# Supplementary Tables and Figures

**Table S1** Genetic instrumental variables utilized in the Mendelian randomization analysis of polycystic ovary syndrome on periodontitis

| SNP | Chr:Pos | Nearest Gene | EA/OA | EAF | Association with PCOS | | | Association with periodontitis | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Beta | SE | *P*-value | Beta | SE | *P*-value |
| rs2178575 | 2:213391766 | ERBB4 | A/G | 0.15 | 0.166 | 0.022 | $3.34 \times 10^{-14}$ | -0.019 | 0.025 | 0.43 |
| rs11031005 | 11:30226356 | ARL14EP/FSHB | T/C | 0.85 | -0.159 | 0.022 | $8.66 \times 10^{-13}$ | -0.017 | 0.026 | 0.51 |
| rs804279 | 8:11623889 | GATA4/NEIL2 | A/T | 0.26 | 0.128 | 0.018 | $3.76 \times 10^{-12}$ | -0.024 | 0.021 | 0.24 |
| rs11225154 | 11:102043240 | YAP1 | A/G | 0.09 | 0.179 | 0.027 | $5.44 \times 10^{-11}$ | -0.029 | 0.032 | 0.37 |
| rs9696009 | 9:126619233 | DENND1A | A/G | 0.07 | 0.202 | 0.031 | $7.96 \times 10^{-11}$ | -0.007 | 0.034 | 0.83 |
| rs13164856 | 5:131813204 | IRF1/RAD50 | T/C | 0.73 | 0.124 | 0.019 | $1.45 \times 10^{-10}$ | 0.015 | 0.020 | 0.47 |
| rs1784692 | 11:113949232 | ZBTB16 | T/C | 0.82 | 0.144 | 0.023 | $1.88 \times 10^{-10}$ | 0.011 | 0.023 | 0.65 |
| rs7563201 | 2:43561780 | THADA | A/G | 0.45 | -0.108 | 0.017 | $3.68 \times 10^{-10}$ | -0.003 | 0.019 | 0.89 |
| rs8043701 | 16:52375777 | TOX3 | A/T | 0.82 | -0.127 | 0.021 | $9.61 \times 10^{-10}$ | 0.002 | 0.024 | 0.94 |
| rs1795379 | 12:75941042 | KRR1 | T/C | 0.24 | -0.117 | 0.020 | $1.81 \times 10^{-9}$ | -0.031 | 0.021 | 0.14 |
| rs2271194 | 12:56477694 | ERBB3/RAB5B | A/T | 0.42 | 0.097 | 0.017 | $4.57 \times 10^{-9}$ | -0.026 | 0.019 | 0.16 |
| rs10739076 | 9:5440589 | PLGRKT | A/C | 0.31 | 0.110 | 0.020 | $2.51 \times 10^{-8}$ | -0.022 | 0.022 | 0.31 |
| rs7864171 | 9:97723266 | C9orf3 | A/G | 0.43 | -0.093 | 0.017 | $2.95 \times 10^{-8}$ | 0.010 | 0.018 | 0.59 |

**Abbreviations:** Beta represents one-unit change in the log-odds of developing PCOS or periodontitis per additional effect allele; Chr:Pos, Chromosome and position according to GRCh37/hg19 genome assembly; EA/OA, effect allele/reference allele; EAF, effect allele frequency; PCOS, polycystic ovary syndrome; SE, standard error; SNP, single nucleotide polymorphism.

**Table S2** Look-up of potential pleiotropic associations ($P < 5 \times 10^{-8}$) of instrumental SNPs for PCOS in the GWAS Catalog

| SNP | Chr | Nearest Gene | Traits and Studies |
|---|---|---|---|
| rs7563201 | 2 | THADA | NA |
| rs2178575 | 2 | ERBB4 | NA |
| rs13164856 | 5 | IRF1/RAD50 | Asthma (PMID: 31669095) |
| rs804279 | 8 | GATA4/NEIL2 | NA |
| rs10739076 | 9 | PLGRKT | NA |
| rs7864171 | 9 | C9orf3 | NA |
| rs9696009 | 9 | DENND1A | NA |
| rs11031005 | 11 | ARL14EP/FSHB | Testosterone (PMID: 32042192), Follicle-stimulating hormone (PMID: 26014426), Age at menopause (PMID: 30595370), Age at menarche (PMID: 27182965) |
| rs11225154 | 11 | YAP1 | NA |
| rs1784692 | 11 | ZBTB16 | NA |
| rs2271194 | 12 | ERBB3/RAB5B | Autoimmune thyroid disease (PMID: 32581359) |
| rs1795379 | 12 | KRR1 | NA |
| rs8043701 | 16 | TOX3 | NA |

**Abbreviations**: CHR, chromosome; GWAS, genome-wide association study; PCOS, polycystic ovary syndrome; SNP, Single-nucleotide polymorphism.

**Table S3** Assessment of genetic instrumental variables for polycystic ovary syndrome

| SNP | Chr:Pos | Effect allele | MAF | Beta | *P*-value | $R^2$ | *F* |
|---|---|---|---|---|---|---|---|
| rs7563201 | 2:43561780 | A | 0.45 | -0.11 | $3.68 \times 10^{-10}$ | 0.0058 | 39.5 |
| rs2178575 | 2:213391766 | A | 0.15 | 0.17 | $3.34 \times 10^{-14}$ | 0.0071 | 57.6 |
| rs13164856 | 5:131813204 | T | 0.27 | 0.12 | $1.45 \times 10^{-10}$ | 0.0060 | 40.9 |
| rs804279 | 8:11623889 | A | 0.26 | 0.13 | $3.76 \times 10^{-12}$ | 0.0063 | 48.1 |
| rs10739076 | 9:5440589 | A | 0.31 | 0.11 | $2.51 \times 10^{-8}$ | 0.0051 | 31.0 |
| rs7864171 | 9:97723266 | A | 0.43 | -0.09 | $2.95 \times 10^{-8}$ | 0.0043 | 30.8 |
| rs9696009 | 9:126619233 | A | 0.07 | 0.20 | $7.96 \times 10^{-11}$ | 0.0052 | 42.2 |
| rs11031005 | 11:30226356 | T | 0.15 | -0.16 | $8.66 \times 10^{-13}$ | 0.0063 | 51.0 |
| rs11225154 | 11:102043240 | A | 0.09 | 0.18 | $5.44 \times 10^{-11}$ | 0.0054 | 43.2 |
| rs1784692 | 11:113949232 | T | 0.18 | 0.14 | $1.88 \times 10^{-10}$ | 0.0060 | 40.5 |
| rs2271194 | 12:56477694 | A | 0.42 | 0.10 | $4.57 \times 10^{-9}$ | 0.0046 | 34.2 |
| rs1795379 | 12:75941042 | T | 0.24 | -0.12 | $1.81 \times 10^{-9}$ | 0.0050 | 36.2 |
| rs8043701 | 16:52375777 | A | 0.18 | -0.13 | $9.61 \times 10^{-10}$ | 0.0049 | 37.5 |

**Note**: Proportion of variance explained was calculated using formula**:** $R^2 = 2 \times MAF \times (1\text{-}MAF) \times Beta^2$, and total variance ~ 6.2% was further utilized in the power calculation (https://shiny.cnsgenomics.com/mRnd/). Strength of each SNP was assessed by ***F*-statistic** $= R^2(N\text{-}2)/(1\text{-}R^2)$, where $F < 10$ was deemed as a weak instrument.

**Abbreviations:** SNP, Single-nucleotide polymorphism; MAF, minor allele frequency; $R^2$, proportion of variance explained; N = 113, 238 was the sample size of the GWAS of polycystic ovary syndrome.

**Table S4** Genetic instrumental variables utilized in the Mendelian randomization analysis of periodontitis on polycystic ovary syndrome

| SNP | Chr:Pos | Nearest Gene | EA/OA | EAF | Association with periodontitis | | | Association with PCOS | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Beta | SE | *P*-value | Beta | SE | *P*-value |
| rs4956201 | 4:109527782 | RPL34-AS1 | A/C | 0.89 | -0.241 | 0.047 | $3.89 \times 10^{-7}$ | -0.130 | 0.065 | 0.05 |
| rs2976950 | 8:8249082 | SGK223 | A/G | 0.60 | 0.096 | 0.020 | $7.99 \times 10^{-7}$ | 0.032 | 0.033 | 0.33 |
| rs151226594 | 11:64256137 | LOC100996455 | T/G | 0.01 | -0.367 | 0.077 | $1.75 \times 10^{-6}$ | -0.066 | 0.130 | 0.60 |
| rs78422482 | 4:19970150 | SLIT2 | A/G | 0.01 | 0.243 | 0.051 | $2.02 \times 10^{-6}$ | -0.099 | 0.090 | 0.27 |
| rs13005050 | 2:52705571 | MIR4431 | T/C | 0.14 | -0.143 | 0.031 | $3.76 \times 10^{-6}$ | 0.015 | 0.050 | 0.76 |
| rs6816769 | 4:122216017 | QRFPR | T/C | 0.89 | -0.135 | 0.029 | $4.57 \times 10^{-6}$ | -0.018 | 0.051 | 0.73 |
| rs117710629 | 18:39372393 | PIK3C3 | A/G | 0.01 | -0.552 | 0.121 | $4.96 \times 10^{-6}$ | -0.057 | 0.160 | 0.72 |

**Abbreviations:** Beta represents one-unit change in the log-odds of developing PCOS or periodontitis per additional effect allele; Chr:Pos, Chromosome and position according to GRCh37/hg19 genome assembly; EA/OA, effect allele/reference allele; EAF, effect allele frequency; PCOS, polycystic ovary syndrome; SE, standard error; SNP, single nucleotide polymorphism.

**Table S5** Look-up of potential pleiotropic associations ($P < 5 \times 10^{-8}$) of instrumental SNPs for periodontitis in the GWAS Catalog

| SNP | Chr | Nearest Gene | Traits and Studies |
|---|---|---|---|
| rs13005050 | 2 | MIR4431 | NA |
| rs78422482 | 4 | SLIT2 | NA |
| rs4956201 | 4 | RPL34-AS1 | NA |
| rs6816769 | 4 | QRFPR | NA |
| rs2976950 | 8 | SGK223 | NA |
| rs151226594 | 11 | LOC100996455 | NA |
| rs117710629 | 18 | PIK3C3 | NA |

**Abbreviations**: CHR, chromosome; GWAS, genome-wide association study; PCOS, polycystic ovary syndrome; SNP, Single-nucleotide polymorphism.

**Table S6** Assessment of genetic instrumental variables for periodontitis

| SNP | Chr:Pos | Effect allele | MAF | Beta | *P*-value | $R^2$ | *F* |
|---|---|---|---|---|---|---|---|
| rs13005050 | 2:52705571 | T | 0.14 | -0.14 | $3.76 \times 10^{-6}$ | 0.0049 | 171.3 |
| rs78422482 | 4:19970150 | A | 0.01 | 0.24 | $2.02 \times 10^{-6}$ | 0.0012 | 40.5 |
| rs4956201 | 4:109527782 | A | 0.11 | -0.24 | $3.89 \times 10^{-7}$ | 0.0114 | 398.2 |
| rs6816769 | 4:122216017 | T | 0.11 | -0.14 | $4.57 \times 10^{-6}$ | 0.0036 | 124.0 |
| rs2976950 | 8:8249082 | A | 0.40 | 0.10 | $7.99 \times 10^{-7}$ | 0.0044 | 153.8 |
| rs151226594 | 11:64256137 | T | 0.01 | -0.37 | $1.75 \times 10^{-6}$ | 0.0027 | 92.6 |
| rs117710629 | 18:39372393 | A | 0.01 | -0.55 | $4.96 \times 10^{-6}$ | 0.0050 | 172.4 |

**Note**: Proportion of variance explained was calculated using formula**:** $R^2 = 2 \times MAF \times (1\text{-}MAF) \times Beta^2$, and total variance ~ 3.3% was further utilized in the power calculation (https://shiny.cnsgenomics.com/mRnd/). Strength of each SNP was assessed by $F\text{-statistic} = R^2(N\text{-}2)/(1\text{-}R^2)$, where $F < 10$ was deemed as a weak instrument. MAF, was from the 1000Genomes European panel, since allele frequency variable has been removed to prevent re-identification of individuals in the shared summary-level dataset of periodontitis.

**Abbreviations:** SNP, Single-nucleotide polymorphism; MAF, minor allele frequency; $R^2$, proportion of variance explained; N = 34, 615 was the sample size of the GWAS of periodontitis.

**Table S7** Results of Mendelian randomization sensitivity analyses

| MR analyses | MR-Egger regression | | MR-PRESSO global test | | Cochran's *Q* test | |
|---|---|---|---|---|---|---|
| | **Intercept** | ***P*-value** | **$RSS_{obs}$** | ***P*-value** | ***Q*-statistic** | ***P*-value** |
| PCOS on periodontitis | -0.009 | 0.75 | 10.62 | 0.69 | 9.07 | 0.70 |
| Periodontitis on PCOS | 0.008 | 0.86 | 7.34 | 0.50 | 5.20 | 0.52 |

**Abbreviations:** MR, Mendelian randomization; PRESSO, Pleiotropy RESidual Sum and Outlier model; PCOS, polycystic ovary syndrome; $RSS_{obs}$, observed residual sum of squares

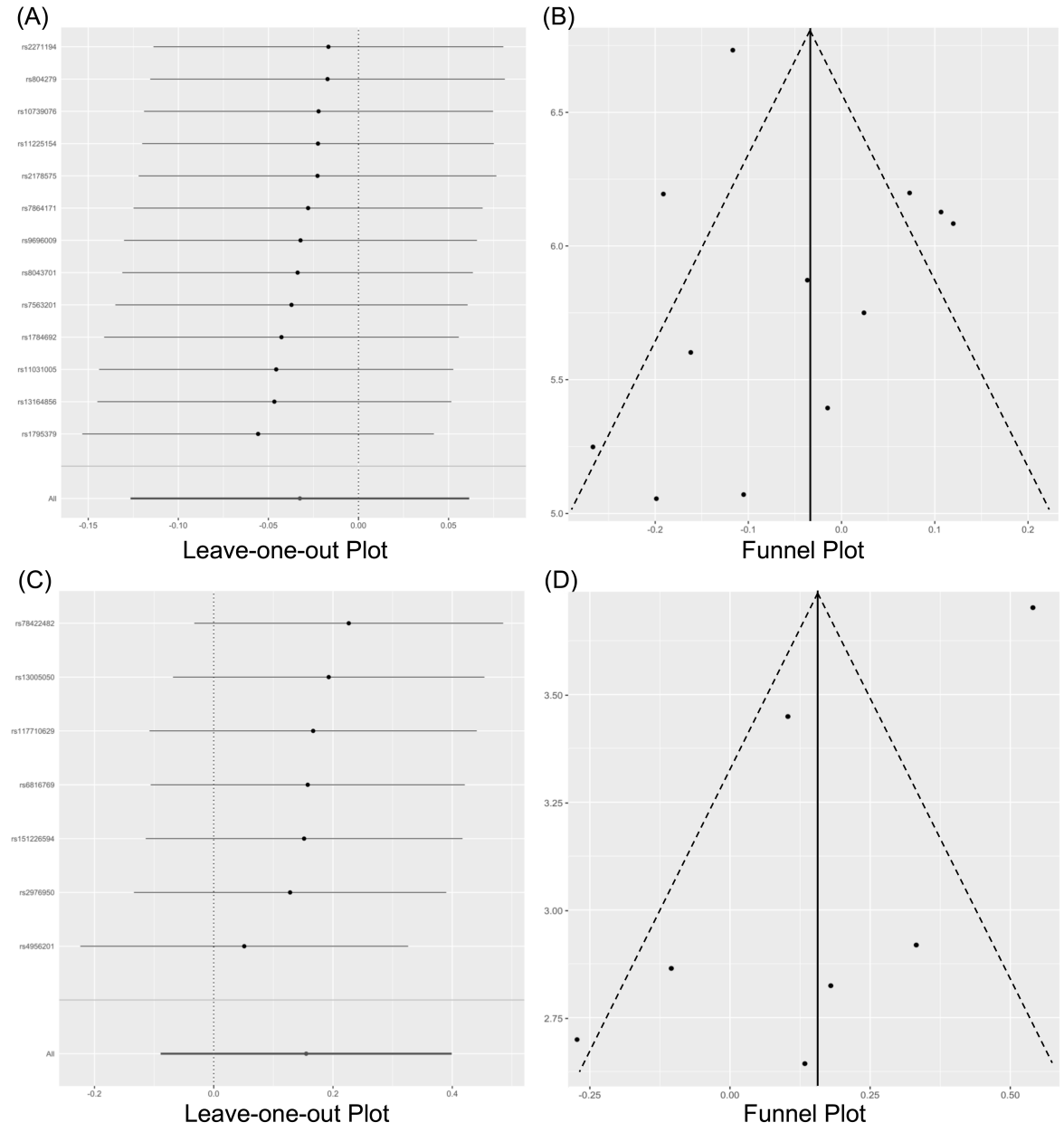


**Figure S1. Leave-one-out plots and funnel plots in the sensitivity analyses**. The leave-one-out plot (**A**) visualized how the causal estimates (point with horizontal line) for the effect of polycystic ovary syndrome (PCOS) on periodontitis were influenced by the removal of single variant. The funnel plot (**B**) illustrated the overall symmetry of causal estimates across all instrumental variables. Each point denoted corresponding inverse standard error against the individual causal estimate. The leave-one-out plot (**C**) and funnel plot (**D**) in the sensitivity analysis of the periodontitis-PCOS relationship were presented likewise.