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# Mendelian randomization analysis of the association between human blood cell traits and uterine polyps

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Human blood cells (HBCs) play essential roles in multiple biological processes but their roles in development of uterine polyps are unknown. Here we implemented a Mendelian randomization (MR) analysis to investigate the effects of 36 HBC traits on endometrial polyps (EPs) and cervical polyps (CPs). The random-effect inverse-variance weighted method was adopted as standard MR analysis and three additional MR methods (MR-Egger, weighted median, and MR-PRESSO) were used for sensitivity analyses. Genetic instruments of HBC traits was extracted from a large genome-wide association study of 173,480 individuals, while data for EPs and CPs were obtained from the UK Biobank. All samples were Europeans. Using genetic variants as instrumental variables, our study found that both eosinophil count (OR 0.85, 95% CI 0.79–0.93, P = 1.06 × 10⁻⁴) and eosinophil percentage of white cells (OR 0.84, 95% CI 0.77–0.91, P = 2.43 × 10⁻⁵) were associated with decreased risk of EPs. The results were robust in sensitivity analyses and no evidences of horizontal pleiotropy were observed. While we found no significant associations between HBC traits and CPs. Our findings suggested eosinophils might play important roles in the pathogenesis of EPs. Besides, out study provided novel insight into detecting uterine polyps biomarkers using genetic epidemiology approaches.

**Abbreviations**

| | |
|---|---|
| Eps | Endometrial polyps |
| CPs | Cervical polyps |
| IV | Instrumental variable |
| MR | Mendelian randomization |
| GWAS | Genome-wide association study |
| HBC | Human blood cell |
| IVW | Inverse-variance weighted |
| MR-PRESSO | MR-pleiotropy residual sum and outlier |
| InSIDE | Instrument strength independent of direct effect |
| SNP | Single nucleotide polymorphism |
| WBC# | White blood cell count |
| EO% | Eosinophil percentage of white cells |
| BASO% | Basophil percentage of white cells |
| NEUT% | Neutrophil percentage of white cells |
| MONO% | Monocyte percentage of white cells |
| LYMPH% | Lymphocyte percentage of white cells |
| EO# | Eosinophil count |
| EO%GRAN | Eosinophil percentage of granulocytes |
| (EO + BASO)# | Sum eosinophil basophil counts |
| BASO# | Basophil count |
| BASO%GRAN | Basophil percentage of granulocytes |
| (BASO + NEUT)# | Sum basophil neutrophil counts |
| GRAN# | Granulocyte count |
| GRAN%MYELOID | Granulocyte percentage of myeloid white cells |
| MYELOID# | Myeloid white cell count |

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| MONO# | Monocyte count |
|---|---|
| NEUT# | Neutrophil count |
| NEUT%GRAN | Neutrophil percentage of granulocytes |
| (NEUT + EO)# | Sum neutrophil eosinophil counts |
| LYMPH# | Lymphocyte count |
| RBC# | Red blood cell count |
| MCV | Mean corpuscular volume |
| HCT | Hematocrit |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| HGB | Hemoglobin concentration |
| RDW | Red cell distribution width |
| RET# | Reticulocyte count |
| RET% | Reticulocyte fraction of red cells |
| IRF | Immature fraction of reticulocytes |
| HLSR% | High light scatter reticulocyte percentage of red cells |
| HLSR# | High light scatter reticulocyte count |
| PCT | Plateletcrit |
| PDW | Platelet distribution width |
| PLT# | Platelet count |
| MPV | Mean platelet volume |

Polyps are frequently observed pathological growths in the uterus that occur in women during of both reproductive and postmenopausal age[1]. These structures are categorized based on their size, number, location, and presence/absence of a stalk. Endometrial polyps (EPs) are the most commonly diagnosed type of uterine polyps, with an estimated prevalence ranging from 7.8 to 50%, while cervical polyps (CPs) are the second most common (with an estimated prevalence of 2–5%)[2–4]. The polyps are usually asymptomatic but may cause a number of problems, such as abnormal uterine bleeding, subfertility, and risk of malignancy[5–9]. A number of etiological theories have suggested an association between the pathogenesis of EPs and CPs and various factors, including estrogen overstimulation, chronic inflammation, and genetic predisposition[5,10,11]. However, early biomarkers for informing diagnosis and identifying pathological mechanisms are still lacking.

Human blood cells (HBCs) play essential roles in oxygen transport, hemostasis, osmotic regulation, and clearance of necrotic tissue and toxins, and are involved in multiple inflammatory and immune responses of the human body[12–16]. Changes in HBC traits may indicate disturbances in physiological processes and are associated with a series of pathological structural abnormalities, such as cellular degeneration, tissue proliferation, and even tumor formation[17,18]. In fact, chronic inflammation is a known etiological factor for both EPs and CPs, and histopathological examinations have shown that polyps are consistently accompanied by inflammatory infiltration[1,5]. This indicates that HBCs might participate in important biological processes during the development of uterine polyps. However, the associations between HBC traits and uterine polyps have not been investigated.

Mendelian randomization (MR) is a novel study design that uses genetic variants as instrumental variables (IVs) to investigate the relationship between risk factors and clinical outcomes of interest[19]. The fundamental principle utilized in the MR design is that if genetic variants could predict a certain proportion of variance for a modifiable exposure, then they should be also causally associated with an exposure-related disease risk. MR presents a number of advantages over traditional observational studies, including the ability to prevent confounding, reverse causation, and various biases that are common in observational epidemiological studies[20]. Recently, the explosion in publicly available summary statistics of genome-wide association studies (GWASs) has provided extensive resources for the application of MR[21]. Here, by extracting summary data from a GWAS of HBC traits and uterine polyps, our study aims to provide an unbiased investigation of the effects of HBC traits on EPs and CPs.

## Results

**Strength of IVs.** After harmonizing the alleles and effects between single nucleotide polymorphisms (SNP) associations with blood cell traits and GWAS datasets of outcomes, we obtained 46–246 genome-wide SNPs for the 36 HBC traits (Fig. 1; Supplementary Tables 1, 2). On average, the SNPs explained 10.8% (in the range of 2.8–28.3%) of the variance in their corresponding HBC traits. The median F statistic, another parameter for measuring the strength of IVs, was 114.2 (in the range of 75.9–281.9), meaning that all IVs were strong (the recommended F statistic is > 10) for the MR analyses.

**Effects of HBC traits on EPs and CPs.** Primary results of MR estimates are presented in Fig. 2. Following the Bonferroni-corrected significance threshold (P < 6.94 × 10⁻⁴), the random-effect inverse-variance weighted (IVW) method identified four HBC traits that showed significant associations with EPs, including the eosinophil percentage of white cells (EO%; odds ratio [OR] 0.84; 95% Confidence interval [CI] 0.77–0.91; $P_{IVW} = 2.43 \times 10^{-5}$), eosinophil count (EO#; OR 0.85; 95% CI 0.79–0.93; $P_{IVW} = 1.06 \times 10^{-4}$), sum eosinophil basophil counts ([EO + BASO]#; OR 0.84; 95% CI 0.78–0.92; $P_{IVW} = 5.55 \times 10^{-5}$), and neutrophil percentage of granulocytes (NEUT%GRAN; OR 1.18; 95% CI 1.08–1.30; $P_{IVW} = 2.62 \times 10^{-4}$). All four traits were granulocyte-related, and three were related to eosinophils in particular. Notably, the three eosinophil-related traits were associated with a decreased risk of EPs (the ORs range from 0.84 to 0.85), while the NEUT%GRAN was associated with an increased risk of EPs. However, we found no evidence for associations between blood cell traits and CPs.
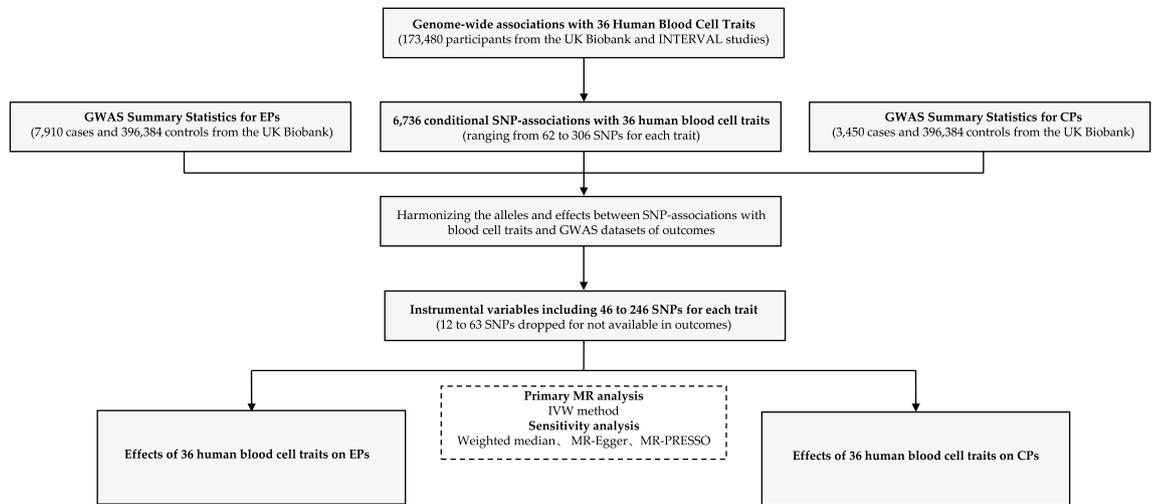
**Figure 1.** Schematic representation of the study design.

**Sensitivity analyses.** Sensitivity analyses showed consistent results with the primary random-effect IVW estimates for all four HBC traits (Table 1), and no strong evidences of horizontal pleiotropy were observed ($P_{intercept} = 0.787$ for EO%, $P_{intercept} = 0.774$ for EO#, $P_{intercept} = 0.513$ for [EO+BASO]#, and $P_{intercept} = 0.433$ for NEUT%GRAN), indicating robust relationships between the four granulocyte-related traits and EPs (Table 1). We further investigated heterogeneity between genetic instruments used which could also indicate pleiotropic effects. However, all four MR associations between HBC traits and EPs presented some evidences of heterogeneity ($I^2 > 25\%$ or Cochran Q-derived P < 0.1). To control for heterogeneity in these MR estimates, we further performed outliers-corrected MR analyses by removing weak or pleiotropic instruments detected by Cochran's Q tests. After removing the identified outliers, the effects of the four HBC traits on EPs were still robust (OR [95% CI] 0.81[0.75,0.88] and $P_{IVW} = 4.89 \times 10^{-7}$ for EO%, OR [95% CI] 0.84[0.77,0.90] and $P_{IVW} = 3.26 \times 10^{-6}$ for EO#, OR [95% CI] 0.83[0.77,0.89] and $P_{IVW} = 1.64 \times 10^{-6}$ for [EO+BASO]#, OR [95% CI] 1.22[1.12,1.32] and $P_{IVW} = 5.98 \times 10^{-6}$ for NEUT%GRAN).
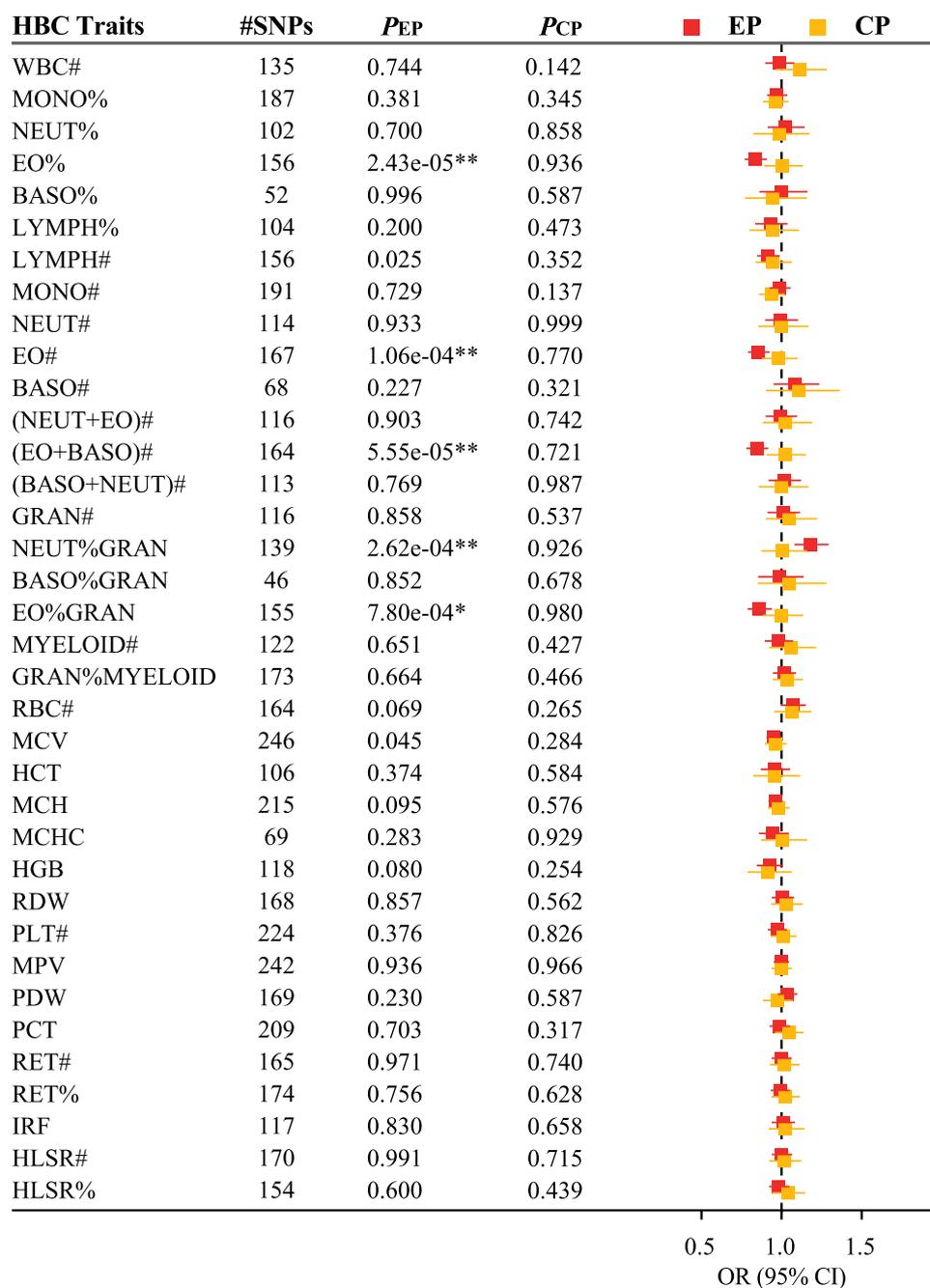
**Multivariable MR analysis.** To control for bias introduced by genetic instrument overlaps among different blood cell traits, we performed multivariable MR analysis adjusting for variables within the same category. The effect of EO# on EP was robust adjusting for NEUT# (OR 0.85; 95% CI 0.78–0.91, $P_{IVW} = 3.38 \times 10^{-5}$), BASO# (OR 0.84; 95% CI 0.77–0.91, $P_{IVW} = 2.79 \times 10^{-5}$), MONO# (OR 0.86; 95% CI 0.79–0.93, $P_{IVW} = 2.31 \times 10^{-4}$), and LYMPH# (OR 0.85; 95% CI 0.79–0.91, $P_{IVW} = 1.13 \times 10^{-5}$) and the effect estimates were consistent with initial MR analysis (Fig. 3A). Similar results were also seen in effects of EO% on EPs (Fig. 3B). Notably, we found that there was interaction between NEUT%GRAN and EO%GRAN when performing multivariable MR on EPs (Fig. 3C,D). More than half of SNPs were overlapped between IVs for NEUT%GRAN (99 out of 139) and EO%GRAN (99 out of 155). Thus, the effect of NEUT%GRAN on EPs might be false positive and the real effect was caused by EO%GRAN changes, considering the fact that there was a shift in the relationship between EO%GRAN and NEUT%GRAN.

**Sub-study MR analysis.** We further performed sub-study MR analysis by utilizing samples separately from the UK Biobank, UK BiLEVE and INTERVAL. The effect estimates of EO# on EPs were consistent (the ORs range from 0.85 to 0.86) across the three studies (Table 2). Similar results were also seen for EO% (the ORs range from 0.83 to 0.84) and (EO+BASO)# (the ORs range from 0.84 to 0.86), suggesting that the effects of EO#, EO% and were (EO+BASO)# robust and potential bias from sample overlaps could be ignored.

## Discussion

Our study provided valuable information for screening novel biomarkers and understanding the pathophysiological mechanisms of EPs and CPs. We identified three eosinophil-related properties that were robustly associated with EPs, suggesting that eosinophils might play important roles in the pathogenesis of EPs. While we found no significant associations between HBC traits and CPs.

The associations between eosinophil properties and EPs had not yet been reported prior to this study. Eosinophils are multifunctional granulocytes involved in the pathogenesis of diverse inflammatory processes, including parasitic infections and allergic reactions[22]. Activated eosinophils release a series of proteins, cytokines, chemokines, and lipid mediators that participate in multiple biological processes such as endothelial proliferation, cell migration, mucus secretion, activation of vascular permeability, and regulation of mucosal homeostasis[23–25]. Eosinophils are widely observed in the endometrial stroma, the luminal and glandular epithelium, and the endometrial-myometrial junction of female genital tracts. However, their biological roles are still not well understood. A previous study reported that the presence of eosinophils in endometrial biopsies might indicate chronic endometritis, as well as disordered proliferative endometrium and EPs[26]. Another study suggested that the

| HBC Traits | #SNPs | $P_{EP}$ | $P_{CP}$ | EP | CP |
|---|---|---|---|---|---|
| WBC# | 135 | 0.744 | 0.142 | | |
| MONO% | 187 | 0.381 | 0.345 | | |
| NEUT% | 102 | 0.700 | 0.858 | | |
| EO% | 156 | 2.43e-05** | 0.936 | | |
| BASO% | 52 | 0.996 | 0.587 | | |
| LYMPH% | 104 | 0.200 | 0.473 | | |
| LYMPH# | 156 | 0.025 | 0.352 | | |
| MONO# | 191 | 0.729 | 0.137 | | |
| NEUT# | 114 | 0.933 | 0.999 | | |
| EO# | 167 | 1.06e-04** | 0.770 | | |
| BASO# | 68 | 0.227 | 0.321 | | |
| (NEUT+EO)# | 116 | 0.903 | 0.742 | | |
| (EO+BASO)# | 164 | 5.55e-05** | 0.721 | | |
| (BASO+NEUT)# | 113 | 0.769 | 0.987 | | |
| GRAN# | 116 | 0.858 | 0.537 | | |
| NEUT%GRAN | 139 | 2.62e-04** | 0.926 | | |
| BASO%GRAN | 46 | 0.852 | 0.678 | | |
| EO%GRAN | 155 | 7.80e-04* | 0.980 | | |
| MYELOID# | 122 | 0.651 | 0.427 | | |
| GRAN%MYELOID | 173 | 0.664 | 0.466 | | |
| RBC# | 164 | 0.069 | 0.265 | | |
| MCV | 246 | 0.045 | 0.284 | | |
| HCT | 106 | 0.374 | 0.584 | | |
| MCH | 215 | 0.095 | 0.576 | | |
| MCHC | 69 | 0.283 | 0.929 | | |
| HGB | 118 | 0.080 | 0.254 | | |
| RDW | 168 | 0.857 | 0.562 | | |
| PLT# | 224 | 0.376 | 0.826 | | |
| MPV | 242 | 0.936 | 0.966 | | |
| PDW | 169 | 0.230 | 0.587 | | |
| PCT | 209 | 0.703 | 0.317 | | |
| RET# | 165 | 0.971 | 0.740 | | |
| RET% | 174 | 0.756 | 0.628 | | |
| IRF | 117 | 0.830 | 0.658 | | |
| HLSR# | 170 | 0.991 | 0.715 | | |
| HLSR% | 154 | 0.600 | 0.439 | | |

OR (95% CI)  0.5  1.0  1.5

**Figure 2.** Mendelian randomization estimates of HBC traits on EPs and CPs. Associations were assessed using the random-effect IVW method. Results are expressed as ORs and 95% CIs per 1 SD of each HBC trait. *HBC* human blood cell, *EPs* endometrial polyps, *CPs* cervical polyps, *IVW* inverse-variance weighted. **Multiple-testing-adjusted threshold: $P < 6.94 \times 10^{-4}$. *Suggestive for association: $P < 0.01$.

IL-4 released by eosinophils can promote endometrial stromal cell proliferation and repair genital tissue after infection[27]. Furthermore, elevated eosinophil counts are also frequently observed in patients with nasal polyps, suggesting that eosinophilic inflammation might cause specific mucosal polyps[28–31]. Our study provided some different evidence that higher level of eosinophils had a protective effect on EPs. While up to now, there was no clear evidence regarding the effect of eosinophils on EPs. The results could also vary depending on the source of tissue in the sample being measured. Anyway, our study together with previous studies indicated that eosinophils might be involved in EP pathogenesis.

Our study had several strengths. First, the MR study design not only provided evidences for causal relationships between HBCs and uterine polyps, but also prevented the widespread bias that is common in observational epidemiological studies. Second, the datasets for HBCs and outcomes were all generated from a European population, which avoided the potential bias that might be caused by differences in genetic backgrounds. Third,

| HBC trait | Methods | First-stage MR analyses | | | | Outliers corrected MR analyses[b] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | #SNPs | OR (95% CI) | P value | Heterogeneity test[a] | #SNPs | OR (95% CI) | P value | Heterogeneity test |
| EO% | Random-effect IVW | 156 | 0.84 (0.77, 0.91) | 2.43e−05 | Q = 184.6 I² = 16.0% P = 0.053 | 142 | 0.81 (0.75, 0.88) | 4.89e−07 | Q = 95.6 I² = 0% P = 0.999 |
| | Weighted median | | 0.81 (0.72, 0.92) | 9.91e−04 | | | 0.81 (0.71, 0.91) | 6.42e−04 | |
| | MR-PRESSO | | 0.84 (0.77, 0.91) | 4.13e−05 | | | 0.81 (0.76, 0.87) | 9.29e−09 | |
| | MR-Egger | | 0.86 (0.71, 1.03) | 0.105 | | | 0.77 (0.65, 0.92) | 0.004 | |
| | MR-Egger (intercept) | | – | 0.787 | | | – | 0.527 | |
| EO# | Random-effect IVW | 167 | 0.85 (0.79, 0.93) | 1.06e−04 | Q = 197.2 I² = 15.8% P = 0.049 | 154 | 0.84 (0.77, 0.90) | 3.26e−06 | Q = 123.9 I² = 0% P = 0.959 |
| | Weighted median | | 0.83 (0.70, 0.99) | 0.049 | | | 0.80 (0.71, 0.90) | 2.06e−04 | |
| | MR-PRESSO | | 0.85 (0.79, 0.93) | 1.52e−04 | | | 0.84 (0.78, 0.89) | 7.79e−07 | |
| | MR-Egger | | 0.81 (0.72, 0.92) | 6.42e−04 | | | 0.76 (0.64, 0.90) | 0.001 | |
| | MR-Egger (intercept) | | – | 0.774 | | | – | 0.212 | |
| (EO + BASO)# | Random-effect IVW | 164 | 0.84 (0.78, 0.92) | 5.55e−05 | Q = 194.3 I² = 16.1% P = 0.047 | 152 | 0.83 (0.77, 0.89) | 1.64e−06 | Q = 125.7 I² = 0% P = 0.934 |
| | Weighted median | | 0.80 (0.71, 0.91) | 3.76e−04 | | | 0.80 (0.71, 0.91) | 4.67e−04 | |
| | MR-PRESSO | | 0.84 (0.78, 0.92) | 8.50e−05 | | | 0.83 (0.77, 0.89) | 4.98e−07 | |
| | MR-Egger | | 0.80 (0.66, 0.96) | 0.018 | | | 0.75 (0.63, 0.89) | 9.04e−04 | |
| | MR-Egger (intercept) | | – | 0.513 | | | – | 0.191 | |
| NEUT%GRAN | Random-effect IVW | 139 | 1.18 (1.08, 1.30) | 2.62e−04 | Q = 167.0 I² = 17.3% P = 0.047 | 128 | 1.22 (1.12, 1.32) | 5.98e−06 | Q = 96.8 I² = 0% P = 0.978 |
| | Weighted median | | 1.23 (1.07, 1.41) | 0.004 | | | 1.23 (1.08, 1.41) | 0.002 | |
| | MR-PRESSO | | 1.18 (1.08, 1.30) | 3.71 e−04 | | | 1.22 (1.13, 1.31) | 8.37e−07 | |
| | MR-Egger | | 1.27 (1.04, 1.57) | 0.021 | | | 1.35 (1.11, 1.63) | 0.002 | |
| | MR-Egger (intercept) | | – | 0.433 | | | – | 0.243 | |

**Table 1.** MR estimates of associations between human blood cell (HBC) traits and endometrial polyps (Eps). *HBC* human blood cell, *MR* Mendelian randomization, *EO#* eosinophil count, *EO%* eosinophil percentage of white cells, *(EO + BASO)#* sum eosinophil basophil count, *NEUT%GRAN* neutrophil percentage of granulocytes, *#SNPs* number of single nucleotide polymorphisms, *IVW* inverse-variance weighted, *MR-PRESSO* MR-pleiotropy residual sum and outlier. [a]Heterogeneity was assessed based on the Cochran's Q statistic, quantified $I^2$ index and Cochran's Q-derived *P* value according to the IVW model. [b]Outliers were detected using individual components of Cochran's Q according to the IVW model. Secondary MR analyses were performed after removing the detected outliers.

the large sample size of the GWAS on HBCs guaranteed the strength of the IVs (*F* statistic > 10) used to detect the relationships between HBCs and uterine polyps. All generated IVs were strong instruments for MR analyses.

There were also limitations. First, although MR is a powerful tool for inferring causality, the results should be further verified by experimental studies, and the mechanisms behind the pathogenesis of EPs and CP should be further explored. Second, the study samples of outcomes were limited to females. Gender differences between datasets of exposures and outcomes might introduce bias to the MR estimates. Third, the sample sizes for EPs and CPs were relatively small, more data should be collected to increase the statistical power. Additionally, we did not investigate the associations of the IVs with potential confounders in the two-sample MR estimates.

## Conclusion

The present MR study found that decreased levels of eosinophils were causally associated with a higher risk of EPs. By identifying possible biomarkers for uterine polyps, our study provides novel insight into the pathogenesis of EPs. Our findings may be used to inform clinical diagnostic procedures and future uterine polyp biomarker studies.
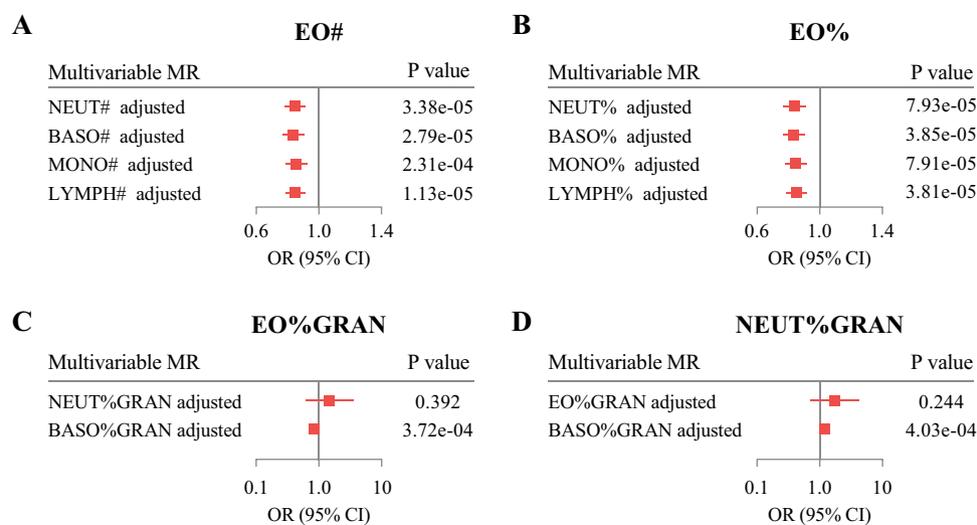
**Figure 3.** Multivariable MR analysis for four HBC traits adjusting for variables within the same category. (**A**) Effect of EO# on EPs, adjusting for NEUT#, BASO#, MONO#, and LYMPH#; (**B**) effect of EO% on EPs, adjusting for NEUT%, BASO%, MONO%, and LYMPH%; (**C**) effect of EO%GRAN on EPs, adjusting for NEUT%GRAN and BASO%GRAN; (**D**) effect of NEUT%GRAN on EPs, adjusting for EO%GRAN and BASO%GRAN. Results are expressed as ORs and 95% CIs per 1 SD of each HBC trait. *HBC* human blood cell, *EPs* endometrial polyps.

| Exposure | Study | Sample size | OR (95% CI) | P value |
|---|---|---|---|---|
| EO# | UK Biobank | 87,265 | 0.86 (0.79, 0.93) | 1.41e−04 |
| | UK BiLEVE | 45,694 | 0.86 (0.79, 0.93) | 1.59e−04 |
| | INTERVAL | 40,521 | 0.86 (0.79, 0.93) | 9.58e−05 |
| | Combined | 173,480 | 0.85 (0.79, 0.93) | 1.06e−04 |
| EO% | UK Biobank | 87,265 | 0.84 (0.77, 0.91) | 2.33e−05 |
| | UK BiLEVE | 45,694 | 0.84 (0.78, 0.92) | 7.02e−05 |
| | INTERVAL | 40,521 | 0.84 (0.77, 0.91) | 2.77e−05 |
| | Combined | 173,480 | 0.84 (0.77, 0.91) | 2.55e−05 |
| (EO + BASO)# | UK Biobank | 87,265 | 0.85 (0.79, 0.93) | 1.06e−04 |
| | UK BiLEVE | 45,694 | 0.85 (0.78, 0.92) | 7.00e−05 |
| | INTERVAL | 40,521 | 0.85 (0.79, 0.92) | 3.88e−05 |
| | Combined | 173,480 | 0.84 (0.78, 0.92) | 5.55e−05 |

**Table 2.** Sub-study MR analysis of eosinophil properties on EPs. MR estimates were performed using samples separately from UK Biobank, UK BiLEVE and INTERVAL. Associations were assessed using the random-effect IVW method. Results are expressed as ORs and 95% CIs per 1 SD of each HBC trait. *EPs* endometrial polyps, *IVW* inverse-variance weighted.

## Methods

**Identifying genetic instruments for the 36 HBC traits.** The overall flow diagram of this MR study is illustrated in Fig. 1. We used the findings from a large GWAS on 173,480 European-ancestry participants to identify IVs for the 36 HBC traits[32]. The total study samples were composed of three large-scale UK studies, which respectively were 87,265 individuals from the UK Biobank[33], 45,694 individuals from the UK BiLEVE (a selected subset of the UK Biobank cohort)[34], and 40,521 individuals form the INTERVAL[35]. HBC traits were measured using clinical hematology analyzers at the centralized processing laboratory of the UK Biocenter (Stockport, UK). Genotyping was performed on the Affymetrix GeneTitan Multi-Channel (MC) Instrument according to the Affymetrix axiom 2.0 assay Automated Workflow. Detailed information for genotype imputation, quality control, and association analysis can be found in a previously published study[32]. Finally, a total of 6736 conditionally independent trait-variant pairs (corresponding to 3755 conditional lead variants) with significance level at $P < 8.31 \times 10^{-9}$ (a threshold estimated for genome-wide analyses of common, low frequency and rare variants) were identified to compose IVs for the 36 HBC traits. The identified IVs were further mapped to the GWAS datasets of outcomes and SNPs were dropped while not available in datasets of outcomes. The strength of the IVs were evaluated by tow parameters: the proportion of variance explained ($R^2$), which was calculated using the formula $2 \times MAF \times (1 - MAF) \times (\beta$ estimate in SD units$)^2$, and the F statistic, which could be calculated from the

$R^2$ statistic as $F = (N - K - 1)/K \times R^2/(1 - R^2)$, where N is the sample size and K is the number of SNPs[36]. Typically, a threshold of $F > 10$ is recommended for defining instrument strength in an MR analysis[37].

**GWAS of EPs and CPs.** Genetic associations with EPs and CPs were obtained from the Michigan PheWeb v1.1.17 (http://pheweb.sph.umich.edu/UKBiobank)[38]. The total study sample comprised 7910 EP cases and 3450 CP cases, as well as 396,384 shared heathy controls from the UK Biobank. Cases were diagnosed according to the International Classification of Disease (ICD) codes. Association analyses were performed using SAIGE (https://github.com/weizhouUMICH/SAIGE/), adjusting for genetic relationship, date of birth, as well as the first four principal components. All the data were extracted from the public domain and thus no ethical approval was required for this study.

**Statistical analysis.** MR analyses were performed using the random-effect IVW method. Briefly, the IVW approach makes the fundamental assumption that all included genetic variants are valid IVs. This requires each genetic variant to satisfy three conditions: (i) it is strongly associated with the exposure, (ii) it cannot be associated with any confounders, and (iii) it is associated with the outcome exclusively through the exposure[37]. The IVW method is efficient when all variants satisfy the conditions for IV validity. However, bias occurs if horizontal pleiotropy (referring to a situation in which a variant acts on the outcome through other factors besides the exposure) occurs[39]. To control for widespread horizontal pleiotropy in MR analyses, we further performed three additional MR analyses to serve as sensitivity analyses (MR-Egger, weighted median, and MR-PRESSO). MR-Egger provides consistent estimates even with invalid instruments under the Instrument Strength Independent of Direct Effect (InSIDE) assumption[39]. The weighted median introduces a median-based estimator which tolerated up to 50% of the IVs to be invalid, and provides a consistent estimate of causal relationships[40]. MR-PRESSO is a newly developed method that aims to control for horizontal pleiotropy by detecting and correcting for outliers[41]. We also tested for heterogeneity which could indicate pleiotropic instruments effects using the with the $I^2$ and Cochran Q statistic, and an $I^2 > 25\%$ or Cochran Q-derived $p < 0.1$ was adopted to declare evidence of heterogeneity[42]. Weak or pleiotropic instruments were detected according to the individual components of Q statistic and a corrected model were performed without these outliers[43]. Multivariable MR analyses were performed by using the random-effect IVW method to adjust for the effect of overlapped instruments with other blood traits. Sub-study MR analyses were also performed to avoid potential bias that might be introduced by sample overlapping, using effect size of IVs respectively from UK Biobank, UK BiLEVE and INTERVAL study cohorts[44].

All MR analyses were carried out using TwoSampleMR and MVMR packages in R (www.cran.r-project.org). A multiple-testing-adjusted threshold of $P < 6.94 \times 10^{-4}$ (corrected for the total number of comparisons using the Bonferroni method) was defined as the threshold for declaring statistical significance.

**Ethics approval.** The GWAS summary statistics for all traits were extracted from the public domain. Therefore, no ethical approval and consent was required for this study.

## Data availability

Full summary statistics for the 36 human blood cell traits are publicly available from http://www.bloodcellgenetics.org. GWAS summary statistics for Eps and CPs were downloader from the Michigan PheWeb v1.1.17 (http://pheweb.sph.umich.edu/UKBiobank).

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## Author contributions

S.S., Y.L. and X.L. designed and implemented the study. S.S. and Y.L. performed the statistical analysis, prepared figured 1–3 and drafted the manuscript. L.L., M.J. and J.Y. were responsible for the data collection and

management. B.L., W.G. and X.L. contributed to interpretation and editing of the manuscript. All authors read and approved the final manuscript.

## Competing interests
The authors declare no competing interests.

## Additional information
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