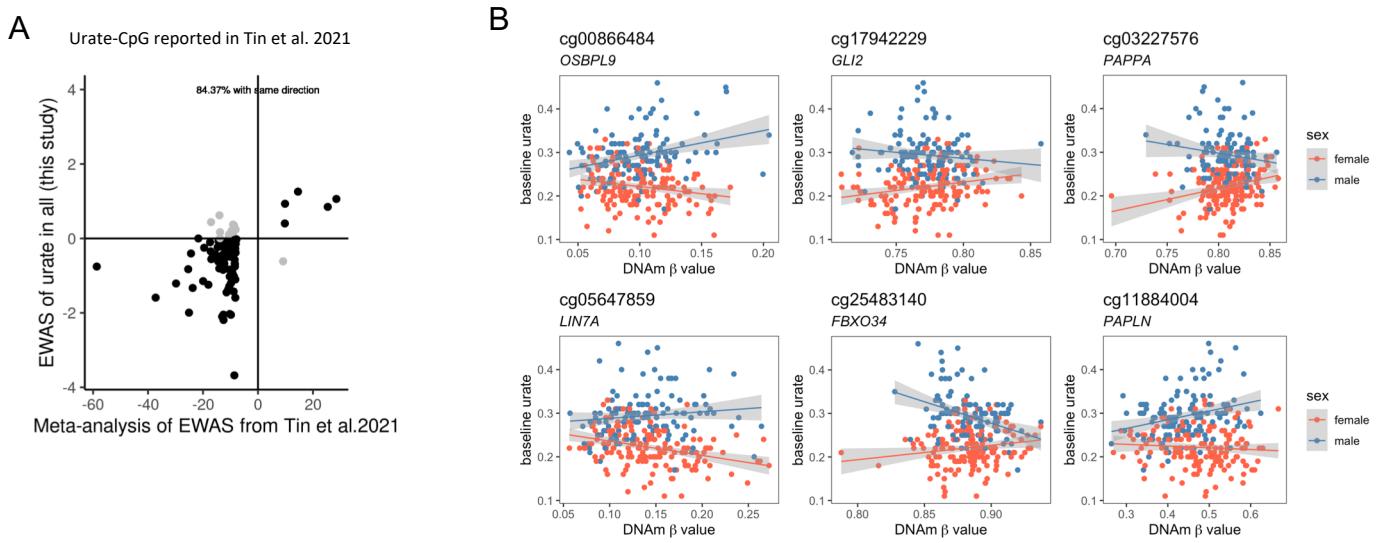
Figure S1. Flow diagram of the number of samples collected in the discovery study.

## Figure S2



**Figure S2. Cell proportions, batch (sample plate), and age were significantly associated with the top PCs calculated from DNAm.** The spearman method was used to calculate the correlation between the continuous variables with the top PCs. Kruskal-Wallis test by rank was used for the discrete variable. \*:  $P < 0.05$ , \*\*:  $P < 0.01$ , \*\*\*:  $P < 0.005$ , \*\*\*\*:  $P < 0.001$ .

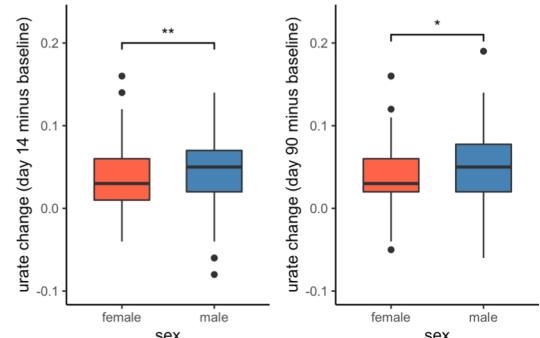
# Figure S3



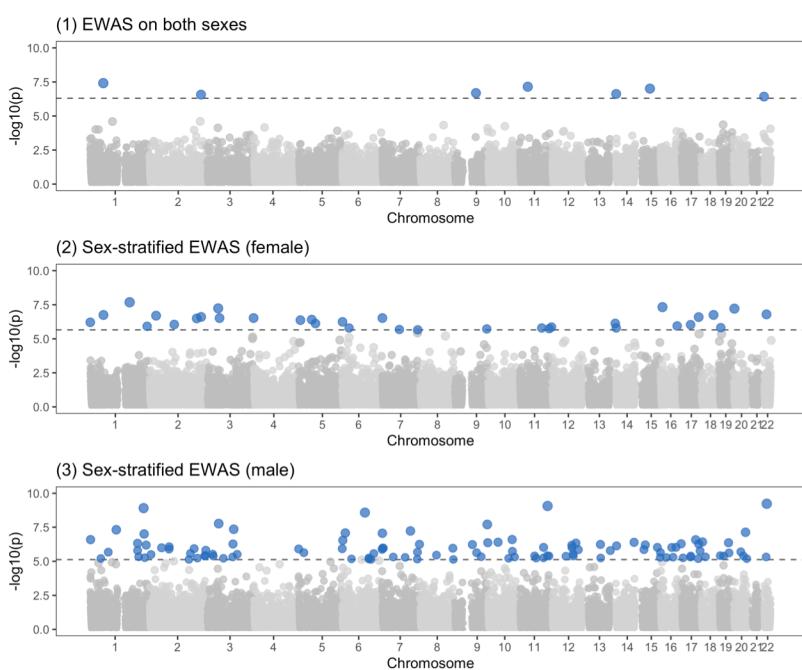
**Figure S3. Interaction analyses identified 6 CpG sites that were associated with urate level at baseline in a sex-dependent manner.** (A) Each dot represented urate-associated CpG sites reported from a large meta-analysis of EWAS from Tin et al. Scatter plot showing the distribution of  $-\log_{10}(P \text{ value}) * \text{sign (effect size)}$  of these reported urate-associated CpG sites in Tin et al. and BCG cohort. Black dots represented CpG sites with the same effect direction, while grey dots represent CpG sites with different effect direction. (B) Scatter plot showing the correlation between  $\text{urate}_{\text{baseline}}$  and  $\text{DNAm}_{\text{baseline}} \beta$  value in females and males separately.

# Figure S4

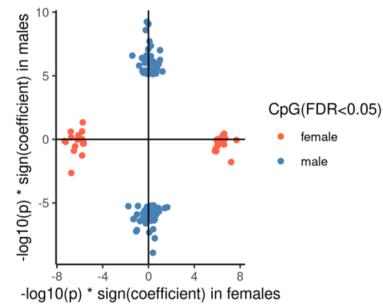
A



B



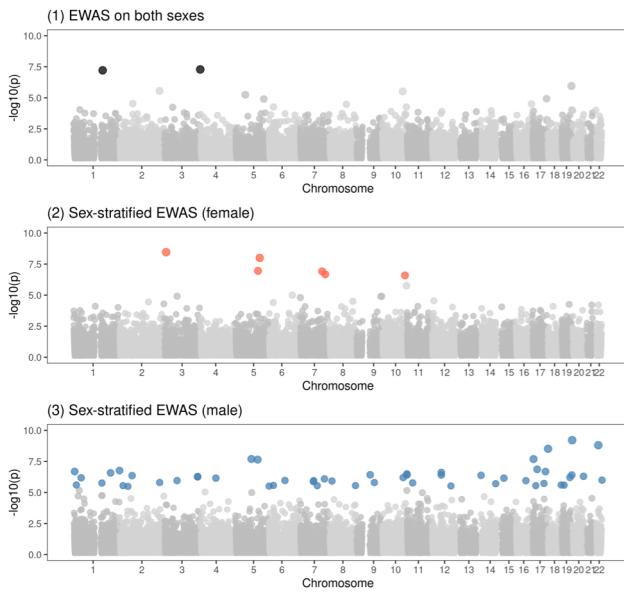
C



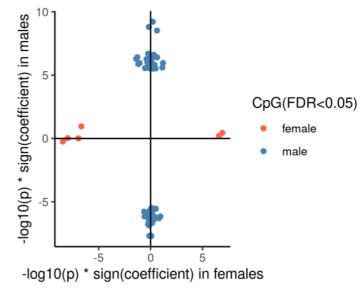
**Figure S4.  $\Delta\text{Urate}_{\text{long}}(\text{day90-day0})$  was associated with  $\text{DNAm}_{\text{baseline}}$  in a sex-specific manner.** (A) Boxplot showing the  $\Delta\text{Urate}_{\text{short}}$  and  $\Delta\text{Urate}_{\text{long}}$  in females and males, color indicating different sex groups. One-sided Wilcoxon rank sum test was used to compare the difference between males and females. \*:  $P < 0.05$ , \*\*:  $P < 0.01$ . (B) Manhattan plots showing the results from EWAS of  $\Delta\text{Urate}_{\text{long}}$  in (1) all participants, (2) females, and (3) males respectively. The CpG sites are ordered by their chromosomal position on the x-axis with their  $-\log_{10}(P$  value) of the association on the y-axis, with dotted horizontal lines indicating the level of significance corrected for multiple testing (FDR < 0.05). Blue dots represent significant CpG sites and grey dots represent non-significant CpG sites. (C) The scatter plot showing the distribution of  $-\log_{10}(P$  value) \* sign(effect size) of the significant sites from EWAS of  $\Delta\text{Urate}_{\text{long}}$  in males and females. The color of the dots represents the significant sites from different sex groups.

# Figure S5

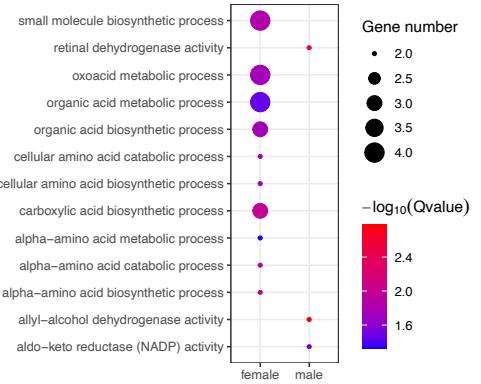
A



B

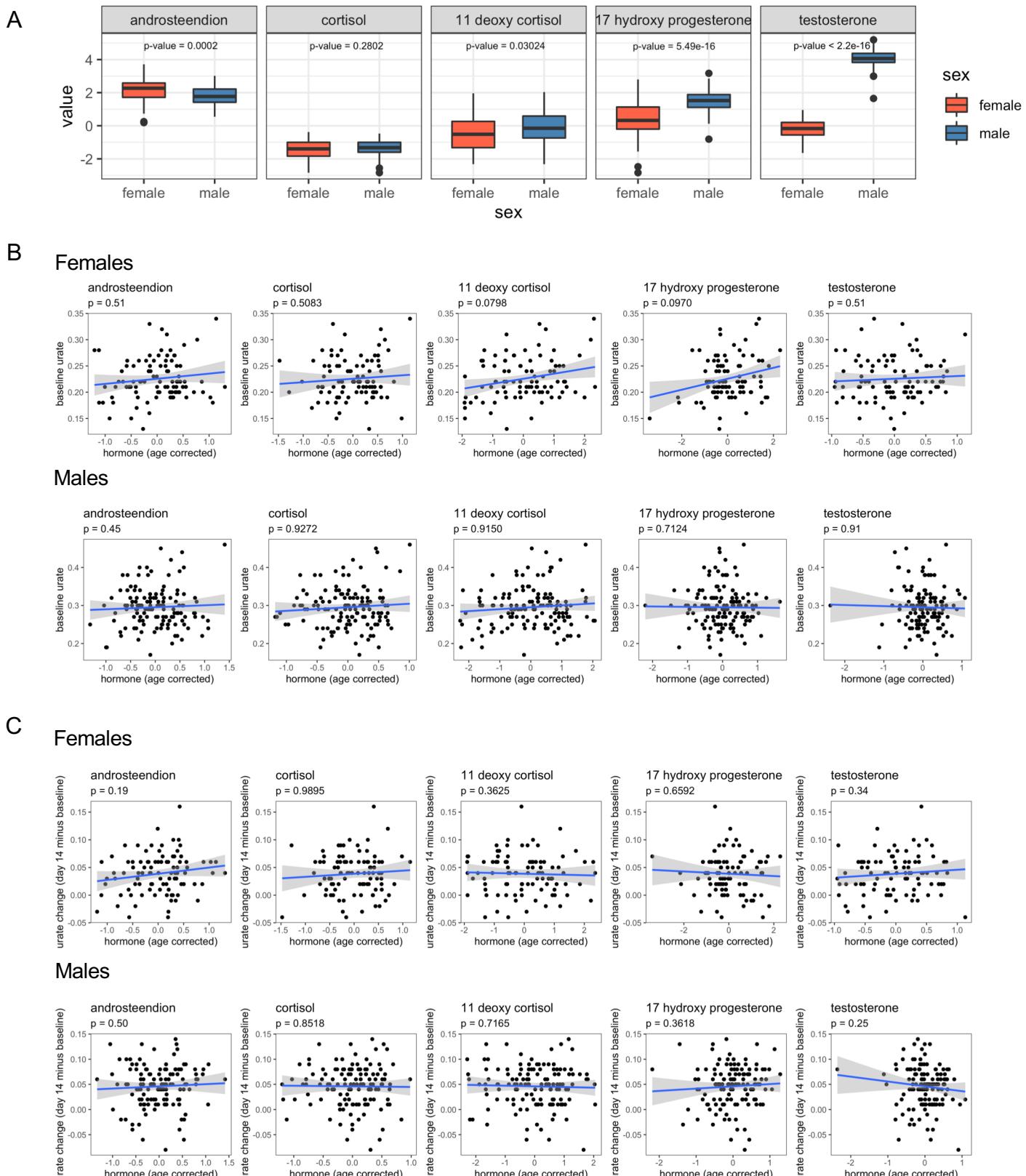


C



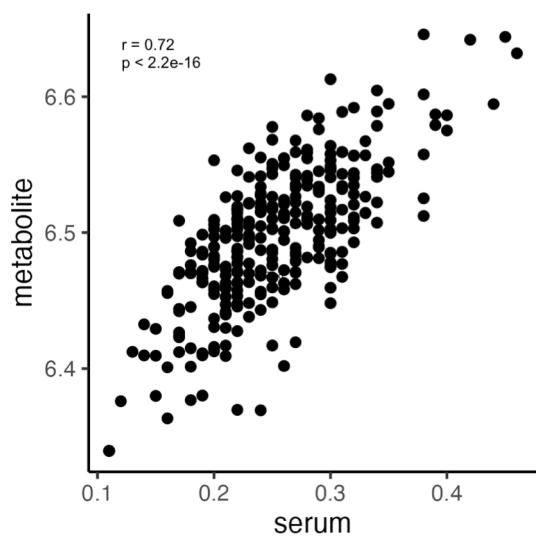
**Figure S5. Δurate(day90-day0) was associated with ΔDNAm(day90-day0) upon BCG vaccination in a sex-specific manner.** (A) The Manhattan plot showing the results from the epigenome-wide association between  $\Delta\text{Urate}_{\text{long}}$  and  $\Delta\text{DNAm}_{\text{long}}$  in all participants (1), females (2), and males (3) respectively. The CpG sites were ordered by their chromosomal position on the x-axis with their  $-\log_{10}(P \text{ value})$  of the association on the y-axis. Colorful dot: significant CpG sites, grey dot: non-significant CpG sites. (B) The scatter plot showing the distribution of  $-\log_{10}(P \text{ value}) * \text{sign}(\text{effect estimate})$  of the significant sites from the epigenome-wide association between  $\Delta\text{Urate}_{\text{long}}$  and  $\Delta\text{DNAm}_{\text{long}}$  in males and females. The color represented the significant sites from different sex groups. (C) Dot plot describing the KEGG enrichment categories of genes annotated to the significant CpG sites identified from the epigenome-wide association between  $\Delta\text{Urate}_{\text{long}}$  and  $\Delta\text{DNAm}_{\text{long}}$ . The color and size of the dot indicated the significance and the number of annotated genes in each category.

# Figure S6



**Figure S6. Baseline hormones were not correlated with urate<sub>baseline</sub> and ΔUrate<sub>short</sub>.** (A) Hormone levels in males and females. (B) Spearman's correlation between urate<sub>baseline</sub> and baseline hormones (after age correction). (C) Spearman's correlation between ΔUrate<sub>short</sub> and baseline hormone (after age correction).

Figure S7



**Figure S7.** Scatter plot showing the strong correlation between two methods for circulating urate measurement.