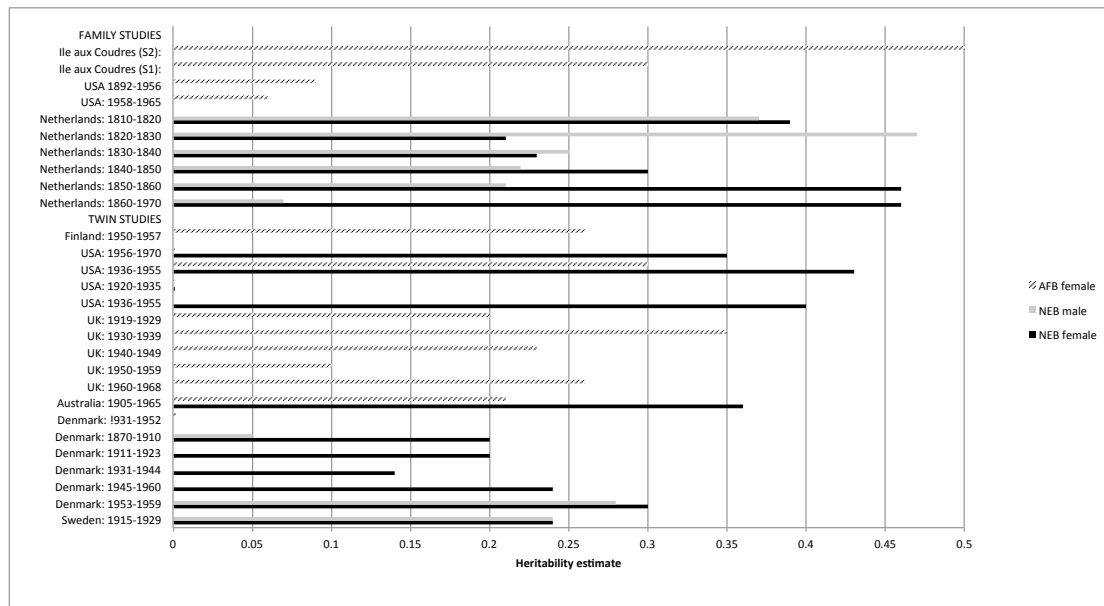


# 1 Supplementary Figures

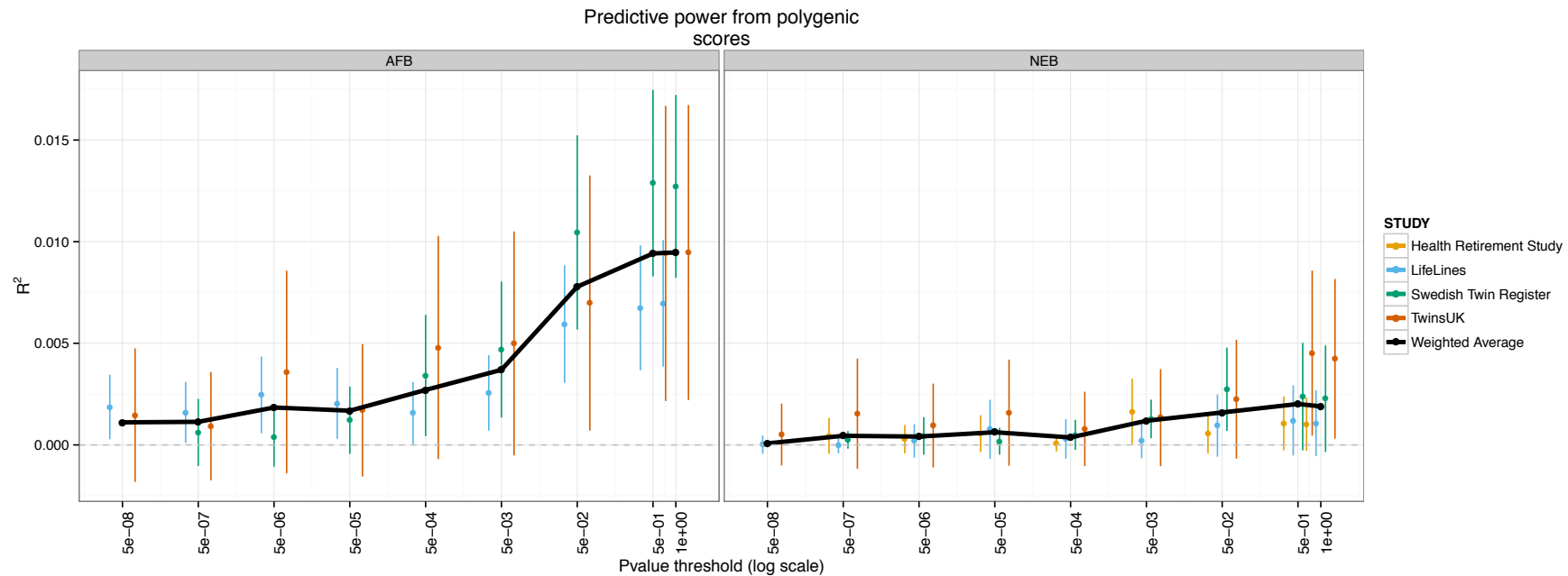
2 *“Genome-wide analysis identifies 12 loci influencing human reproductive*  
3 *behavior”*

4  
5 **Supplementary Figure 1. Summary of fertility heritability estimates by birth**  
6 **cohort and country by fertility trait: (AFB) age at first birth, (NEB) number of**  
7 **children ever born.**

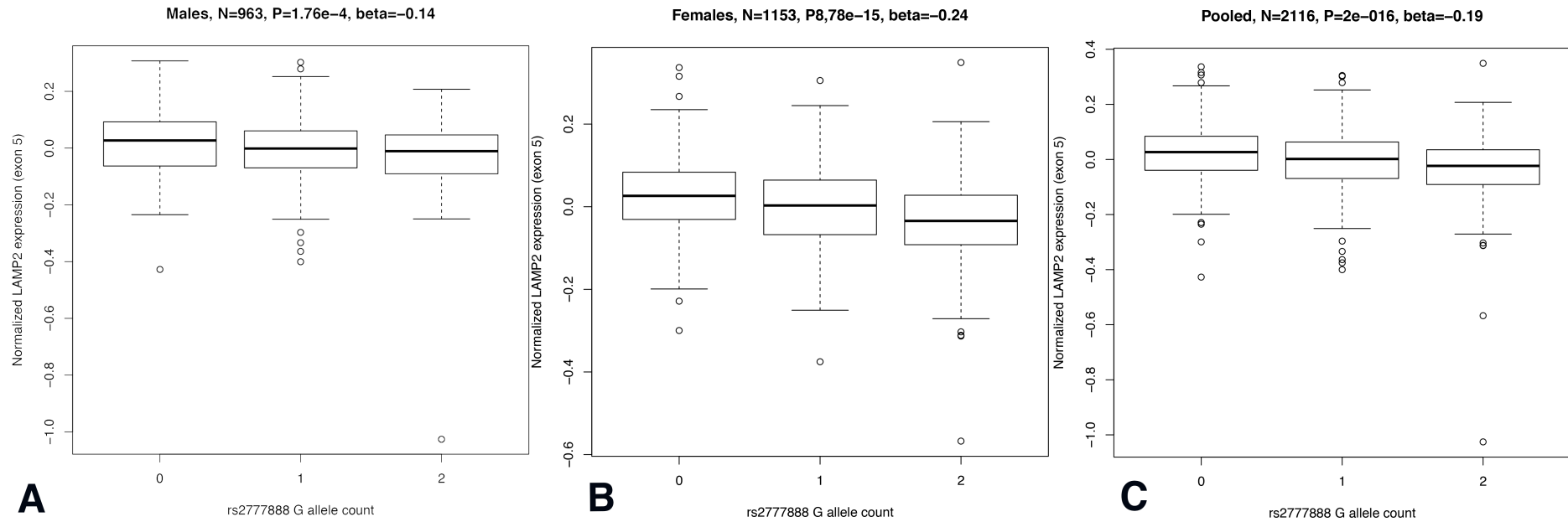


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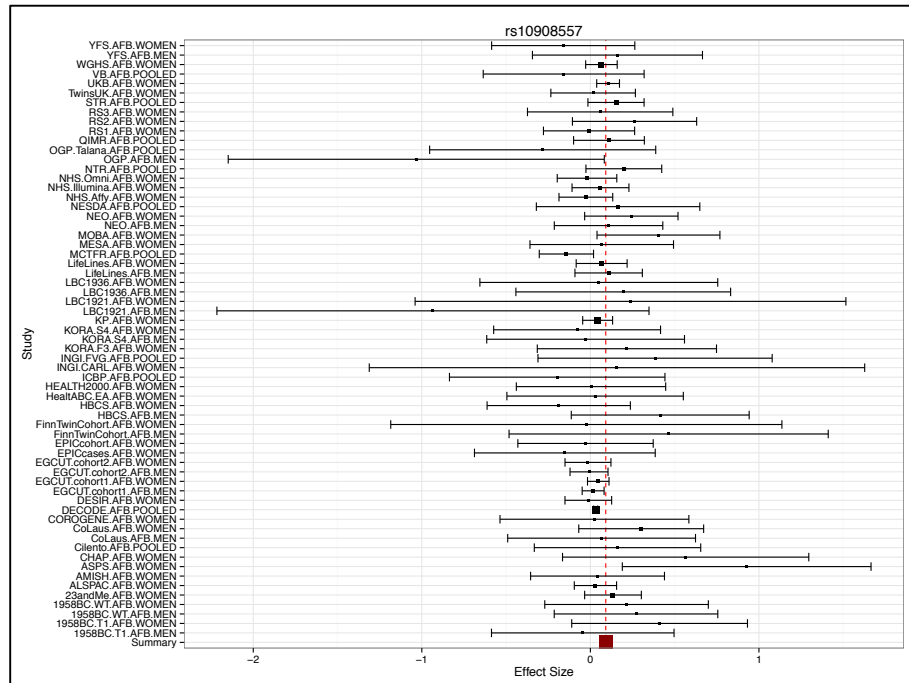
1 **Supplementary Figure 2. Variance explained by AFB and NEB polygenic scores calculated with the inclusion of SNPs at different levels**  
2 **of significance.** Polygenic scores were calculated from the meta-analysis results excluding the validation cohort. The y-axis is the variance  
3 explained (R-squared from OLS regression with polygenic score as sole predictor). The x-axis represents the p-value inclusion threshold used in  
4 the construction of the polygenic score. The black line is the sample-size-weighted mean  $R^2$ . Cohort specific estimates and 95% confidence  
5 intervals obtained with 1,000 bootstrap samples. Results are adjusted for birth cohort, first 10 principal components and sex. Clustered standard  
6 errors have been used for family-based studies.



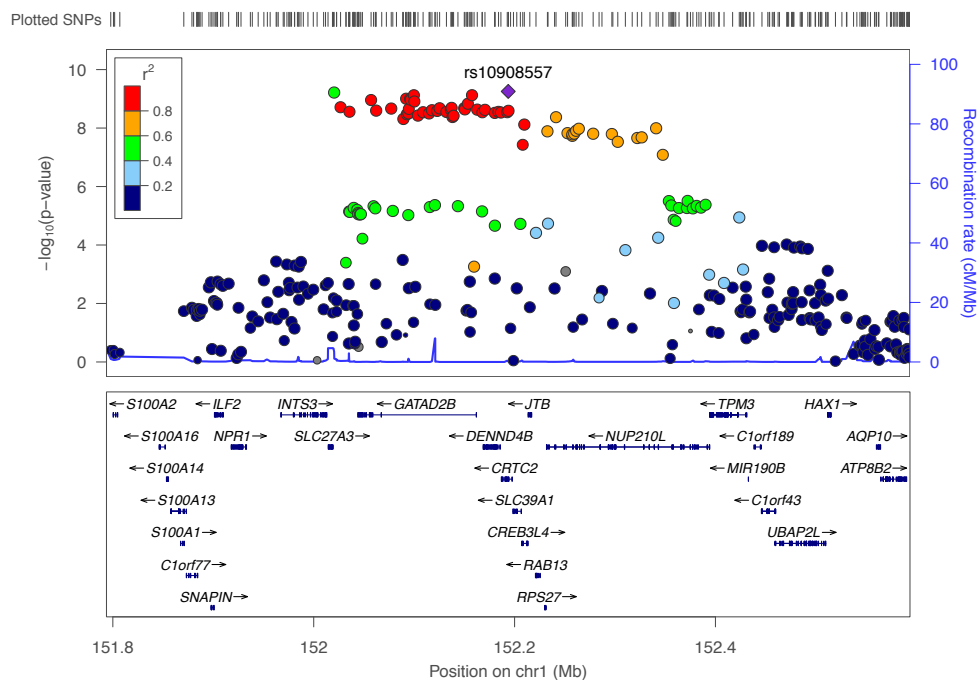
1 **Supplementary Figure 3. Trans eQTL effect of rs2777888 is stronger in females as compared to males.** (a) Normalized LAMP2 (located at the X  
2 chromosome) expression is strongly associated with rs2777888 on chromosome 3 (N=2116, P=2e-016, beta=-0.19), additional analysis shows that this effect  
3 is stronger in females only (b)(N=1153, P=8.78e-15, beta=-0.24) as compared to males (c)(N=963, P=1.76e-4, beta=-0.14) .



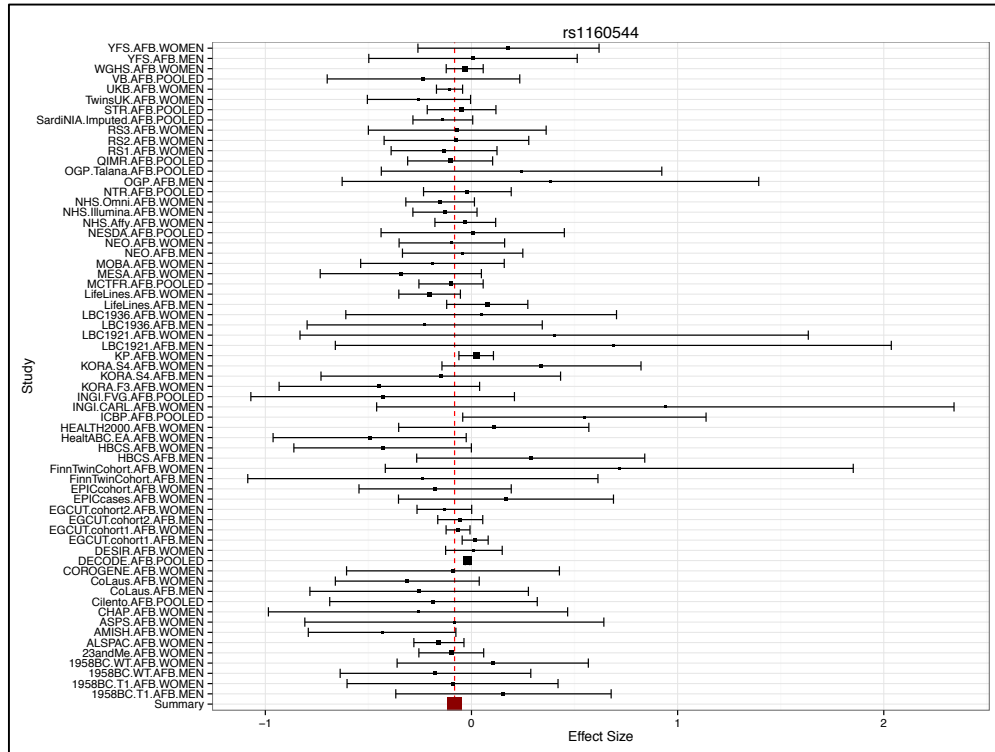
1 **Supplementary Figure 4. Forest plot for *rs10908557* (chr1:153927052), a**  
2 **genome-wide significant SNP for AFB pooled.** The black lines represent 95%  
3 confidence intervals of the effect size estimates. The black rectangles are proportional  
4 to the square-root of the sample size. The red rectangle represents the meta-analysis  
5 estimate.



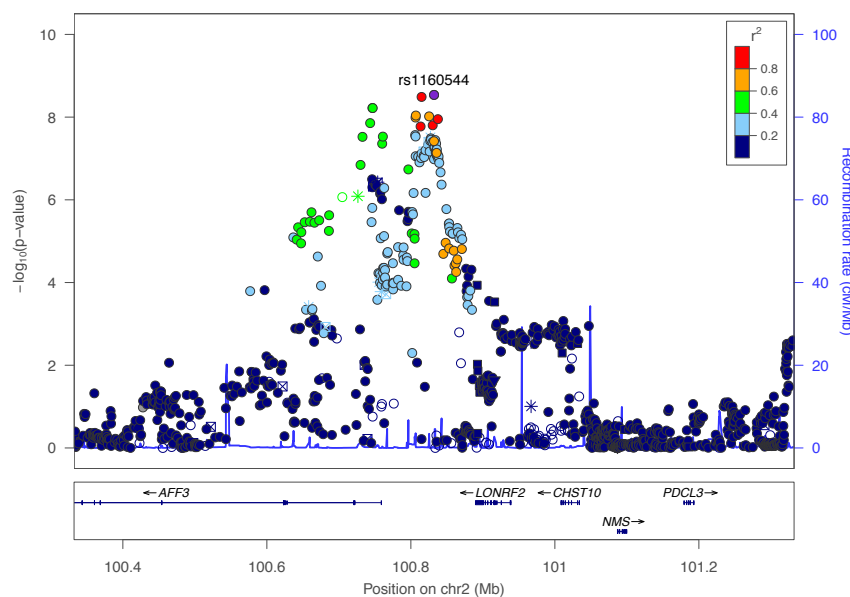
6  
7 **Supplementary Figure 5. Regional association plot of *rs10908557***  
8 **(chr1:153927052), a genome-wide significant SNP for AFB pooled.** The  $R^2$  values  
9 are from the h19/1000 Genomes Nov 2014 EUR reference samples. The figure was  
10 created with LocusZoom (<http://csg.sph.unimch.edu/locuszoom/>). Mb, megabases.



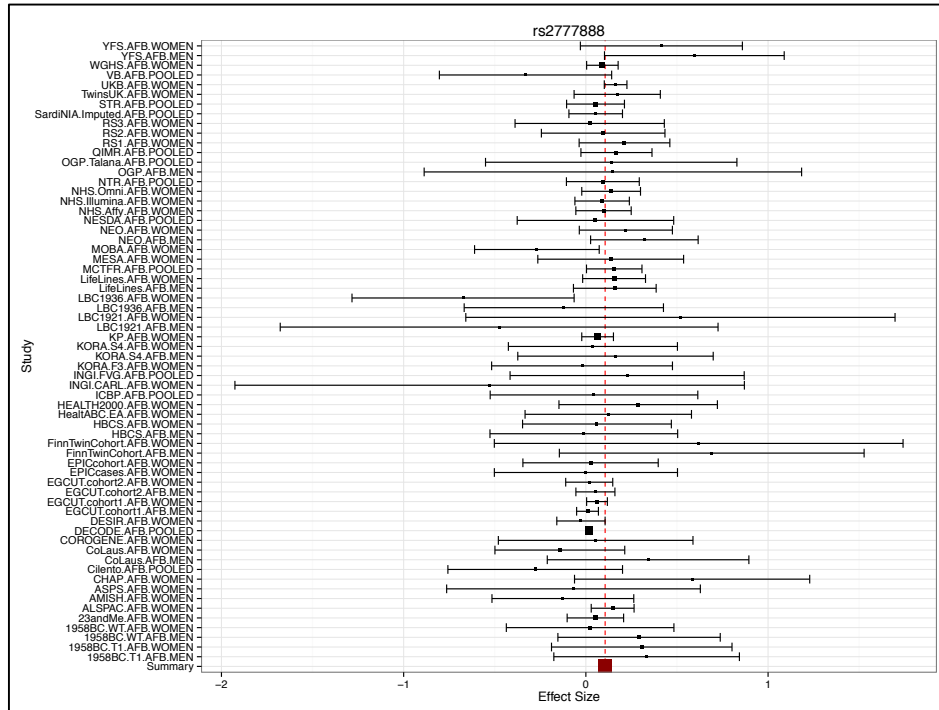
1 **Supplementary Figure 6. Forest plot for *rs1160544* (chr2:100832218), a genome-**  
2 **wide significant SNP for AFB pooled.** The black lines represent 95% confidence  
3 intervals of the effect size estimates. The black rectangles are proportional to the  
4 square-root of the sample size. The red rectangle represents the meta-analysis  
5 estimate.



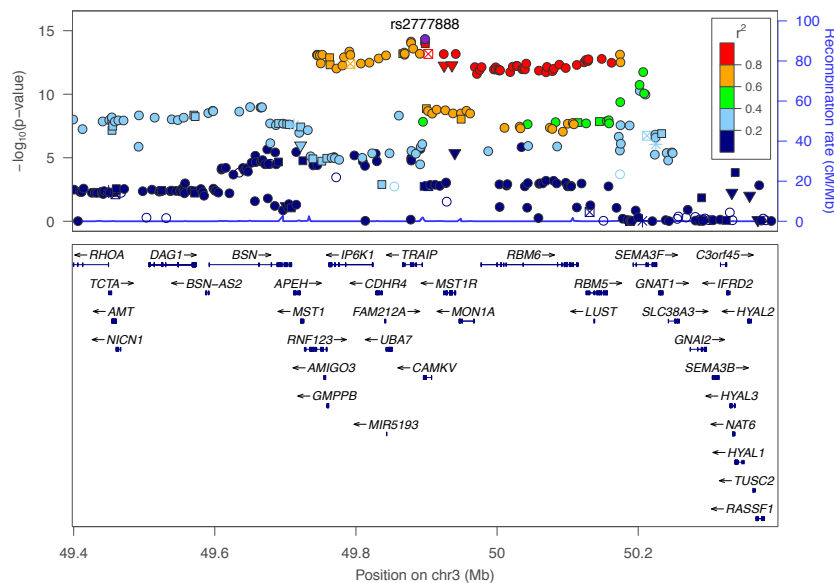
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7 **Supplementary Figure 7. Regional association plot of *rs1160544***  
8 **(chr2:100832218), a genome-wide significant SNP for AFB pooled.** The  $R^2$  values  
9 are from the h19/1000 Genomes Nov 2014 EUR reference samples. The figure was  
10 created with LocusZoom (<http://csg.sph.umich.edu/locuszoom/>). Mb, megabases.



1 **Supplementary Figure 8. Forest plot for *rs2777888* (chr3:4989000), a genome-**  
2 **wide significant SNP for AFB pooled.** The black lines represent 95% confidence  
3 intervals of the effect size estimates. The black rectangles are proportional to the  
4 square-root of the sample size. The red rectangle represents the meta-analysis  
5 estimate.

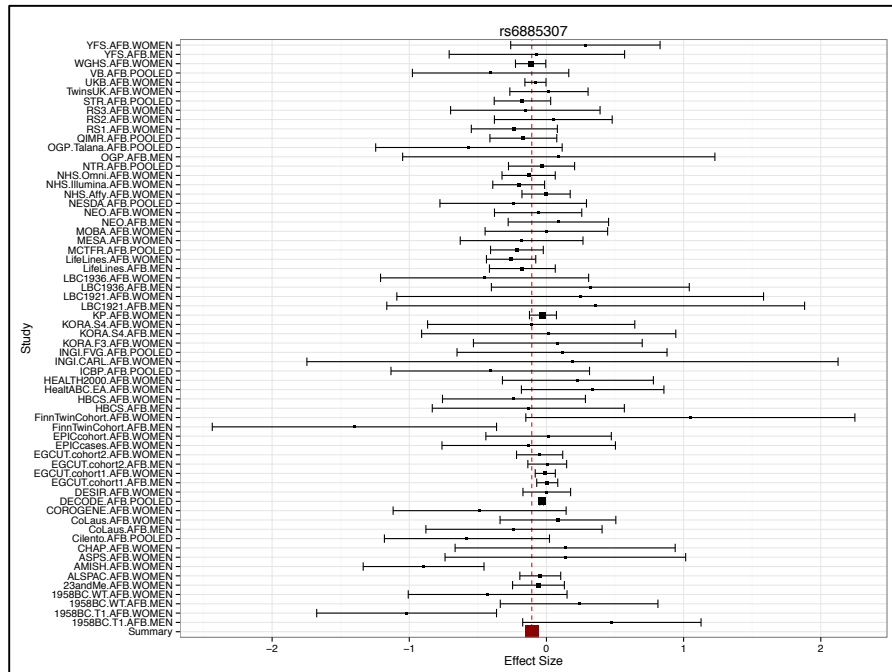


6  
7 **Supplementary Figure 9. Regional association plot of *rs2777888* (chr3:4989000),**  
8 **a genome-wide significant SNP for AFB pooled.** The  $R^2$  values are from the  
9 h19/1000 Genomes Nov 2014 EUR reference samples. The figure was created with  
10 LocusZoom (<http://csg.sph.unimch.edu/locuszoom/>). Mb, megabases.

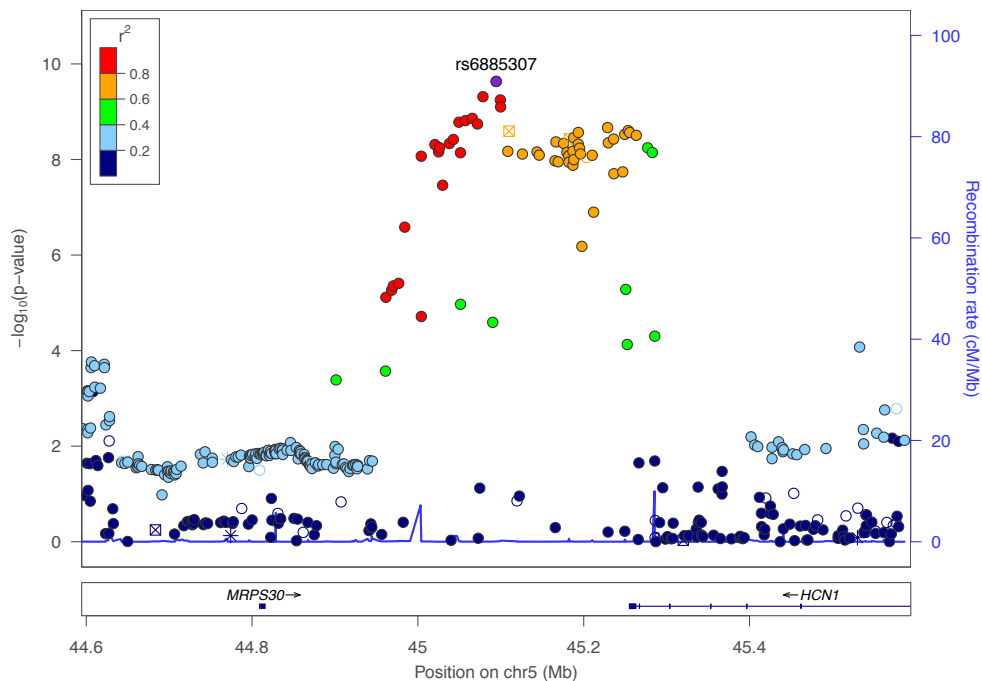


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12

1 **Supplementary Figure 10. Forest plot for *rs6885307* (chr5:45094503), a genome-**  
2 **wide significant SNP for AFB pooled.** The black lines represent 95% confidence  
3 intervals of the effect size estimates. The black rectangles are proportional to the  
4 square-root of the sample size. The red rectangle represents the meta-analysis  
5 estimate.

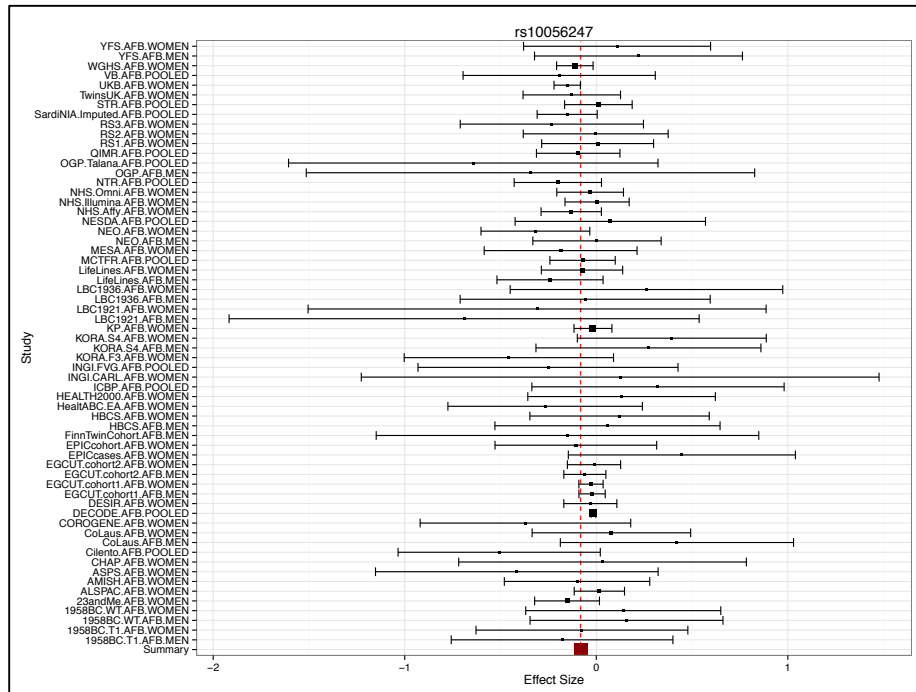


6  
7 **Supplementary Figure 11. Regional association plot of *rs6885307***  
8 **(chr5:45094503), a genome-wide significant SNP for AFB pooled.** The  $R^2$  values  
9 are from the h19/1000 Genomes Nov 2014 EUR reference samples. The figure was  
10 created with LocusZoom (<http://csg.sph.unimch.edu/locuszoom/>). Mb, megabases.

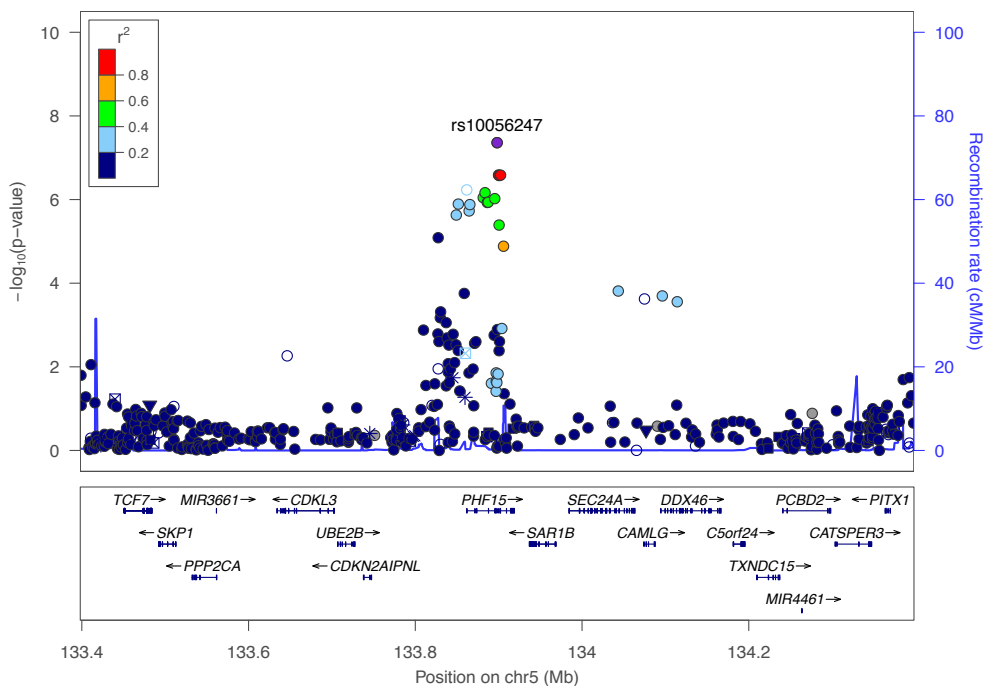


11

1 **Supplementary Figure 12. Forest plot for *rs10056247* (chr5:133898136), a**  
2 **genome-wide significant SNP for AFB pooled.** The black lines represent 95%  
3 confidence intervals of the effect size estimates. The black rectangles are proportional  
4 to the square-root of the sample size. The red rectangle represents the meta-analysis  
5 estimate.

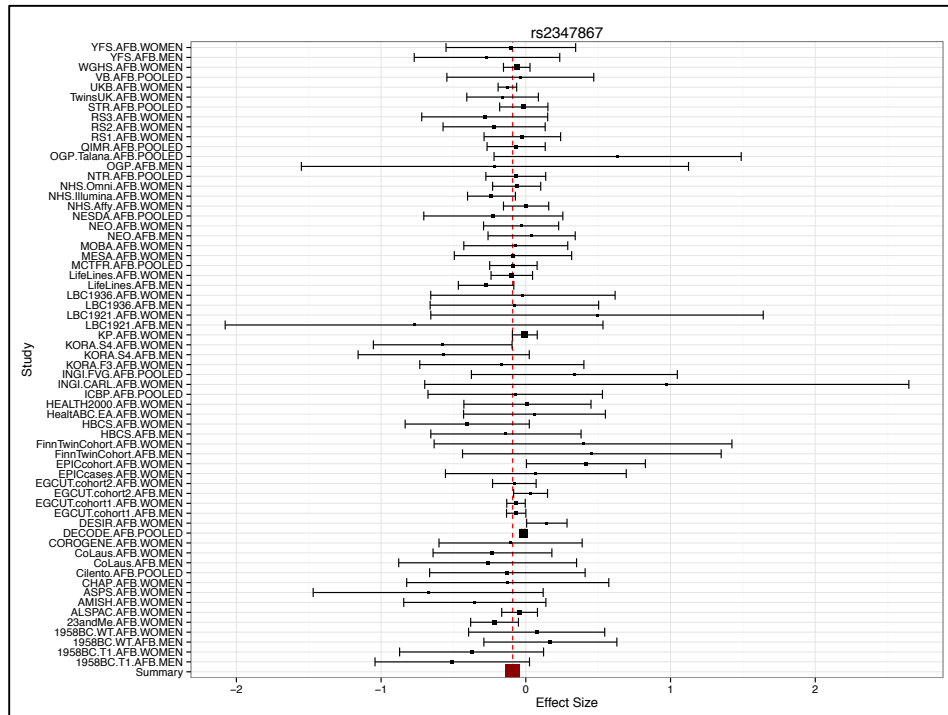


6  
7 **Supplementary Figure 13. Regional association plot of *rs10056247***  
8 **(chr5:133898136), a genome-wide significant SNP for AFB pooled.** The  $R^2$  values  
9 are from the h19/1000 Genomes Nov 2014 EUR reference samples. The figure was  
10 created with LocusZoom (<http://csg.sph.unimch.edu/locuszoom/>). Mb, megabases.

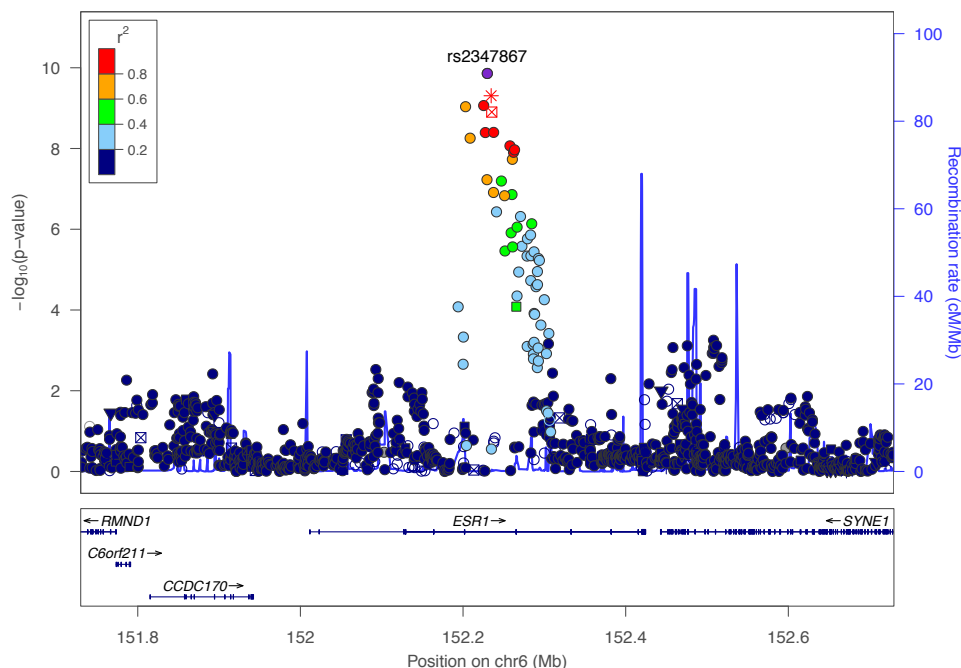




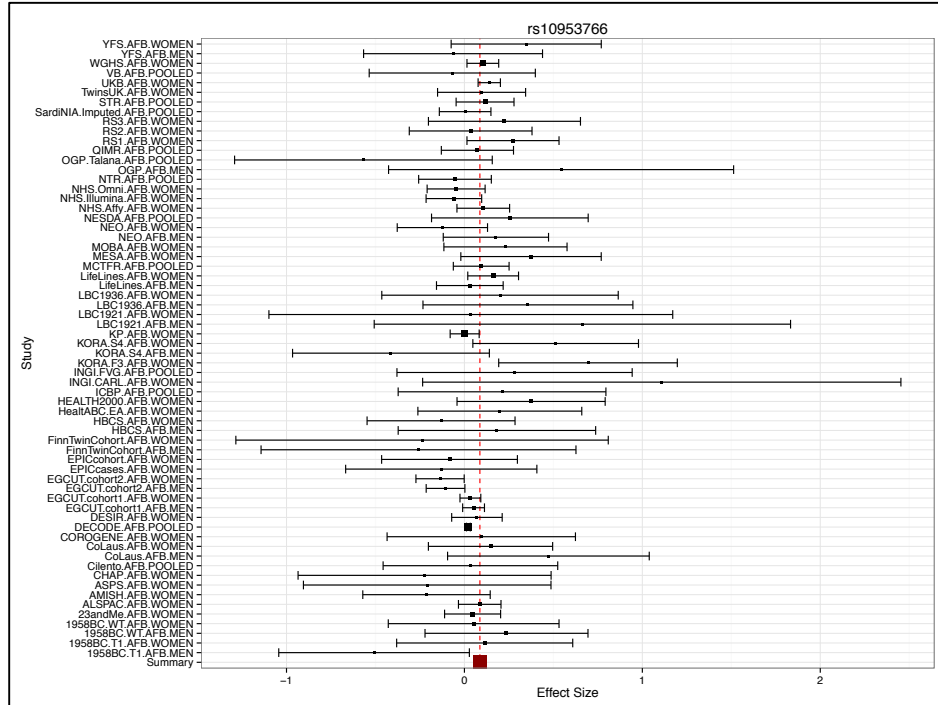
- 1 **Supplementary Figure 14. Forest plot for *rs2347867* (chr6:152229850), a**
- 2 **genome-wide significant SNP for AFB pooled.** The black lines represent 95%
- 3 confidence intervals of the effect size estimates. The black rectangles are proportional
- 4 to the square-root of the sample size. The red rectangle represents the meta-analysis
- 5 estimate.



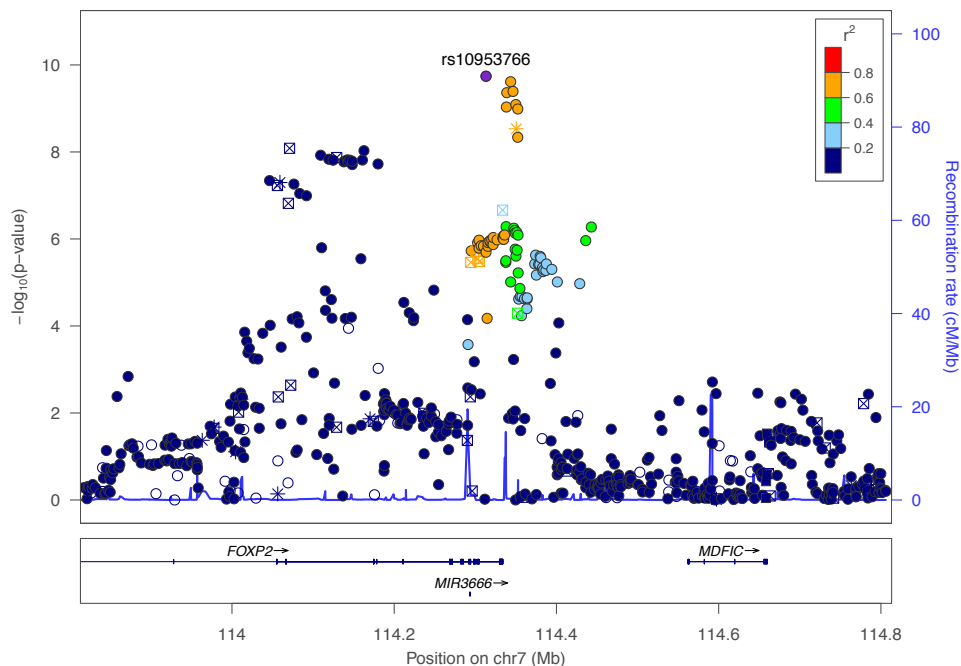
- 6
- 7 **Supplementary Figure 15. Regional association plot of *rs2347867***
- 8 **(chr6:152229850), a genome-wide significant SNP for AFB pooled.** The  $R^2$  values
- 9 are from the h19/1000 Genomes Nov 2014 EUR reference samples. The figure was
- 10 created with LocusZoom (<http://csg.sph.unimch.edu/locuszoom/>). Mb, megabases.



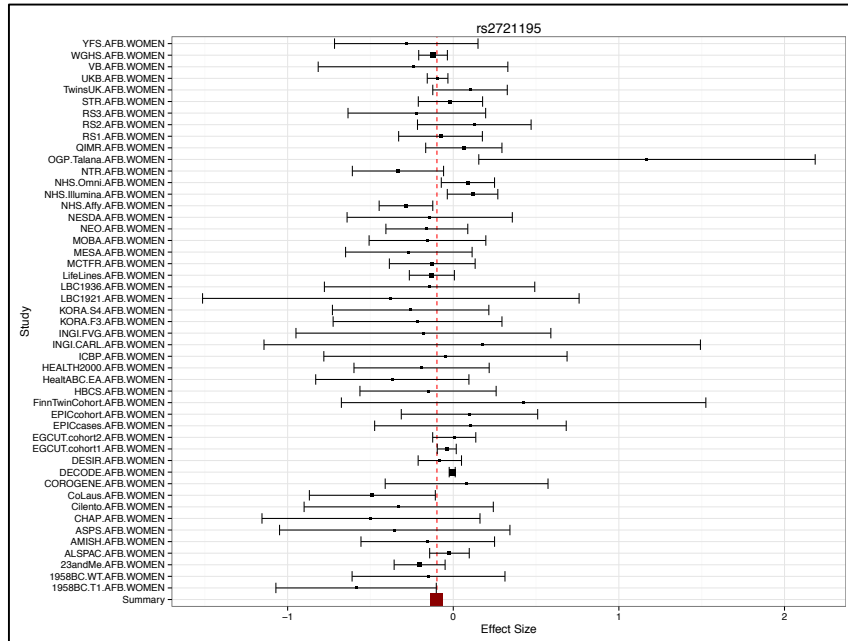
- 1 **Supplementary Figure 16. Forest plot for *rs10953776* (chr7:114313218), a**
- 2 **genome-wide significant SNP for AFB pooled.** The black lines represent 95%
- 3 confidence intervals of the effect size estimates. The black rectangles are proportional
- 4 to the square-root of the sample size. The red rectangle represents the meta-analysis
- 5 estimate.



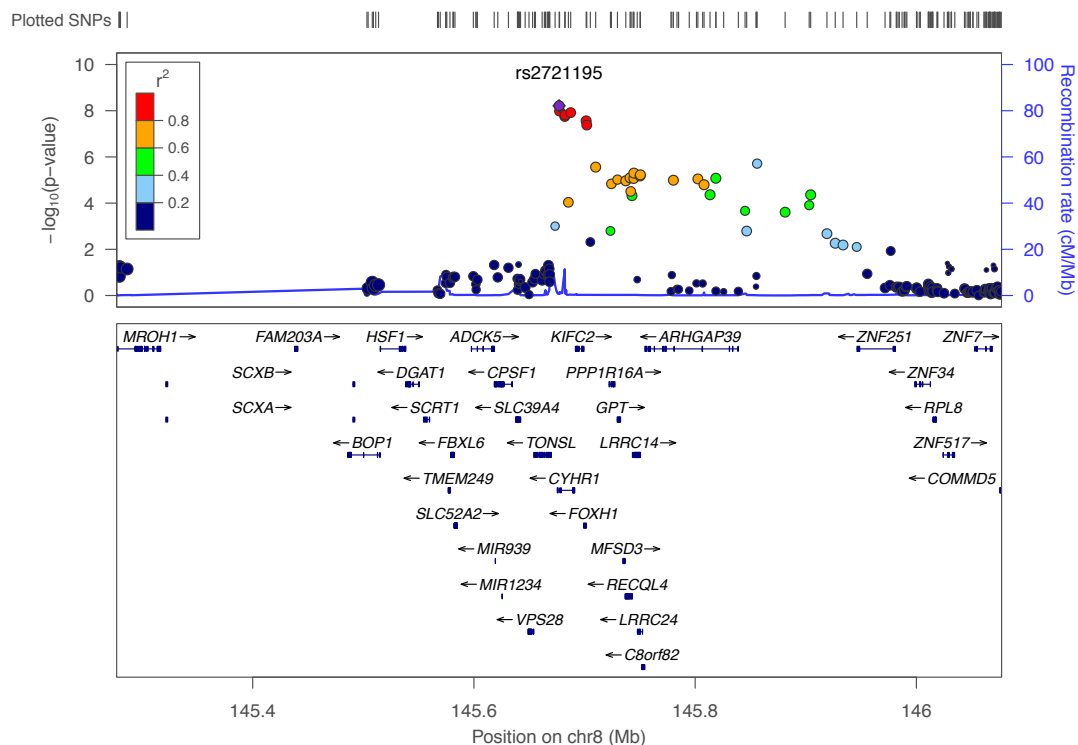
- 6
- 7 **Supplementary Figure 17. Regional association plot of *rs10953776***
- 8 **(chr7:114313218), a genome-wide significant SNP for AFB pooled.** The  $R^2$  values
- 9 are from the h19/1000 Genomes Nov 2014 EUR reference samples. The figure was
- 10 created with LocusZoom (<http://csg.sph.unimch.edu/locuszoom/>). Mb, megabases.



1 **Supplementary Figure 18. Forest plot for *rs2721195* (chr8:145677011), a**  
2 **genome-wide significant SNP for AFB women.** The black lines represent 95%  
3 confidence intervals of the effect size estimates. The black rectangles are proportional  
4 to the square-root of the sample size. The red rectangle represents the meta-analysis  
5 estimate.

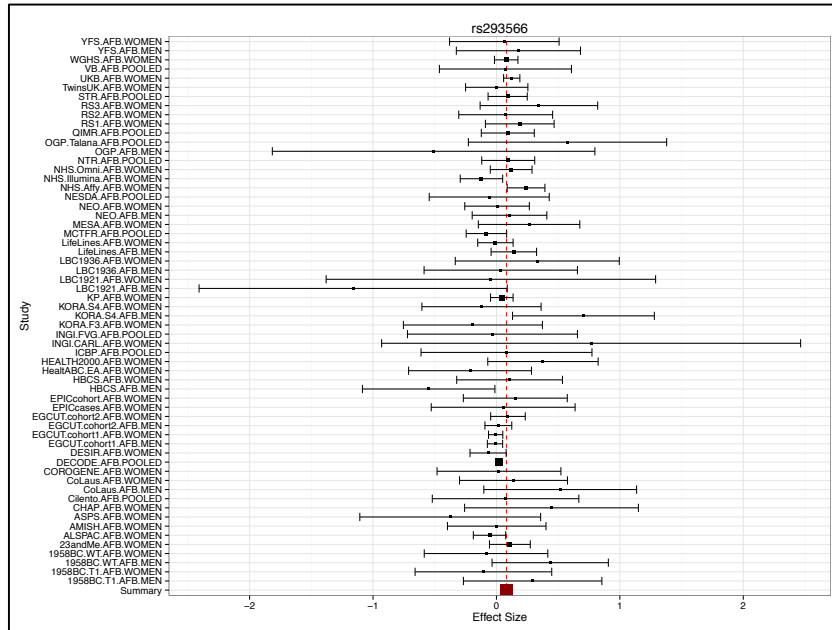


6  
7 **Supplementary Figure 19. Regional association plot of *rs2721195***  
8 **(chr8:145677011), a genome-wide significant SNP for AFB women.** The  $R^2$  values  
9 are from the h19/1000 Genomes Nov 2014 EUR reference samples. The figure was  
10 created with LocusZoom (<http://csg.sph.unimch.edu/locuszoom/>). Mb, megabases.

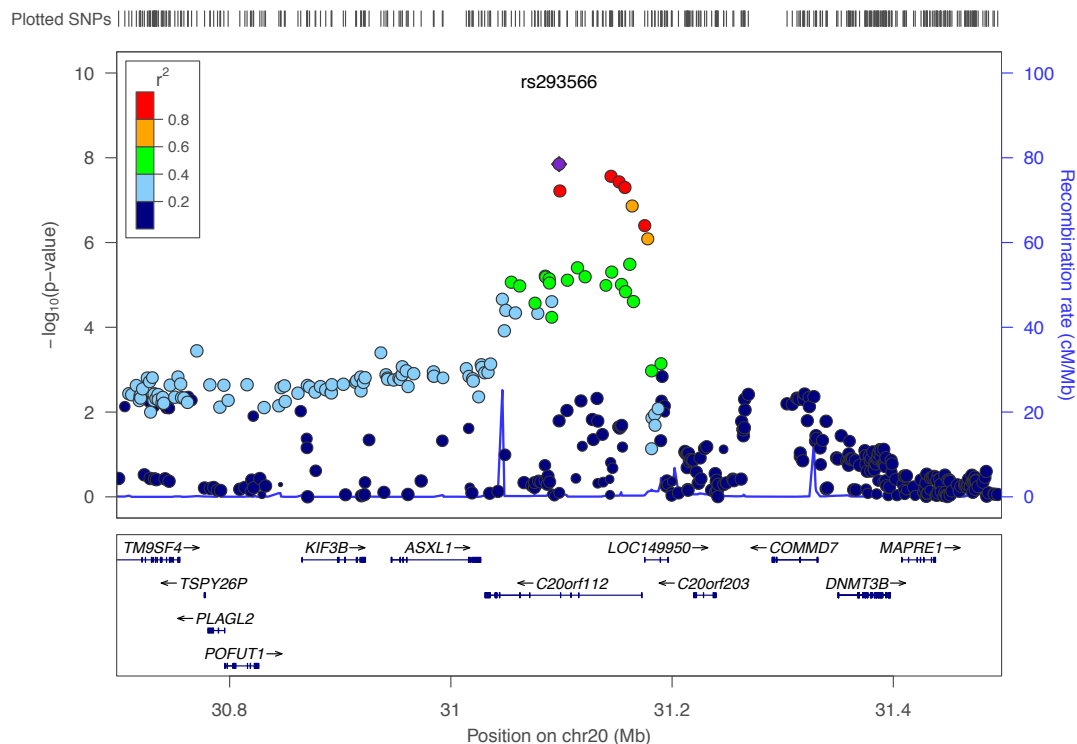


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- 1 **Supplementary Figure 20. Forest plot for *rs293566* (chr20:31097877), a genome-**
- 2 **wide significant SNP for AFB pooled.** The black lines represent 95% confidence
- 3 intervals of the effect size estimates. The black rectangles are proportional to the
- 4 square-root of the sample size. The red rectangle represents the meta-analysis
- 5 estimate.

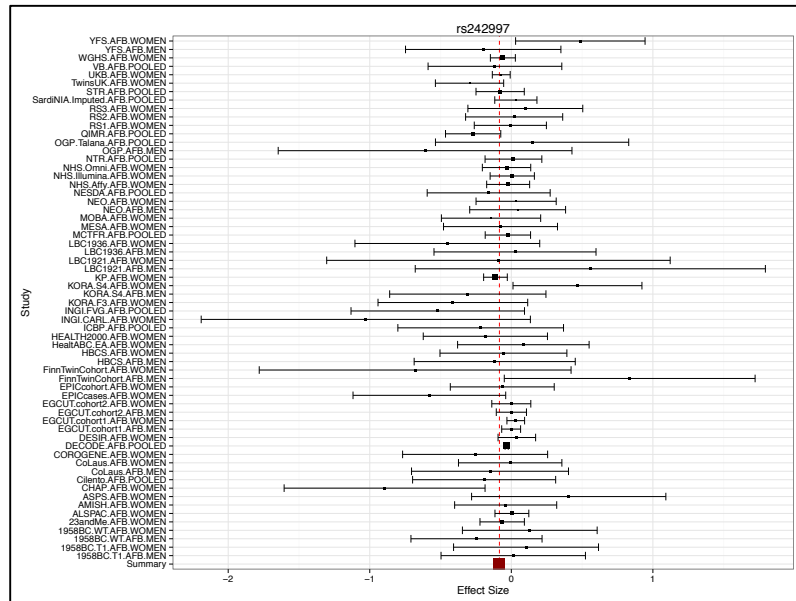


- 6
- 7 **Supplementary Figure 21. Regional association plot of *rs293566***
- 8 **(chr20:31097877), a genome-wide significant SNP for AFB women.** The  $R^2$  values
- 9 are from the h19/1000 Genomes Nov 2014 EUR reference samples. The figure was
- 10 created with LocusZoom (<http://csg.sph.unimch.edu/locuszoom/>). Mb, megabases.

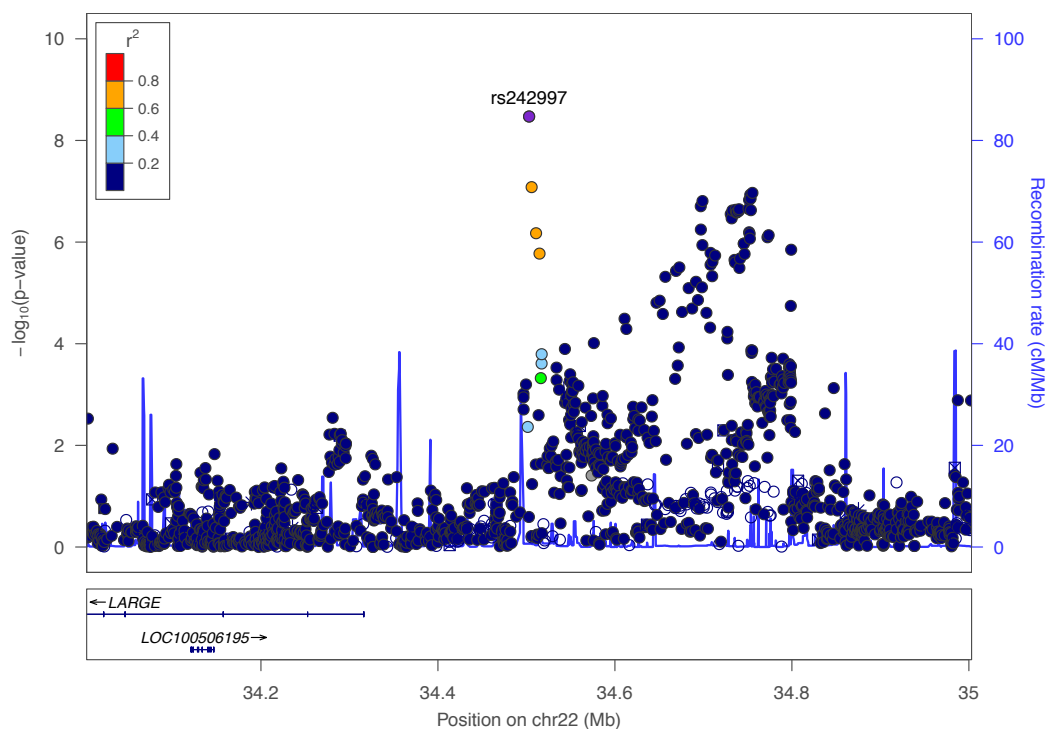


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**Supplementary Figure 22. Forest plot for *rs242997* (chr22:34503059), a genome-wide significant SNP for AFB pooled.** The black lines represent 95% confidence intervals of the effect size estimates. The black rectangles are proportional to the square-root of the sample size. The red rectangle represents the meta-analysis estimate.



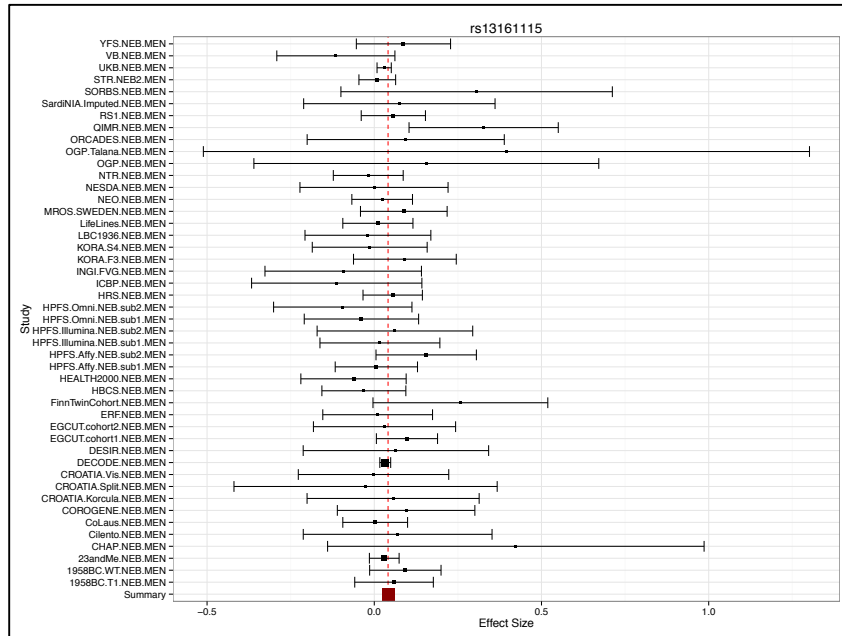
**Supplementary Figure 23. Regional association plot of *rs242997* (chr22:34503059), a genome-wide significant SNP for AFB women.** The  $R^2$  values are from the h19/1000 Genomes Nov 2014 EUR reference samples. The figure was created with LocusZoom (<http://csg.sph.unimch.edu/locuszoom/>). Mb, megabases.





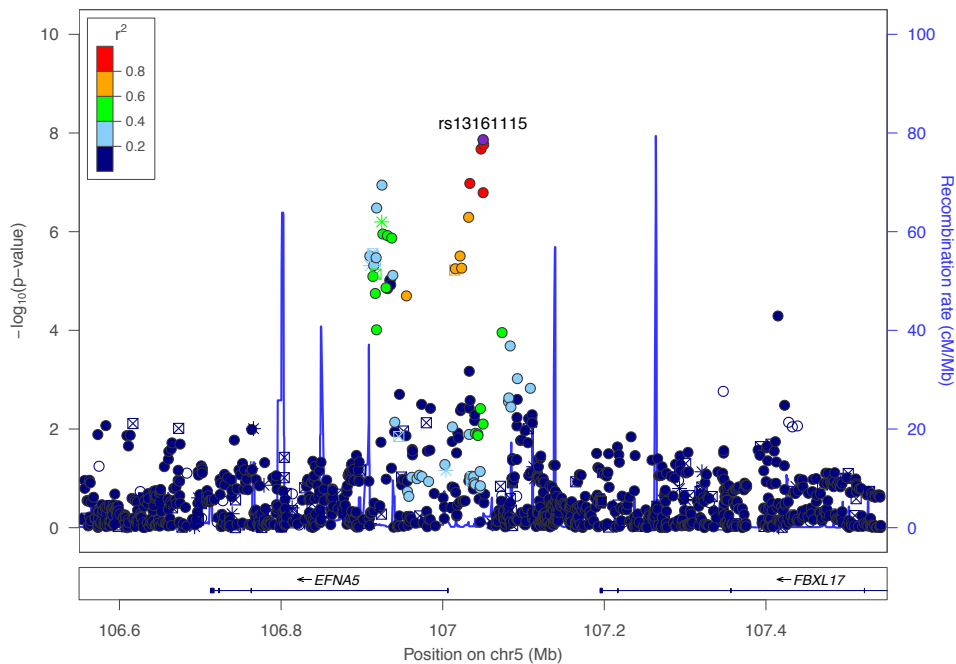
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2 **Supplementary Figure 26. Forest plot for *rs13161115* (chr5:107050002), a**  
 3 **genome-wide significant SNP for NEB men.** The black lines represent 95%  
 4 confidence intervals of the effect size estimates. The black rectangles are proportional  
 5 to the square-root of the sample size. The red rectangle represents the meta-analysis  
 6 estimate.



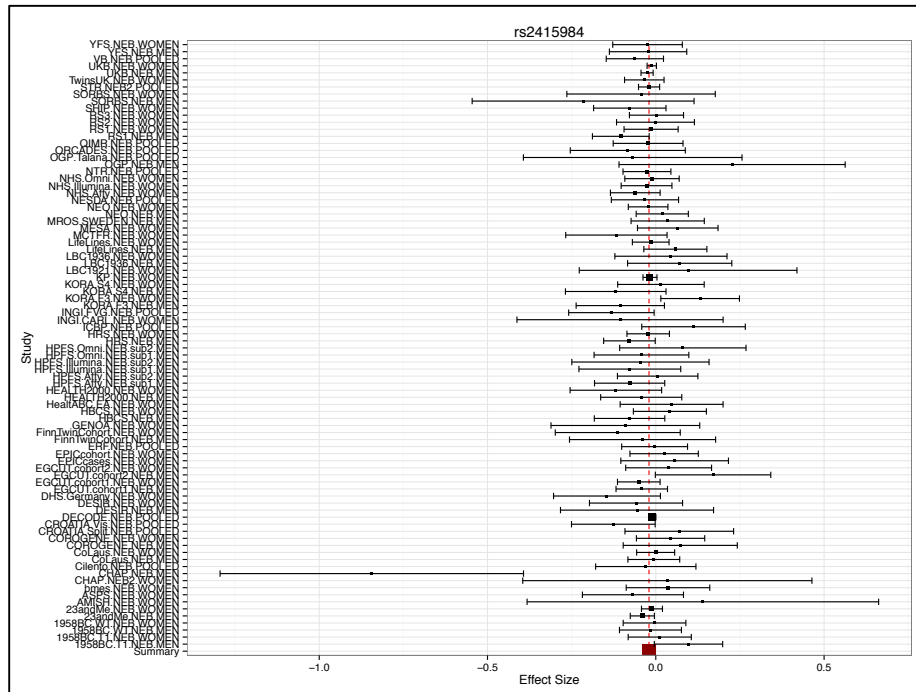
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8 **Supplementary Figure 27. Regional association plot of for *rs13161115***  
 9 **(chr5:107050002), a genome-wide significant SNP for NEB men.** The  $R^2$  values are  
 10 from the h19/1000 Genomes Nov 2014 EUR reference samples. The figure was  
 11 created with LocusZoom (<http://csg.sph.unimch.edu/locuszoom/>). Mb, megabases.

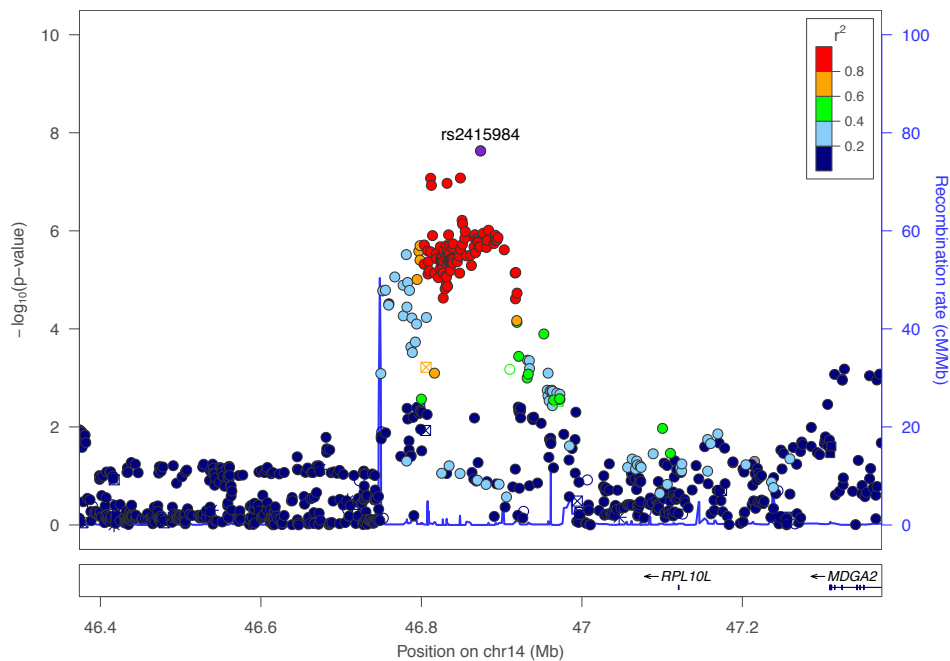


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1 **Supplementary Figure 28. Forest plot for *rs2415984* (chr14:46873776), a**  
2 **genome-wide significant SNP for NEB pooled.** The black lines represent 95%  
3 confidence intervals of the effect size estimates. The black rectangles are proportional  
4 to the square-root of the sample size. The red rectangle represents the meta-analysis  
5 estimate.



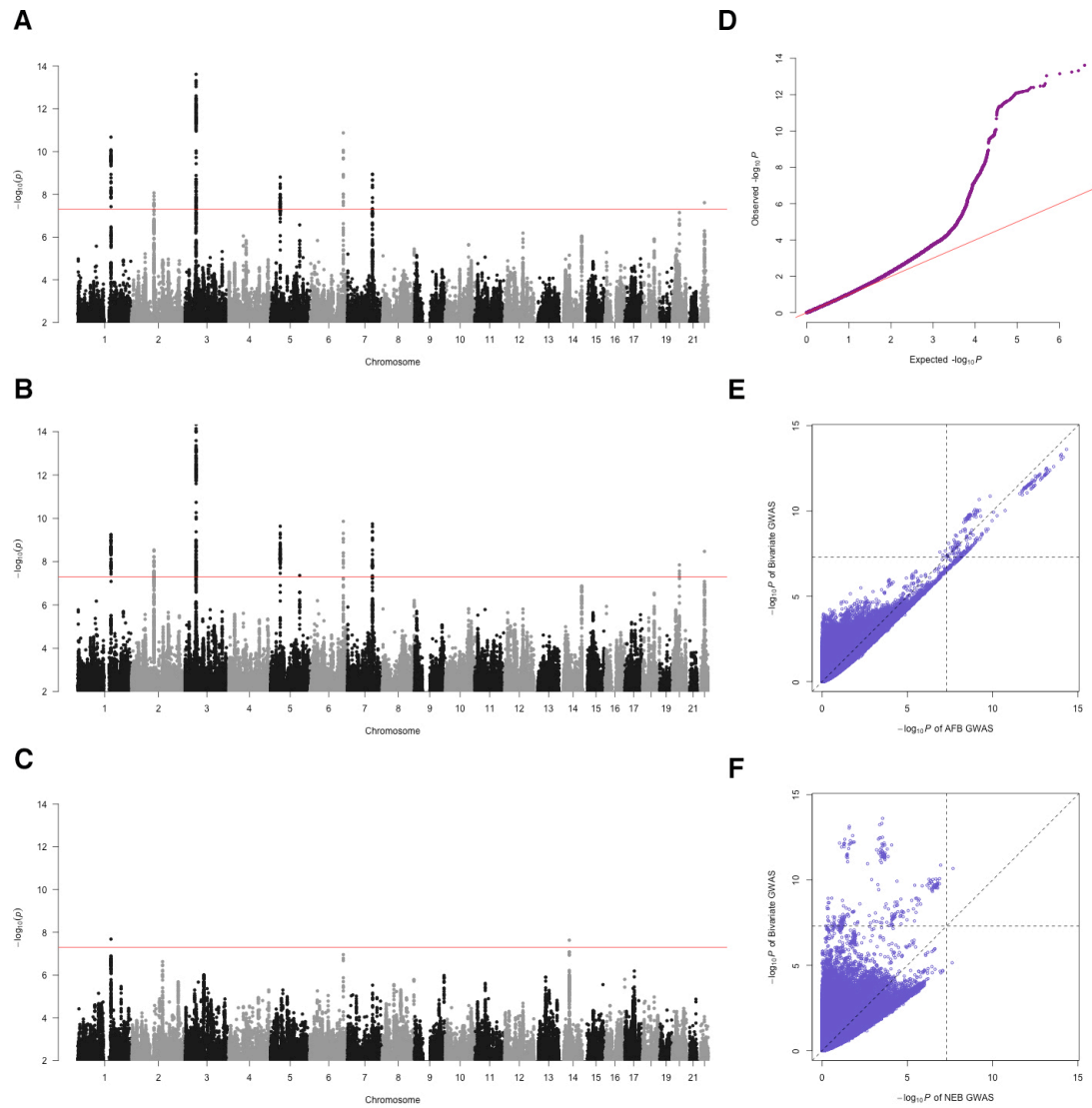
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7 **Supplementary Figure 29. Regional association plot of for *rs2415984***  
8 **(chr14:46873776), a genome-wide significant SNP for NEB pooled.** The  $R^2$  values  
9 are from the h19/1000 Genomes Nov 2014 EUR reference samples. The figure was  
10 created with LocusZoom (<http://csg.sph.unimch.edu/locuszoom/>). Mb, megabases.



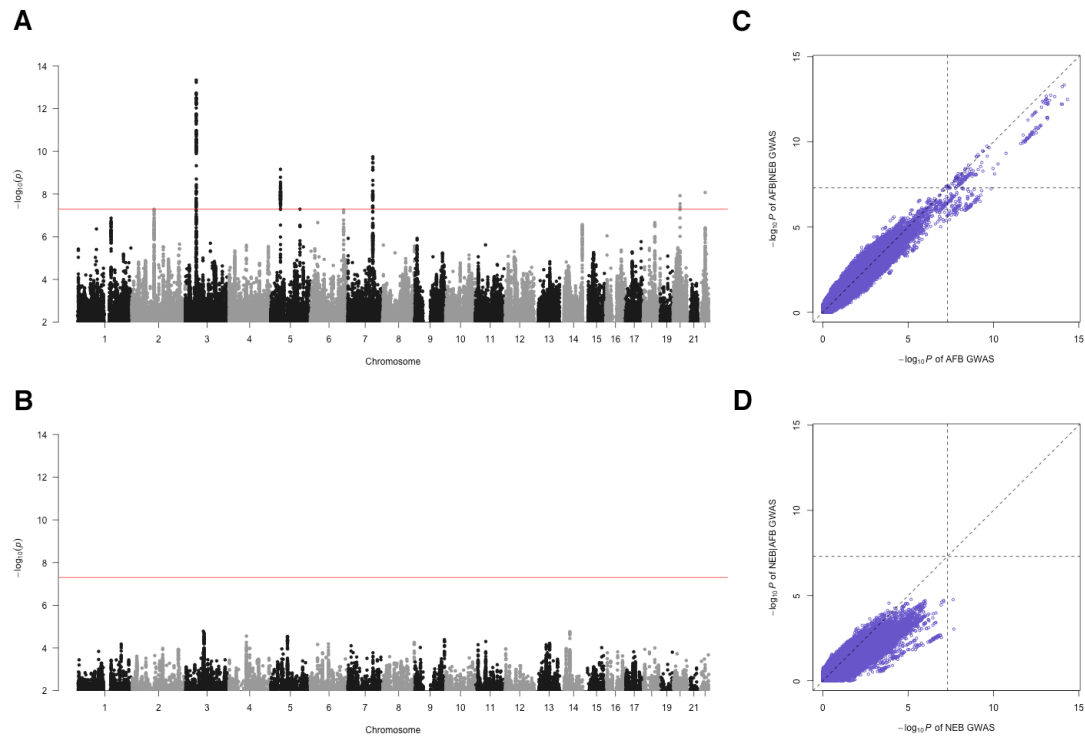
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1  
2 **Supplementary Figure 30. Bivariate analysis of the two fertility-related traits,**  
3 **comparing to each of the single trait analysis.** (A) Manhattan plot of the joint GWA  
4 analysis; (B) Manhattan plot of AFB single-trait GWA analysis; (C) Manhattan plot  
5 of NEB single-trait GWA analysis; (D) Quantile-quantile plot of the  $-\log_{10}P$  values in  
6 the bivariate analysis; (E) Comparison of the AFB  $-\log_{10}P$  values to the bivariate -  
7  $\log_{10}P$  values; (F) Comparison of the NEB  $-\log_{10}P$  values to the bivariate  $-\log_{10}P$   
8 values.

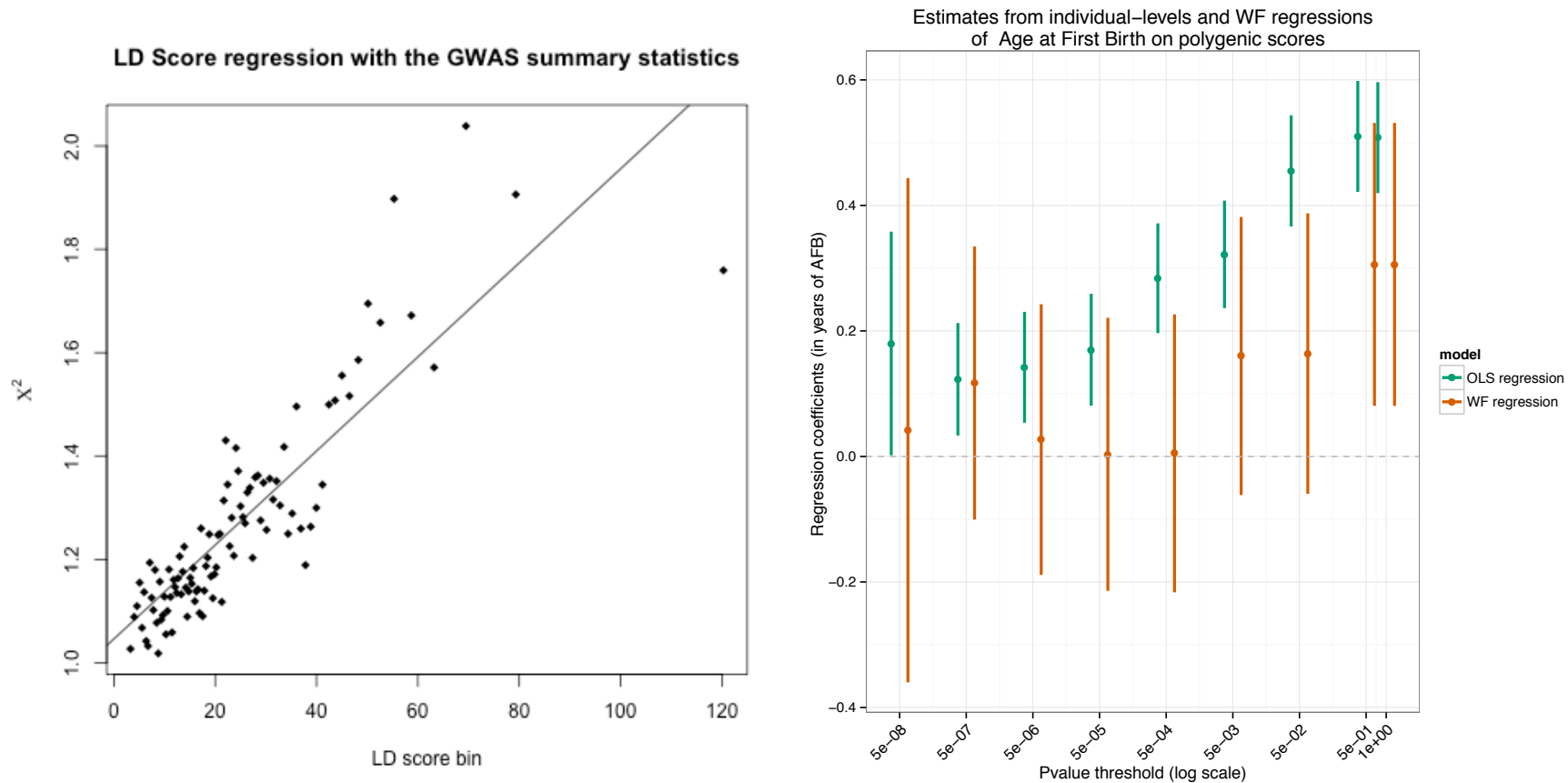


1 **Supplementary Figure 31. Conditional analysis of the two fertility-related traits,**  
2 **comparing to each of the single trait analysis. (A) Manhattan plot of the AFB**  
3 **adjusted for NEB GWA analysis; (B) Manhattan plot of NEB adjusted for AFB GWA**  
4 **analysis; (C) Comparison of the AFB  $-\log_{10}P$  values to the AFB adjusted for NEB -**  
5  **$\log_{10}P$  values; (D) Comparison of the NEB  $-\log_{10}P$  values to the NEB adjusted for**  
6 **AFB  $-\log_{10}P$  values.**



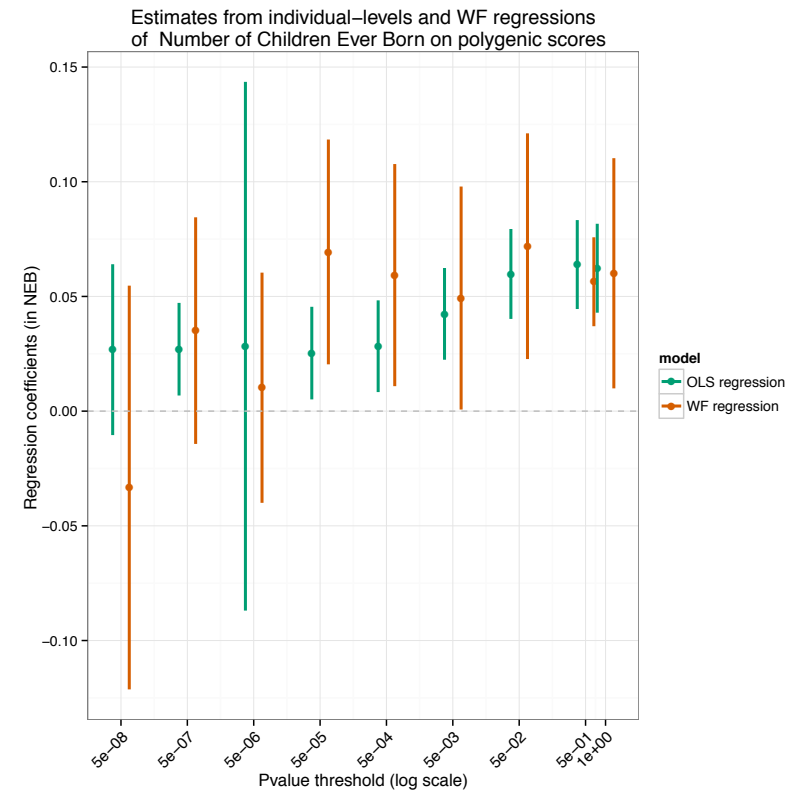
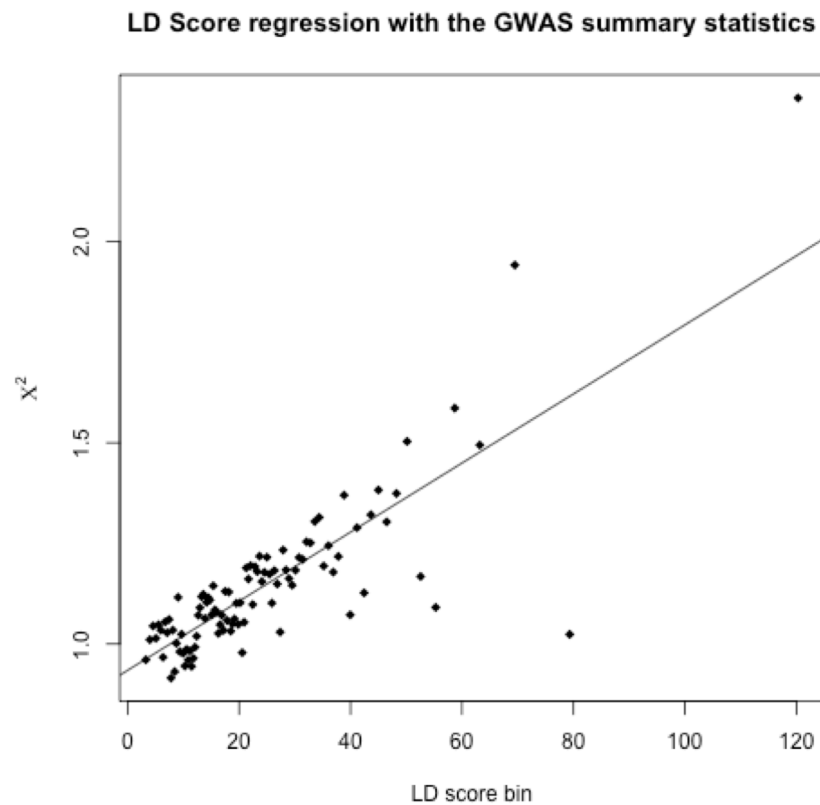
7

- 1 **Supplementary Figure 32. Assessing the extent to which population stratification affects the estimates from the GWAS of age at first**
- 2 **birth. a.** LD score regression plot with the summary results from the AFB GWAS. Each point represents a LD Score percentile for all
- 3 chromosomes. The y-axis represents the average  $\chi^2$  statistics for a given LD score percentile, while the x-axis indicates the average LD score.
- 4 **b.** Estimates and 95% confidence intervals from individual and WF regressions of Age at First Birth (AFB) on polygenic risk scores (PGS), for
- 5 scores constructed with sets of SNPs meeting different P-value thresholds.



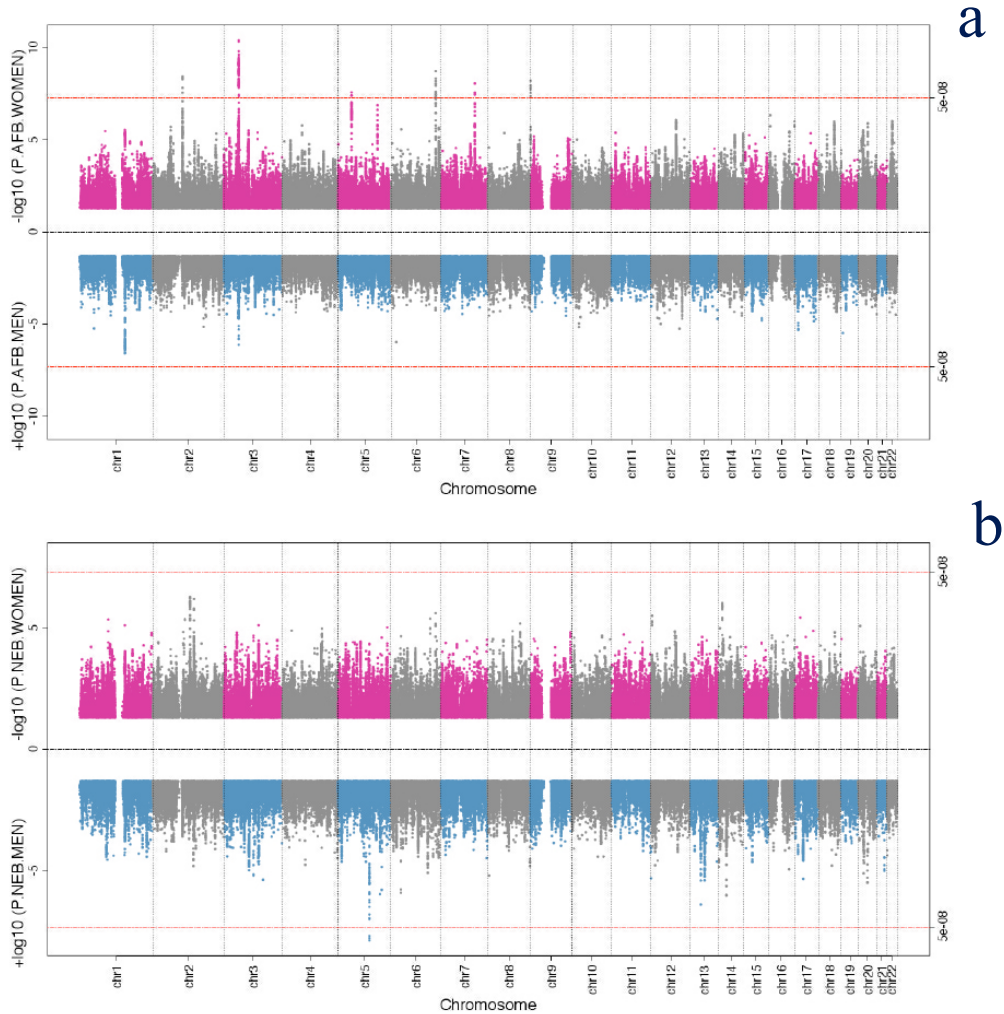
1 **Supplementary Figure 33. Assessing the extent to which population stratification affects the estimates from the GWAS of number of**  
2 **children ever born. a.** LD score regression plot with the summary results from the NEB GWAS. Each point represents a LD Score percentile  
3 for all chromosomes. The y-axis represents the average  $\chi^2$  statistics for a given LD score percentile, while the x-axis indicates the average LD  
4 score. **b.** Estimates and 95% confidence intervals from individual and WF regressions of number of children ever born (NEB) on polygenic risk  
5 scores (PGS), for scores constructed with sets of SNPs meeting different P-value thresholds.

6



**Figure**

1 **Supplementary Figure 34. Miami plots for AFB and NEB sex-specific single**  
2 **genomic control meta-analysis.** SNPs are plotted on the x-axis according to their  
3 position on each chromosome against association with fertility traits. The top part of  
4 the panel indicates the strength of association in the female sample, the bottom part  
5 indicates the association in the male sample. The solid red lines indicate the threshold  
6 for genome-wide significance ( $p < 5 \times 10^{-8}$ ). Panel a shows the Miami plot for age at  
7 first birth (AFB), panel b indicates the Miami plot for number of children (NEB).

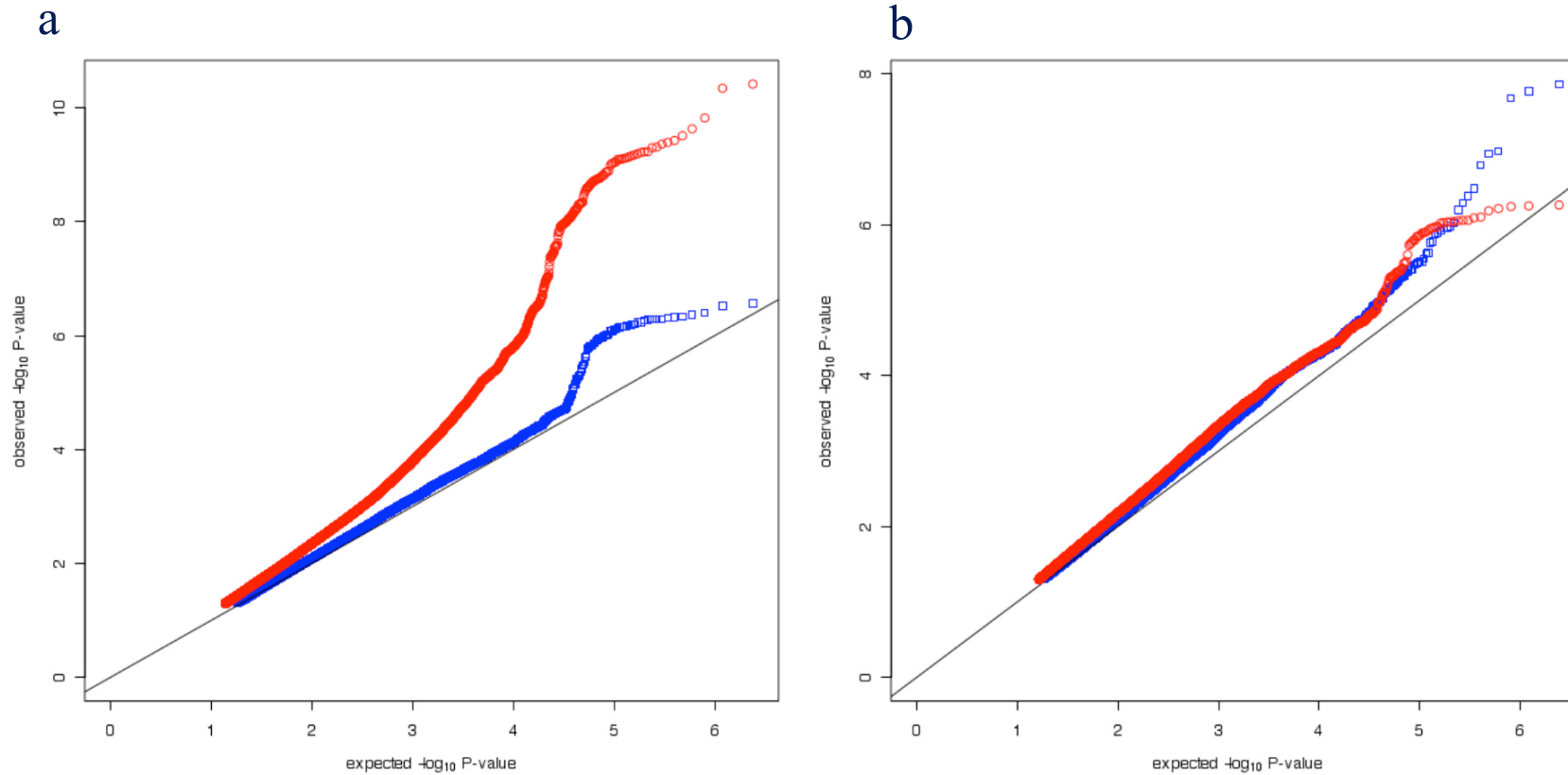


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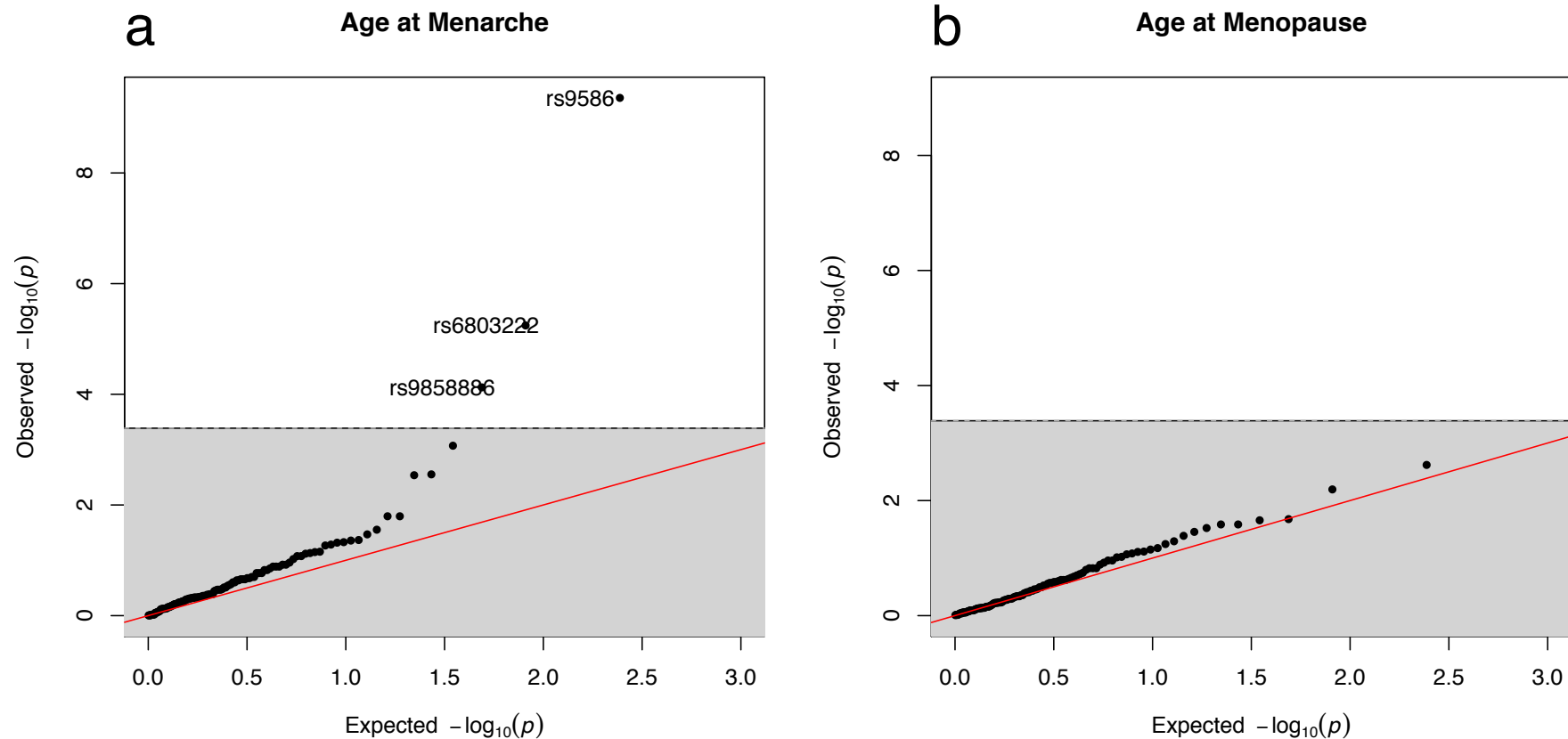
1 **Supplementary Figure 35. Quantile-quantile plots of SNPs for AFB (panel a) and NEB (panel b) in single genomic control, meta-**  
2 **analysis.** The red points indicate the quantiles of the association results among women. The blue points indicate the quantile of the association

3 results among men.

4



- 1 **Supplementary Figure 36. Look-up of female AFB SNPs with  $p < 1 \times 10^{-4}$  for association with age at Menarche and Age at Menopause.**
- 2 **Quantile-quantile plots.** The quasi-replication sample is restricted to non-overlapping cohorts. Panel a shows the look-up for age at menarche.
- 3 The sample size is AFB (N= 100,494) → Age at menarche (N=182,416). Panel b shows the look-up for age at menopause. The sample size is
- 4 AFB (N=106,568) → Age at natural menopause (N= 38,968). SNPs outside the grey area are Bonferroni-corrected significance thresholds that
- 5 correct for the total number of SNPs we tested ( $P < 0.05/122 = 4.10 \times 10^{-4}$ ).



- 1 **Supplementary Figure 37. Comparison of effect size of 10 SNPs associated with AFB in the meta-analysis before and after controlling for**
- 2 **educational attainment and age at first sexual intercourse.** The x-axis indicates the effect size of the association results without controls, the y-axis
- 3 indicates the results after controlling for years of education (EA) and age at first sexual intercourse (AFS). The grey intervals indicate 95% confidence
- 4 intervals on both models. Data are based on UKBiobank, sample size N=50,954.

