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Supplementary information

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APOE-stratified genome-wide association analyses provide insights into the genetic etiology of Alzheimers's disease

In the format provided by the authors and unedited

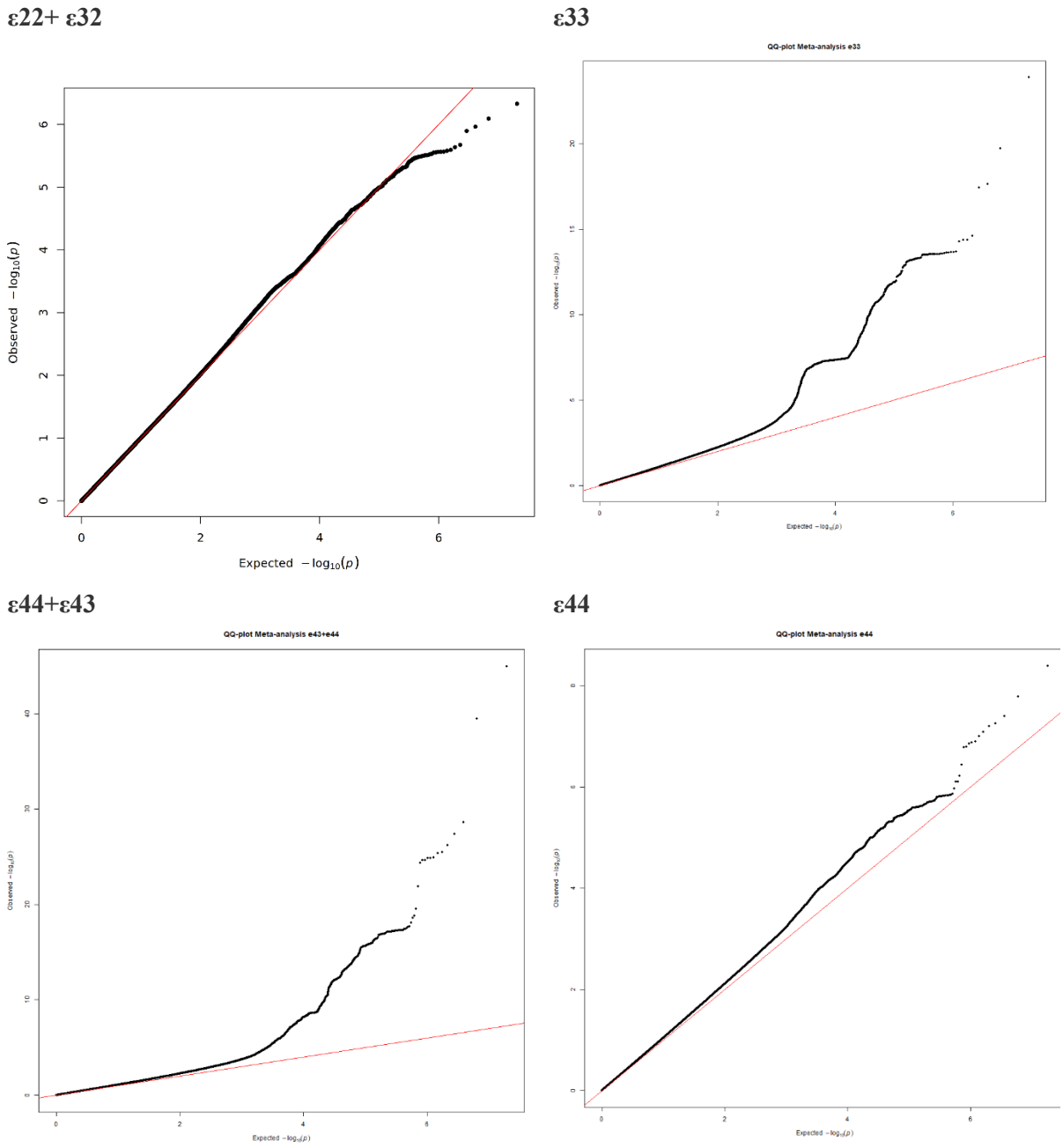
APOE stratified genome-wide association analyses provide insights into the genetic etiology of Alzheimers's disease

Supplementary Figures 1-85

and

Supplementary Note

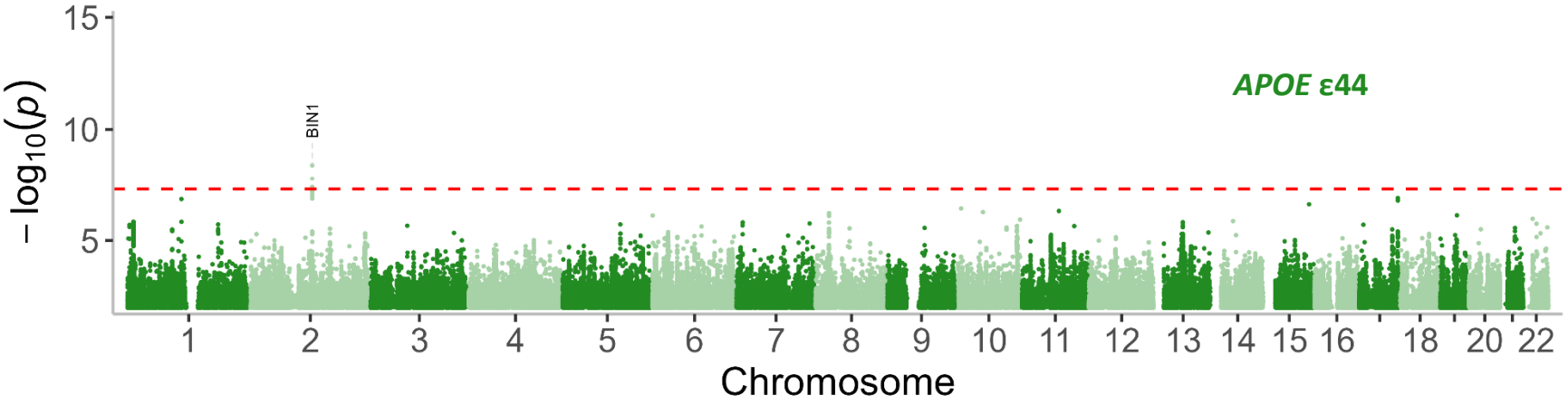
Supplementary Figure 1



Supplementary Figure 1: QQ-plots of *APOE* stratified GWAS meta-analysis

QQ-plots for the respective *APOE* strata for variants MAF>0.01.

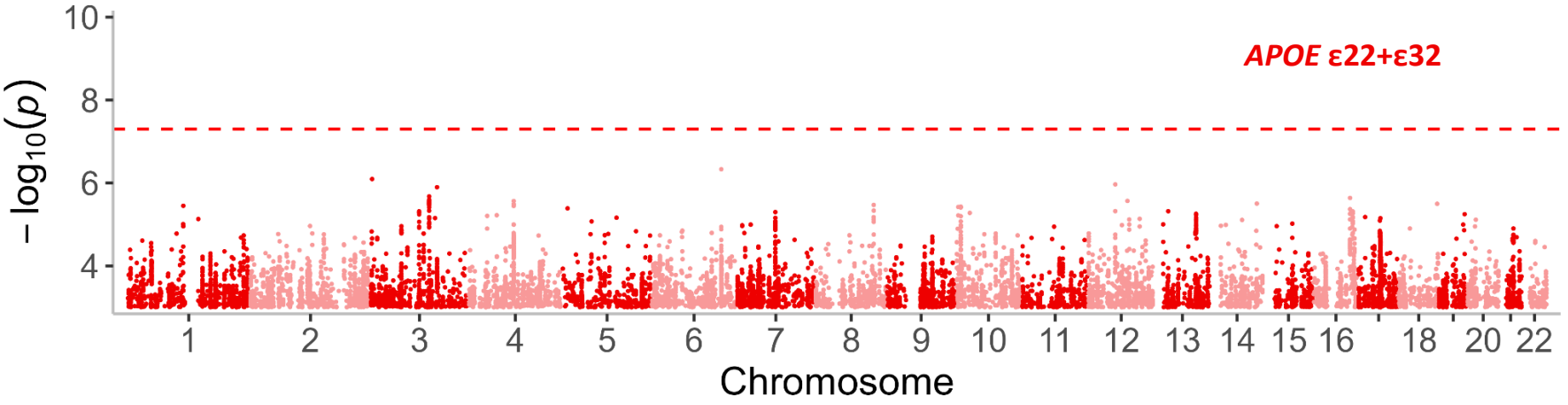
Supplementary Figure 2



Supplementary Figure 2: Manhattan plot of the *APOE* ε44 strata.

Genome wide significant loci are annotated with nearest gene (known loci in black and new in red). Two-sided raw P-values were derived from a fixed-effect meta-analysis. The red dashed line shows the genome-wide significance level ($P=2.5\times10^{-8}$). *APOE*: Apolipoprotein E gene.

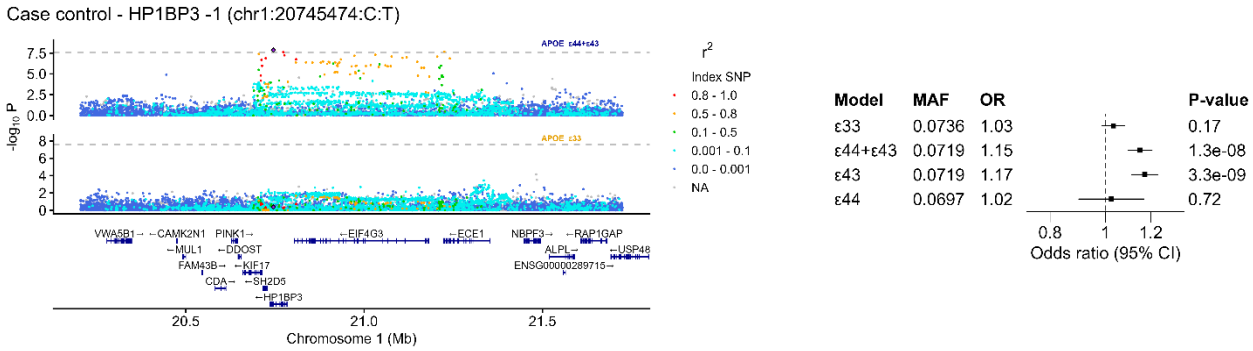
Supplementary Figure 3



Supplementary Figure 3: Manhattan plot of the *APOE* ε22+ε32 strata.

Two-sided raw P-values were derived from a fixed-effect meta-analysis. The red dashed line shows the genome-wide significance level ($P=2.5\times10^{-8}$).
APOE: Apolipoprotein E gene.

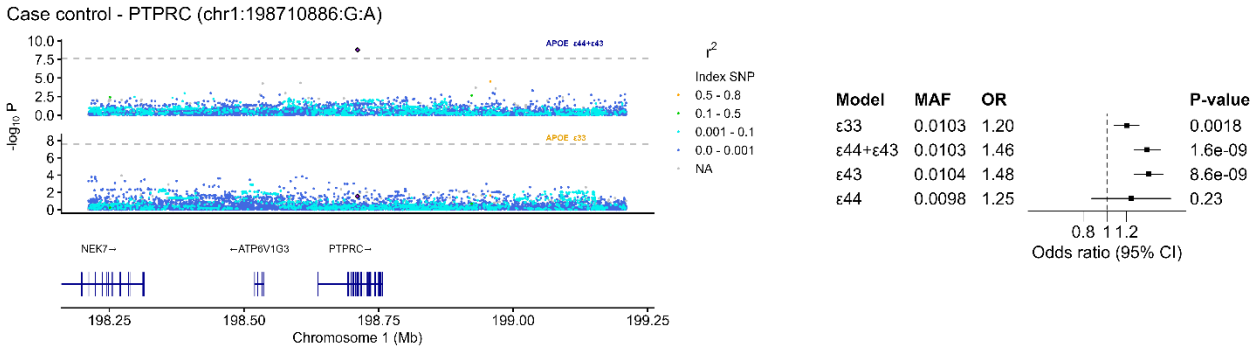
Supplementary Figure 4



Supplementary Figure 4: Loci and forest plot for *HP1BP3*.

Loci plots for *HP1BP3* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *HP1BP3* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

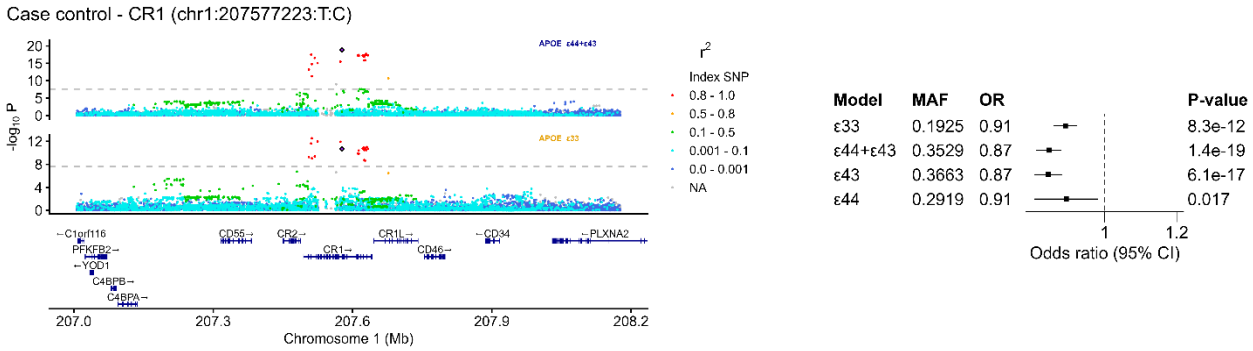
Supplementary Figure 5



Supplementary Figure 5: Loci and forest plot for *PTPRC*.

Loci plots for *PTPRC* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *PTPRC* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

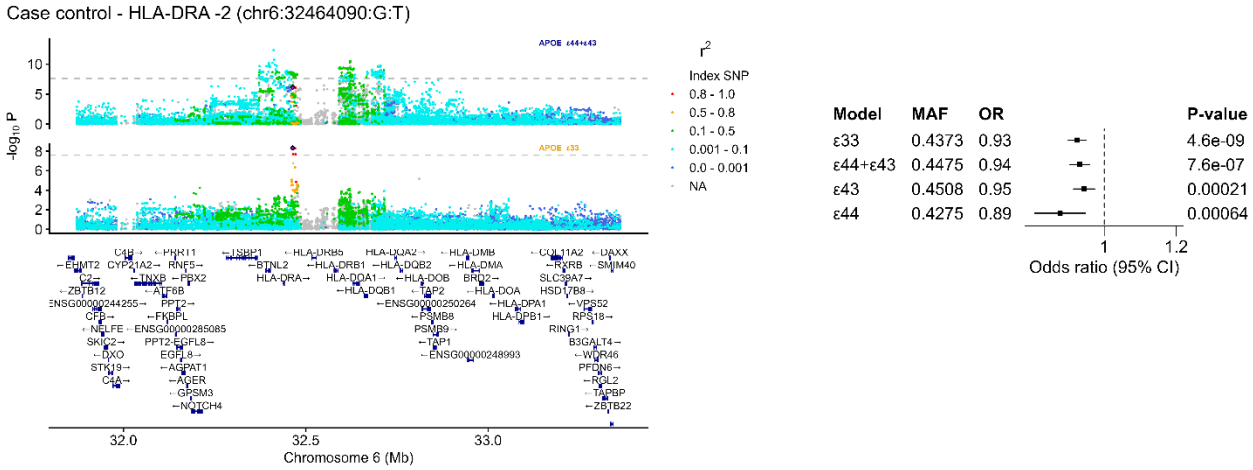
Supplementary Figure 6



Supplementary Figure 6: Loci and forest plot for *CR1*.

Loci plots for *CR1* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *CR1* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

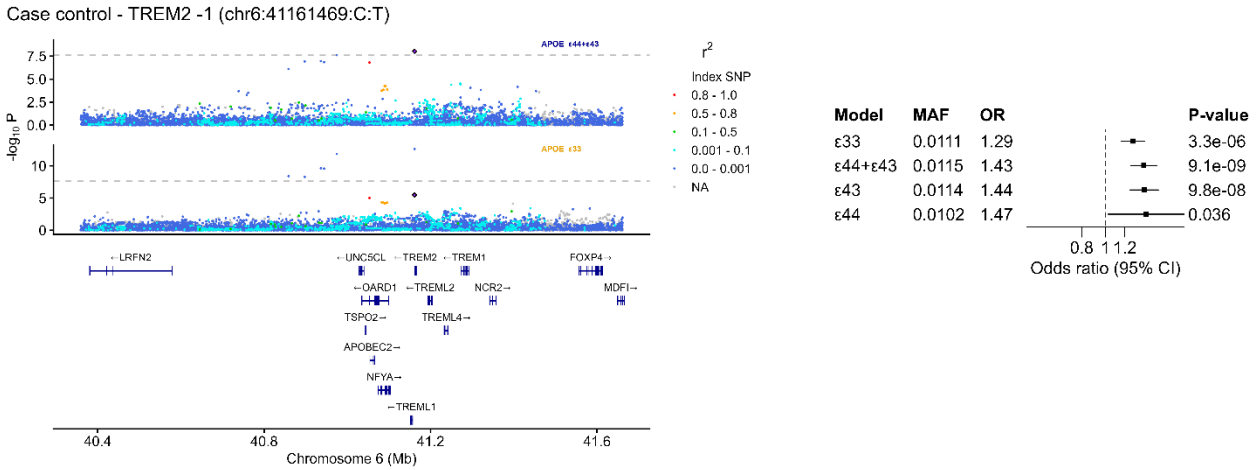
Supplementary Figure 7



Supplementary Figure 7: Loci and forest plot for *HLA-DRA -2*.

Loci plots for *HLA-DRA -2* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *HLA-DRA -2* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

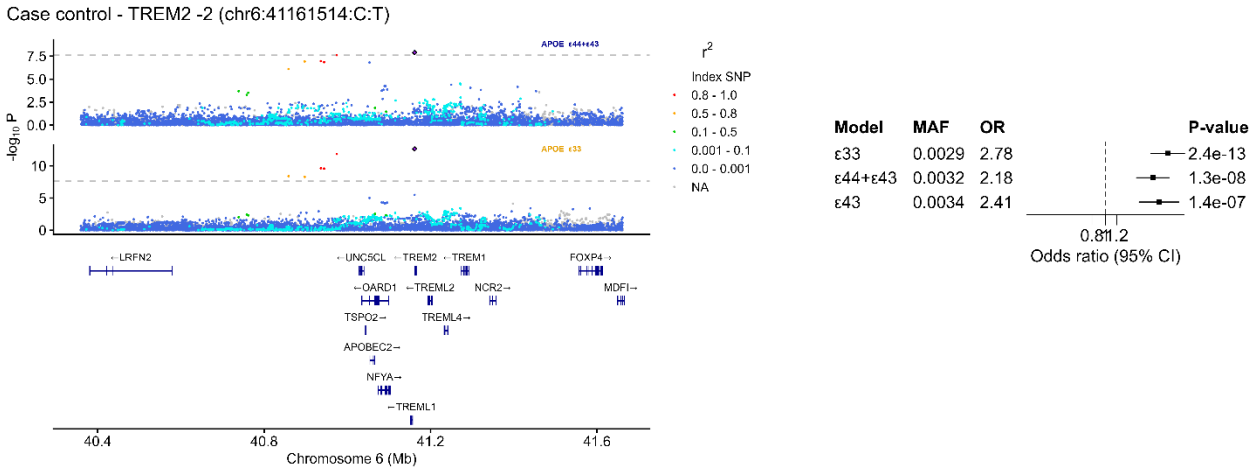
Supplementary Figure 8



Supplementary Figure 8: Loci and forest plot for *TREM2 -1*

Loci plots for *TREM2 -1* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *TREM2 -1* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

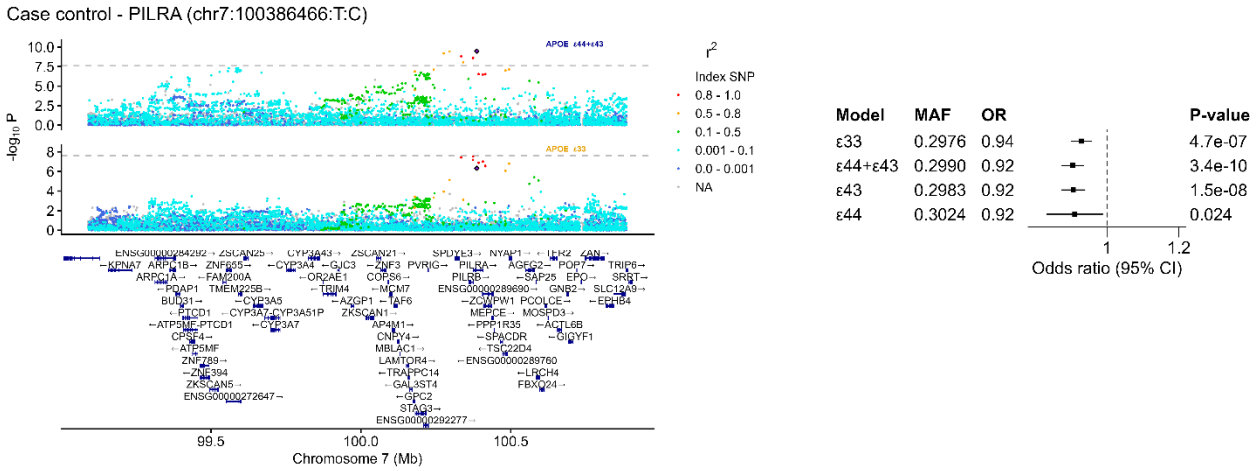
Supplementary Figure 9



Supplementary Figure 9: Loci and forest plot for *TREM2 -2*

Loci plots for *TREM2 -2* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *TREM2 -2* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

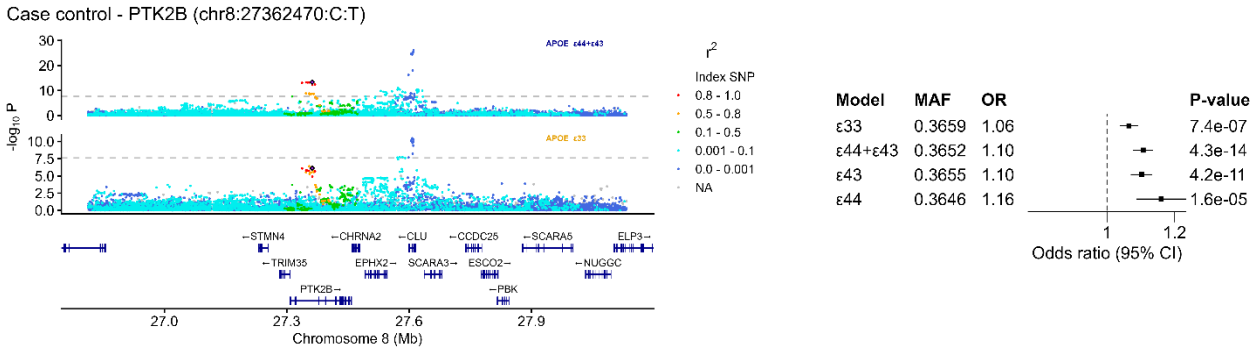
Supplementary Figure 10



Supplementary Figure 10: Loci and forest plot for *PILRA*.

Loci plots for *PLIRA* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *PLIRA* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

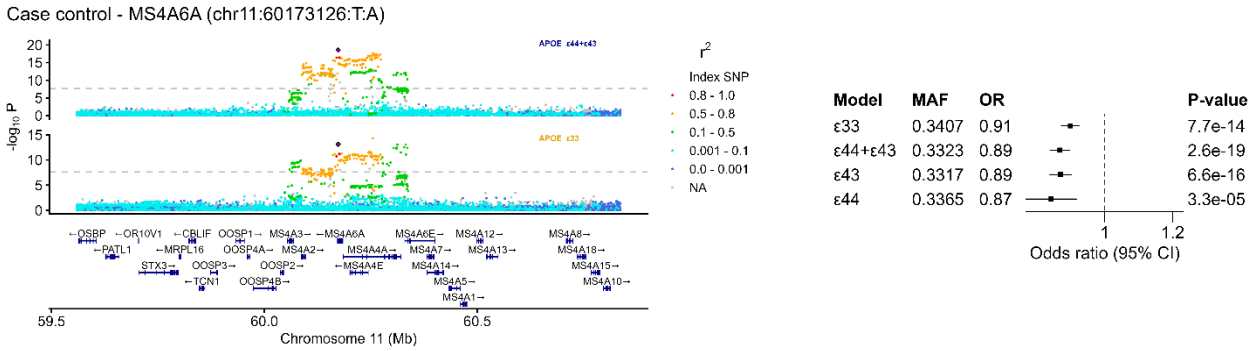
Supplementary Figure 11



Supplementary Figure 11: Loci and forest plot for *PTK2B*.

Loci plots for *PTK2B* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *PTK2B* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

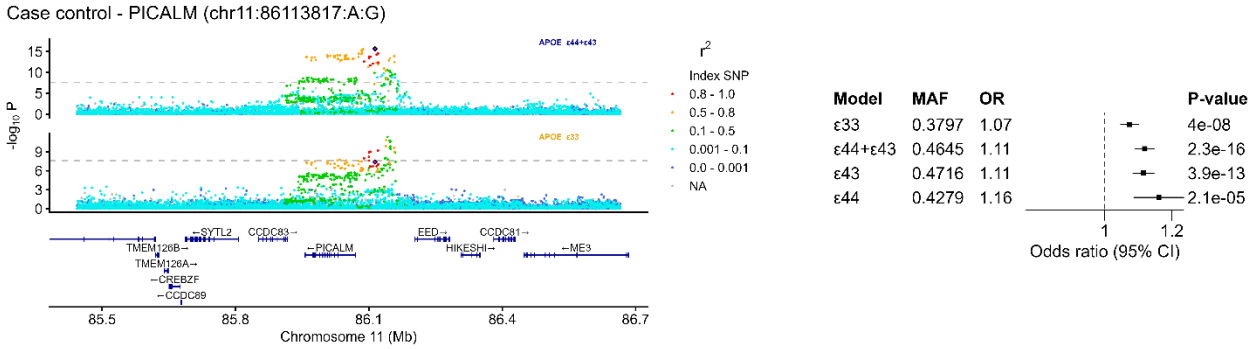
Supplementary Figure 12



Supplementary Figure 12: Loci and forest plot for *MS4A6A*.

Loci plots for *MS4A6A* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *MS4A6A* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

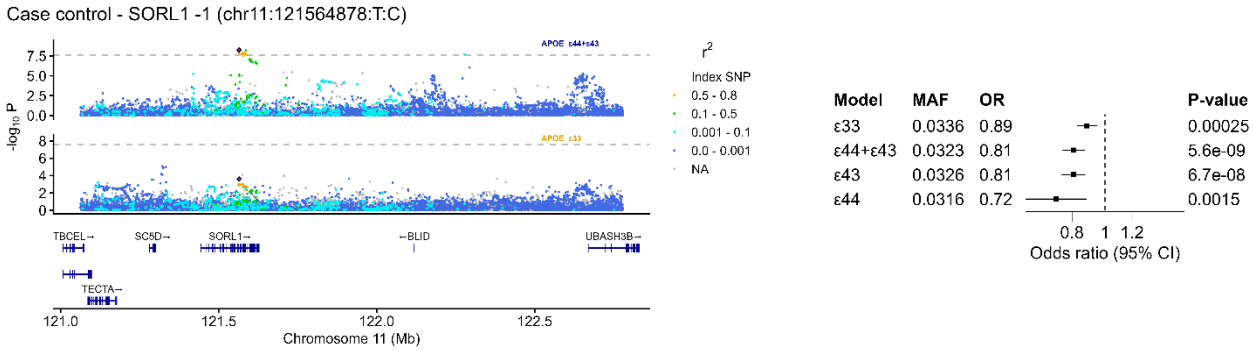
Supplementary Figure 13



Supplementary Figure 13: Loci and forest plot for *PICALM*.

Loci plots for *PICALM* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *PICALM* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

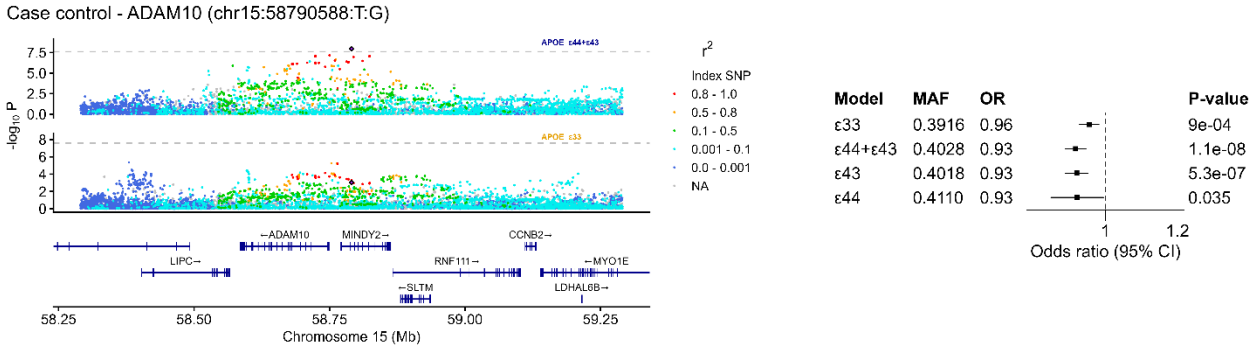
Supplementary Figure 14



Supplementary Figure 14: Loci and forest plot for *SORL1*.

Loci plots for *SORL1* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *SORL1* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

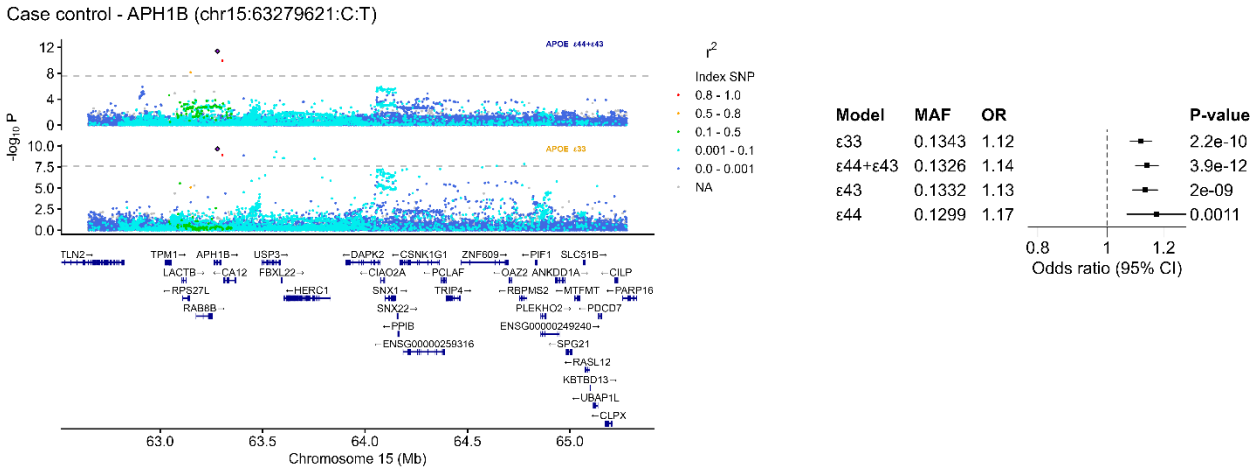
Supplementary Figure 15



Supplementary Figure 15: Loci and forest plot for *ADAM10*.

Loci plots for *ADAM10* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *ADAM10* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

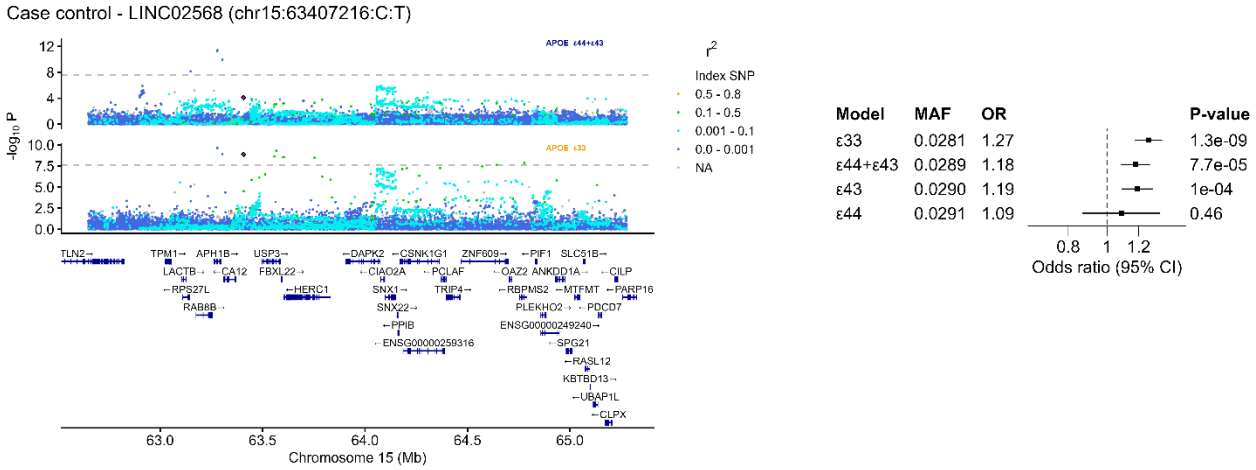
Supplementary Figure 16



Supplementary Figure 16: Loci and forest plot for *APH1B*.

Loci plots for *APH1B* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *APH1B* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

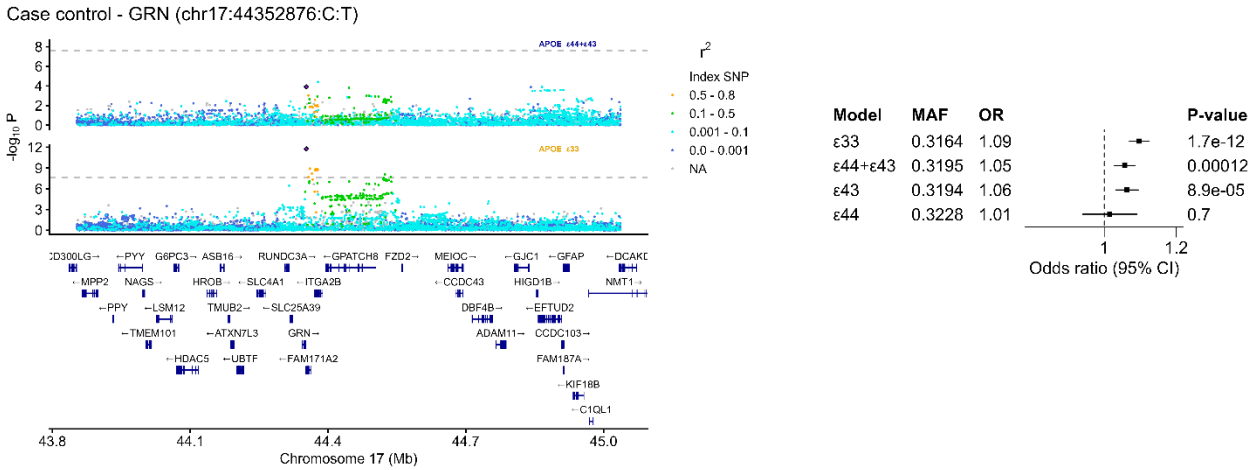
Supplementary Figure 17



Supplementary Figure 17: Loci and forest plot for *LINC02568*.

Loci plots for *LINC02568* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *LINC02568* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

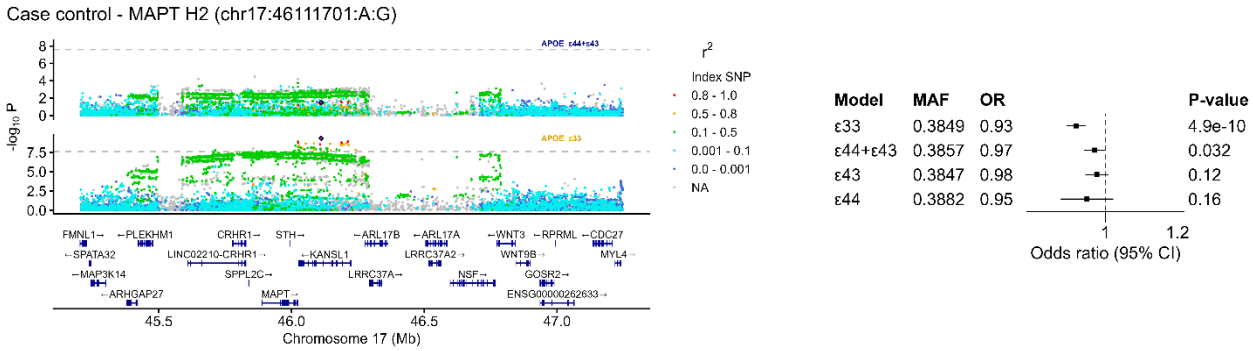
Supplementary Figure 18



Supplementary Figure 18: Loci and forest plot for *GRN*.

Loci plots for *GRN* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *GRN* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

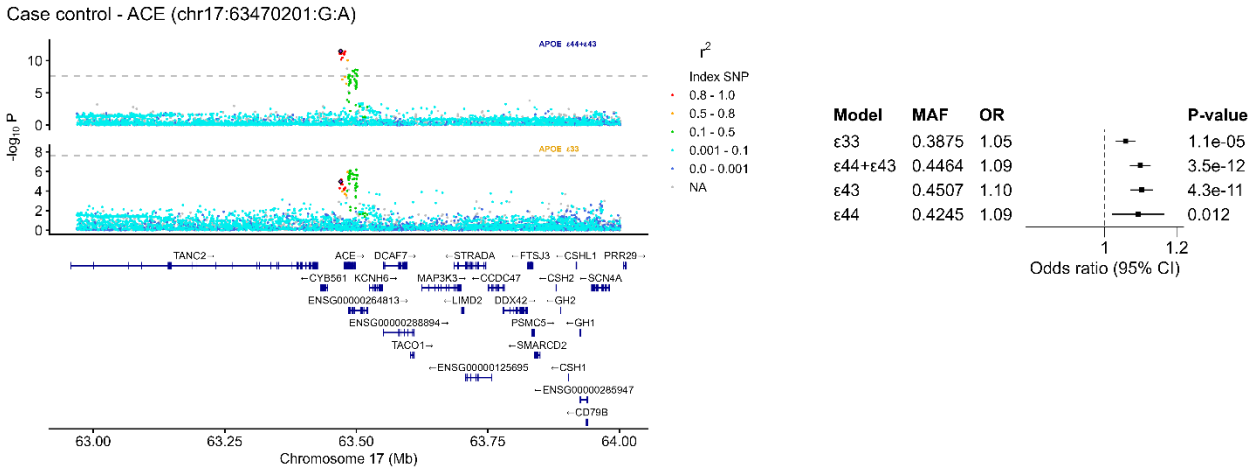
Supplementary Figure 19



Supplementary Figure 19: Loci and forest plot for *MAPT*.

Loci plots for *MAPT* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *MAPT* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

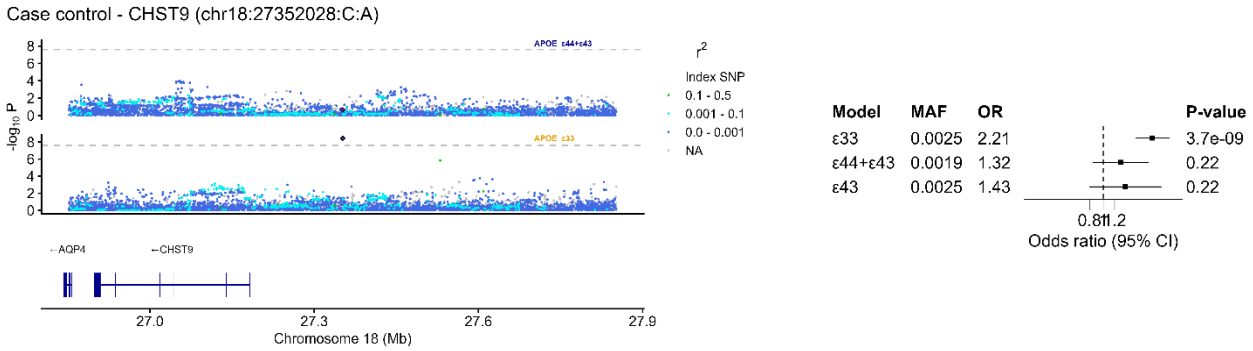
Supplementary Figure 20



Supplementary Figure 20: Loci and forest plot for *ACE.*

Loci plots for *ACE* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *ACE* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

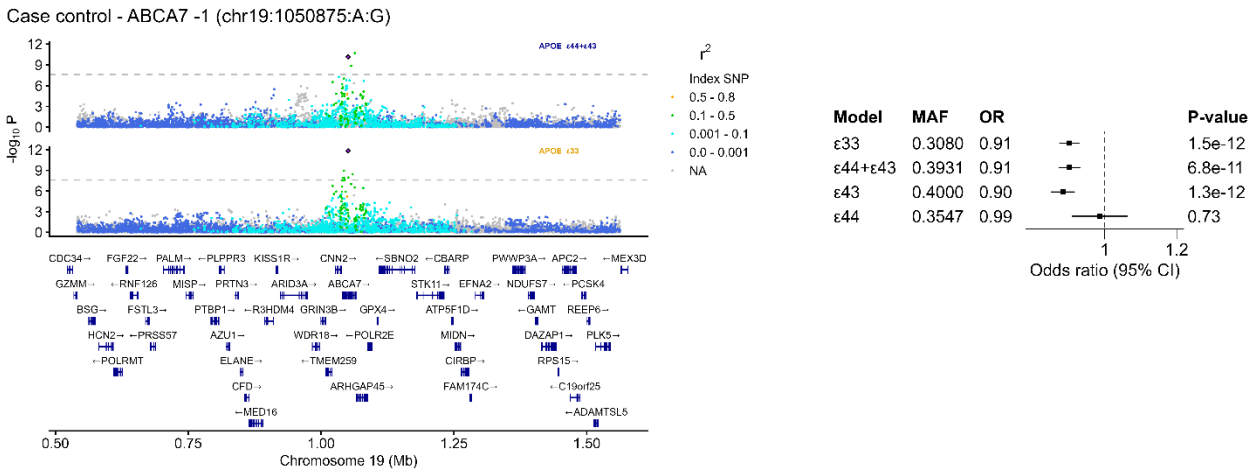
Supplementary Figure 21



Supplementary Figure 21: Loci and forest plot for *CHST9.*

Loci plots for *CHST9* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *CHST9* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

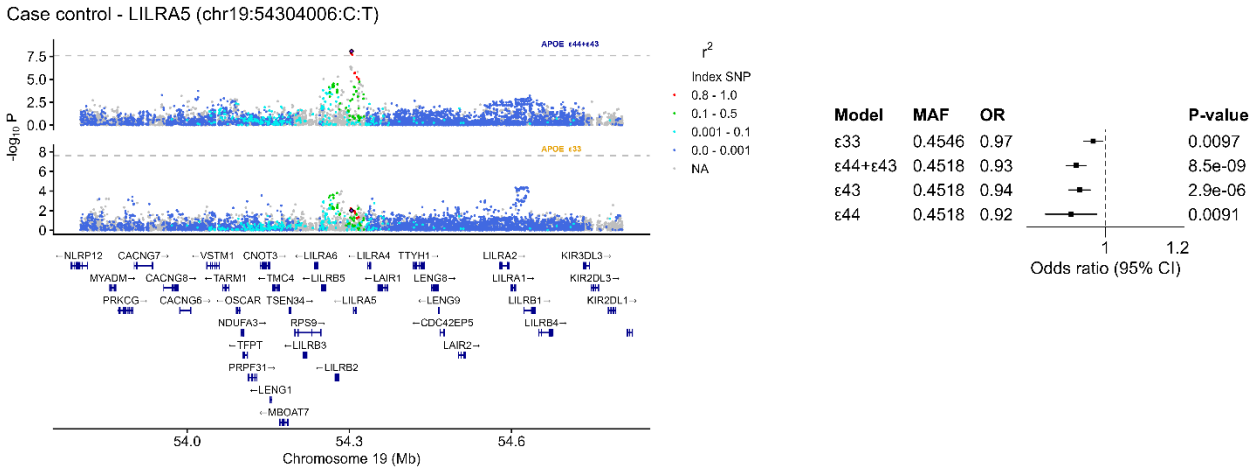
Supplementary Figure 22



Supplementary Figure 22: Loci and forest plot for *ABCA7*.

Loci plots for *ABCA7* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *ABCA7* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

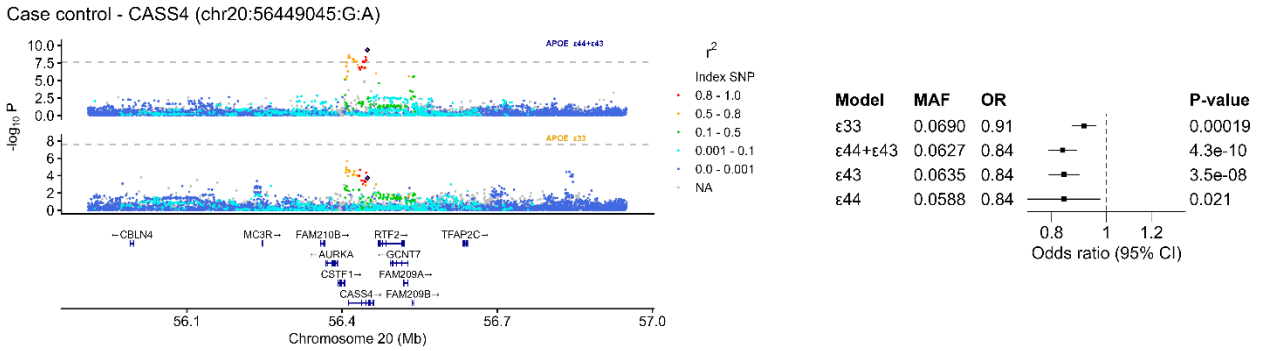
Supplementary Figure 23



Supplementary Figure 23: Loci and forest plot for *LILRA5*.

Loci plots for *LILRA5* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *LILRA5* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

Supplementary Figure 24



Supplementary Figure 24: Loci and forest plot for *CASS4*

Loci plots for *CASS4* in both the *APOE* ε33 and *APOE* ε44+ε43 strata and forest plots for the lead SNPs for *CASS4* in the four *APOE* strata ε33, ε44+ε43, ε43 and ε44. In the forest plot each *APOE* strata is shown to visualize potential dominant or additive interaction.

Supplementary Figure 25

ε44+ε43

Model	MAF	P-value
M3-ADSP-e44+e43	0.0842	0.056
M3-Bonn-e44+e43	0.0803	0.75
M3-Bonn_noage-e44+e43	0.0803	0.61
M3-EADB-e44+e43	0.0820	0.21
M3-EADB_noage-e44+e43	0.0820	0.23
M3-EADI-e44+e43	0.0894	0.53
M3-EADI_noage-e44+e43	0.0894	0.36
M3-FG-e44+e43	0.0522	2.7e-05
M3-GERAD-e44+e43	0.0925	0.47
M3-GERAD_noage-e44+e43	0.0925	0.62
M3-GRACE-e44+e43	0.0796	0.57
M3-UKB-e44+e43	0.0884	6.2e-04
M3-meta-e44+e43	0.0719	1.3e-08

ε33

Model	MAF	P-value
M7-ADSP-e33	0.0858	0.62
M7-Bonn-e33	0.0816	0.89
M7-Bonn_noage-e44+e43	0.0816	0.47
M7-EADB-e33	0.0824	0.25
M7-EADB_noage-e44+e43	0.0824	0.23
M7-EADI-e33	0.0819	0.85
M7-EADI_noage-e44+e43	0.0819	0.73
M7-FG-e33	0.0528	0.18
M7-GERAD-e33	0.0902	0.91
M7-GERAD_noage-e44+e43	0.0902	0.71
M7-GRACE-e33	0.0822	0.083
M7-UKB-e33	0.0881	0.065
M7-meta-e33	0.0736	0.17

0.5 1 1.5 2.5

Odds ratio (95% CI)

ε44

Model	MAF	P-value
M1-ADSP-e44	0.0860	0.21
M1-EADB-e44	0.0829	0.87
M1-EADB_noage-e44+e43	0.0829	0.87
M1-EADI-e44	0.0778	0.67
M1-EADI_noage-e44+e43	0.0778	1
M1-FG-e44	0.0493	0.63
M1-GERAD-e44	0.1136	0.8
M1-UKB-e44	0.0856	0.97
M1-meta-e44	0.0697	0.72

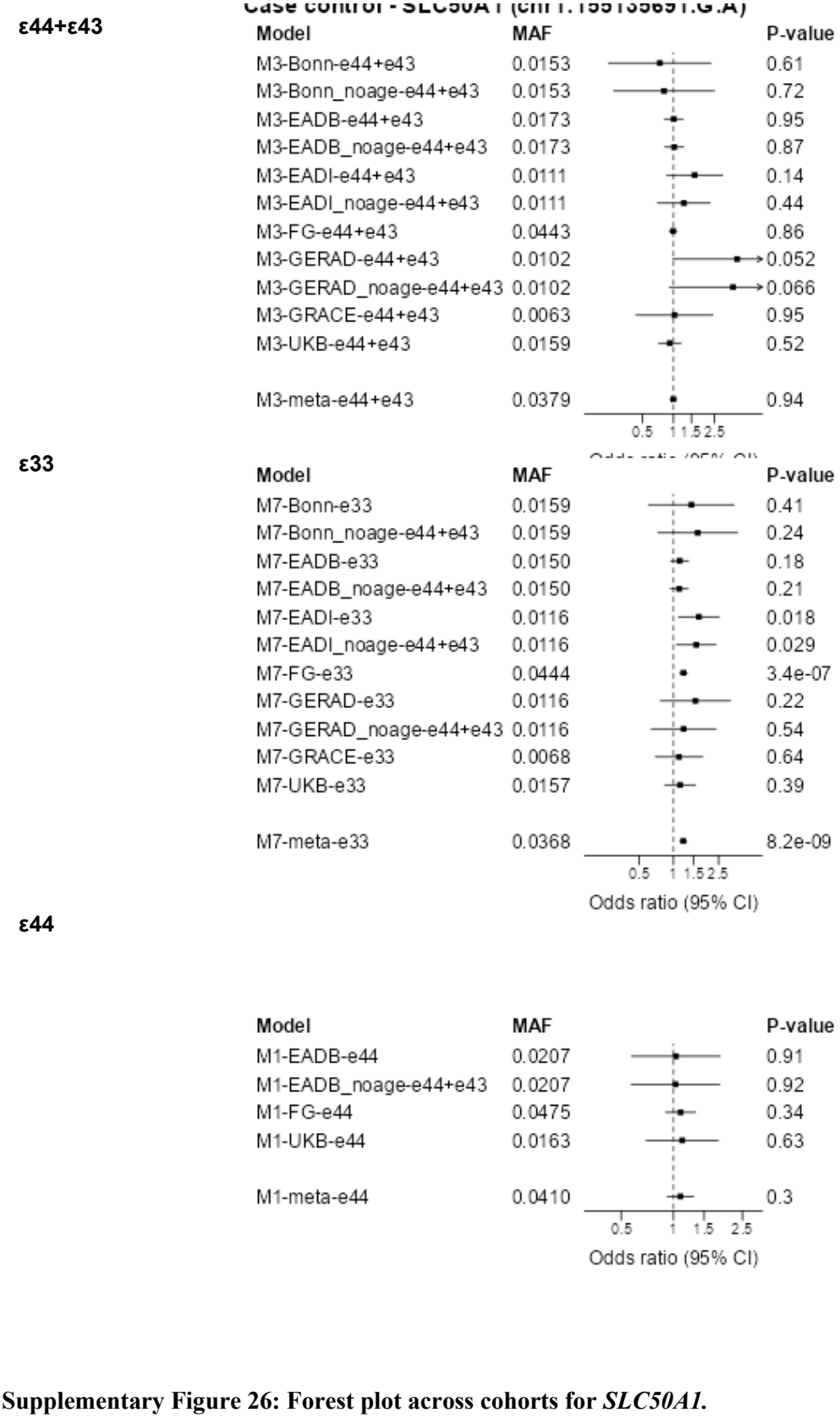
0.5 1 1.5 2.5

Odds ratio (95% CI)

Supplementary Figure 25: Forest plot across cohorts for *HP1BP3.*

Forest plots across cohorts for the lead SNPs for *HP1BP3* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

Supplementary Figure 26

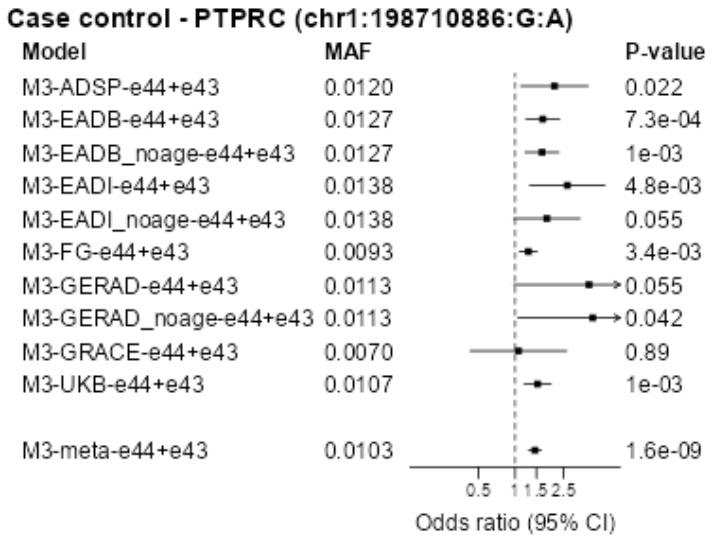


Supplementary Figure 26: Forest plot across cohorts for *SLC50A1.*

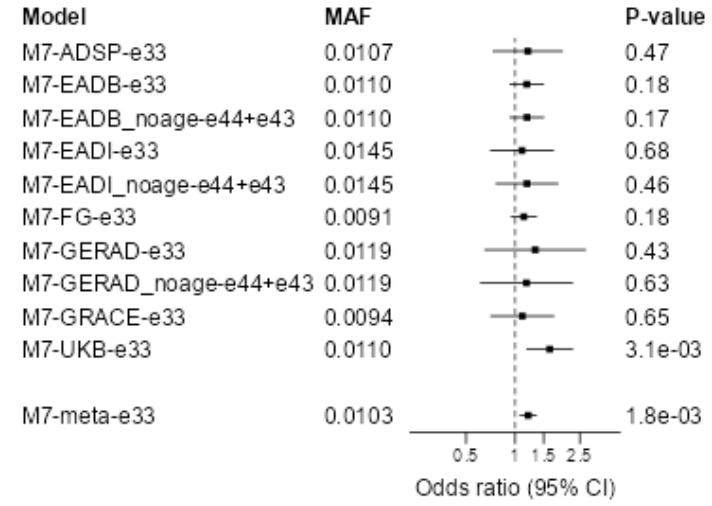
Forest plots across cohorts for the lead SNPs for *SLC50A1* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

Supplementary Figure 27

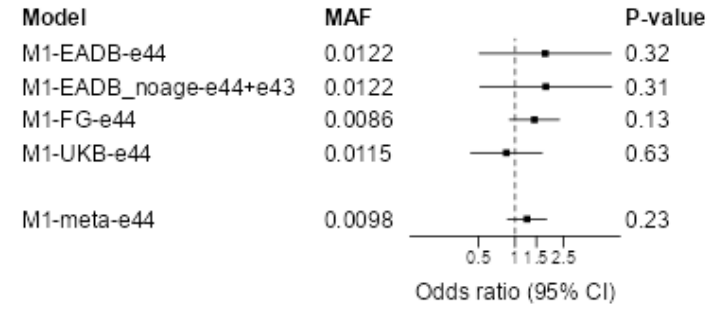
ε44+ε43



ε33



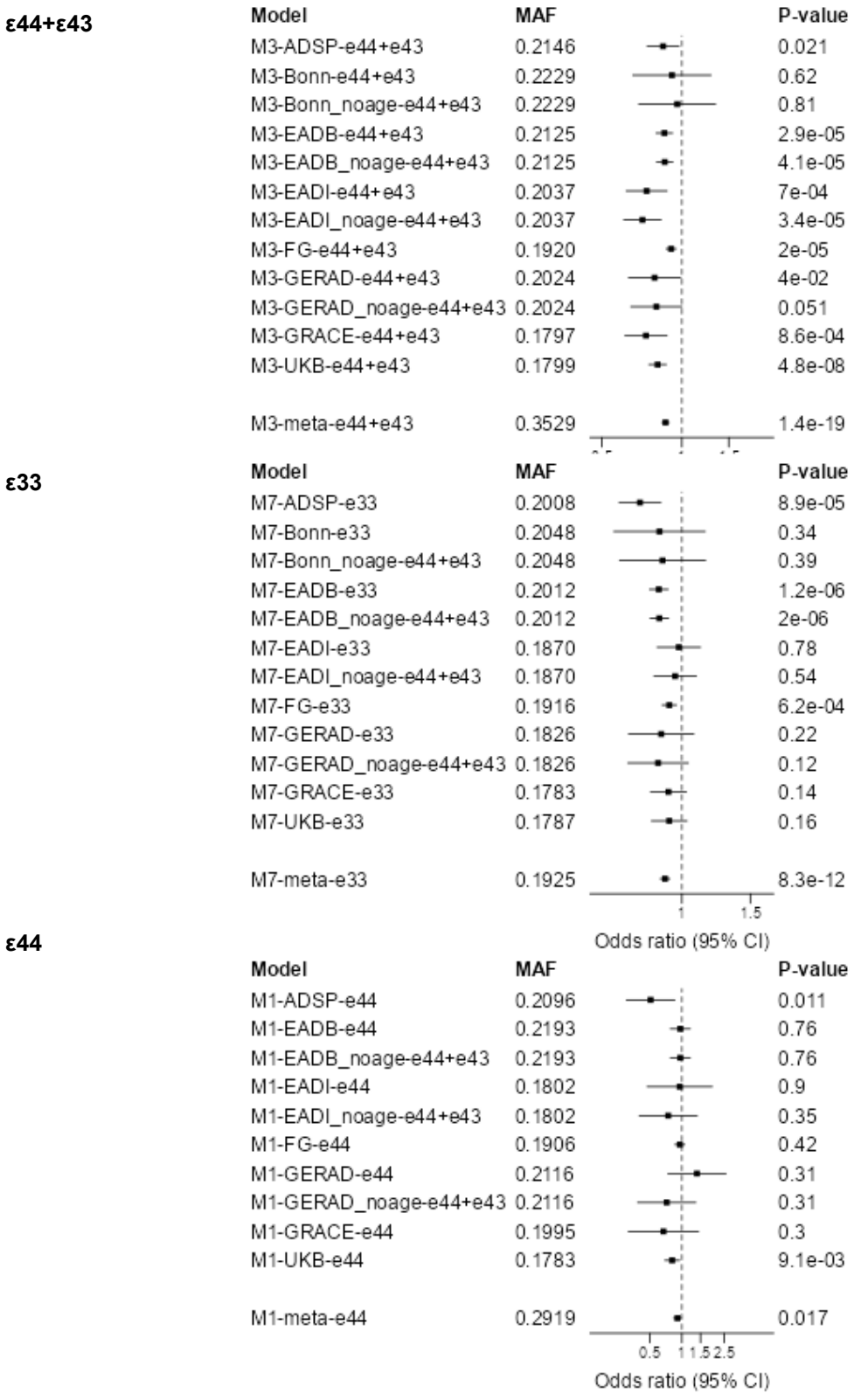
ε44



Supplementary Figure 27 Forest plot across cohorts for *PTPRC*.

Forest plots across cohorts for the lead SNPs for *PTPRC* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

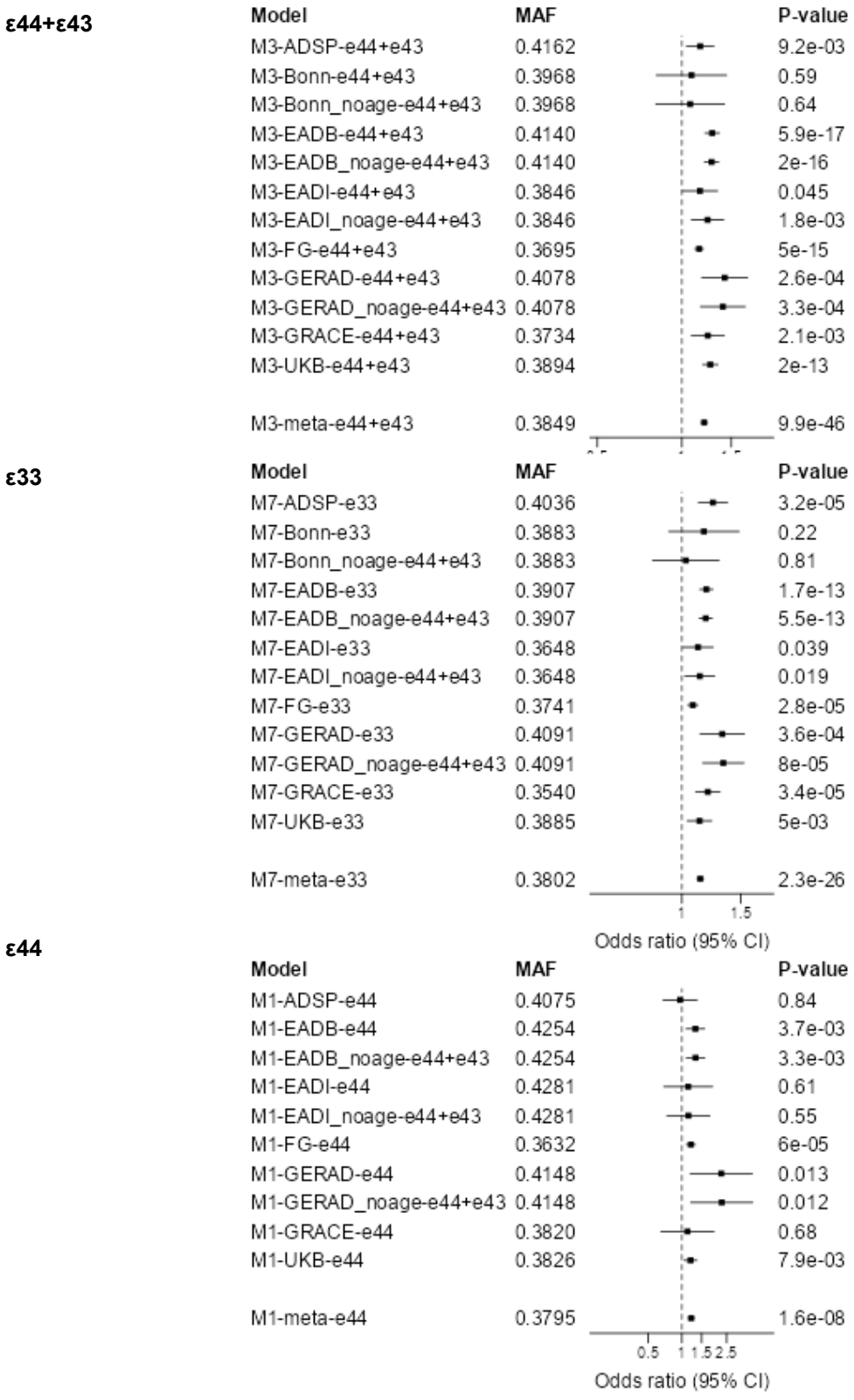
Supplementary Figure 28



Supplementary Figure 28: Forest plot across cohorts for *CR1*.

Forest plots across cohorts for the lead SNPs for *CR1* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

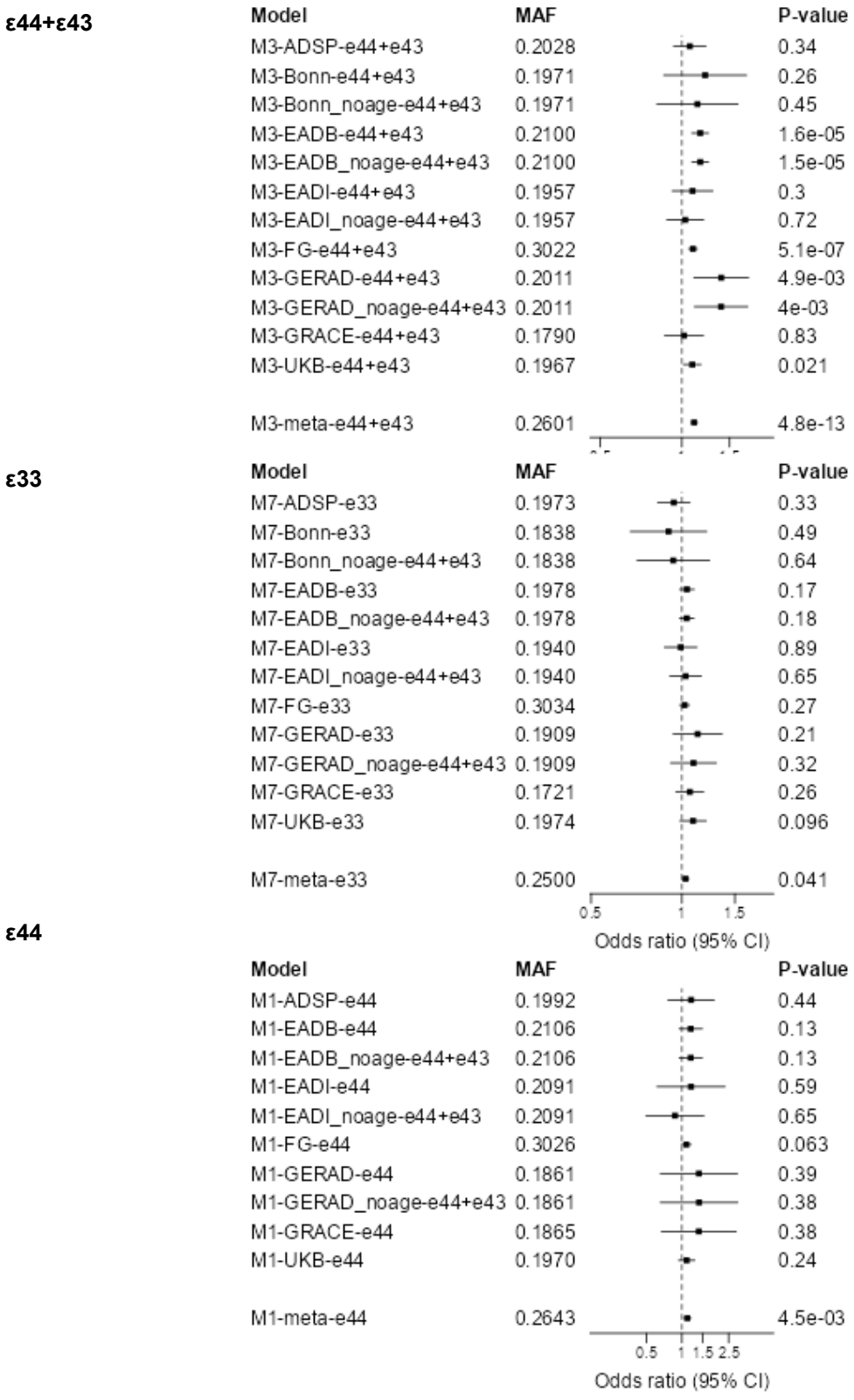
Supplementary Figure 29



Supplementary Figure 29: Forest plot across cohorts for *BIN1*.

Forest plots across cohorts for the lead SNPs for *BIN1* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

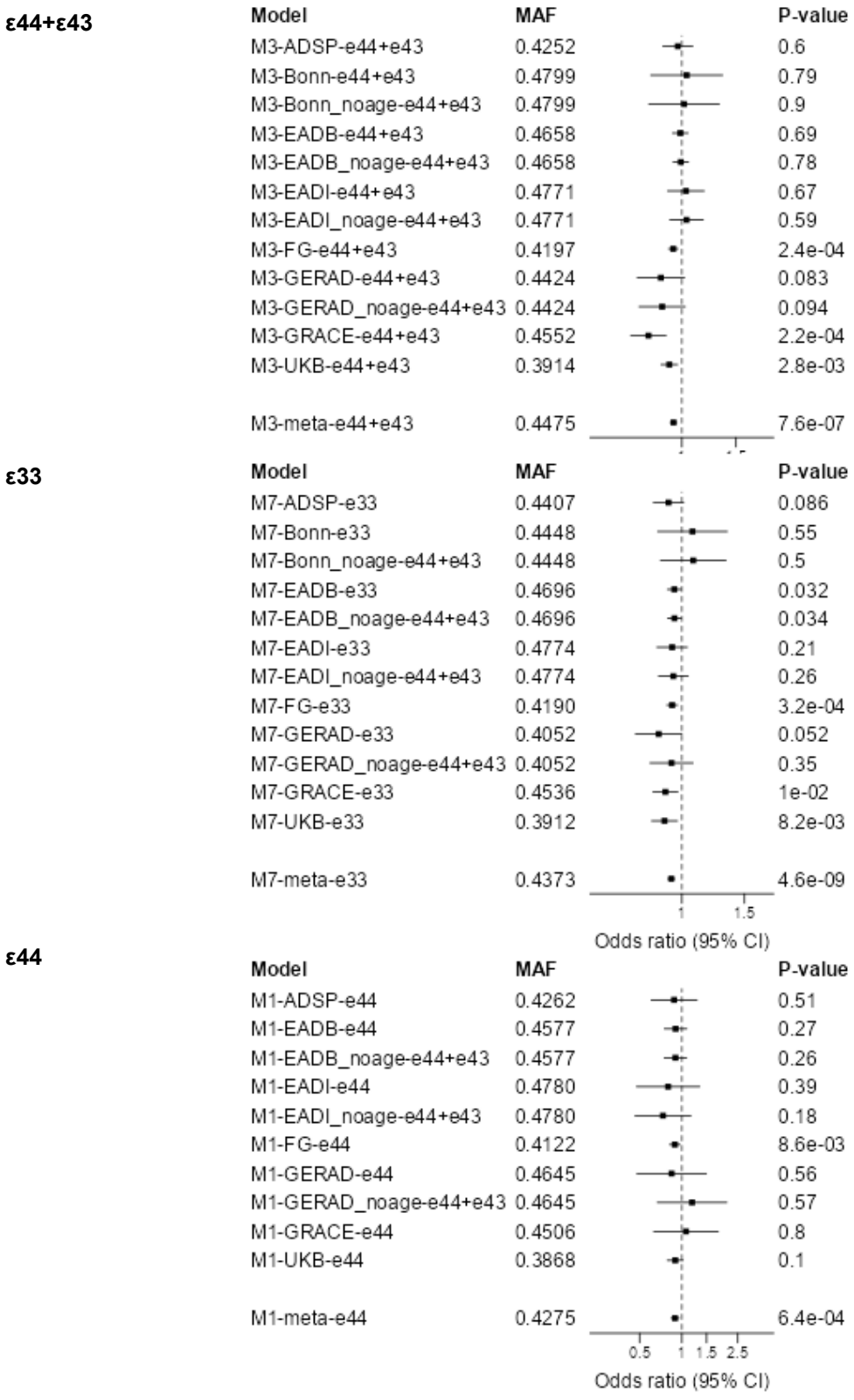
Supplementary Figure 30



Supplementary Figure 30: Forest plot across cohorts for *HLA-DRA -1.*

Forest plots across cohorts for the lead SNPs for *HLA-DRA -1* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

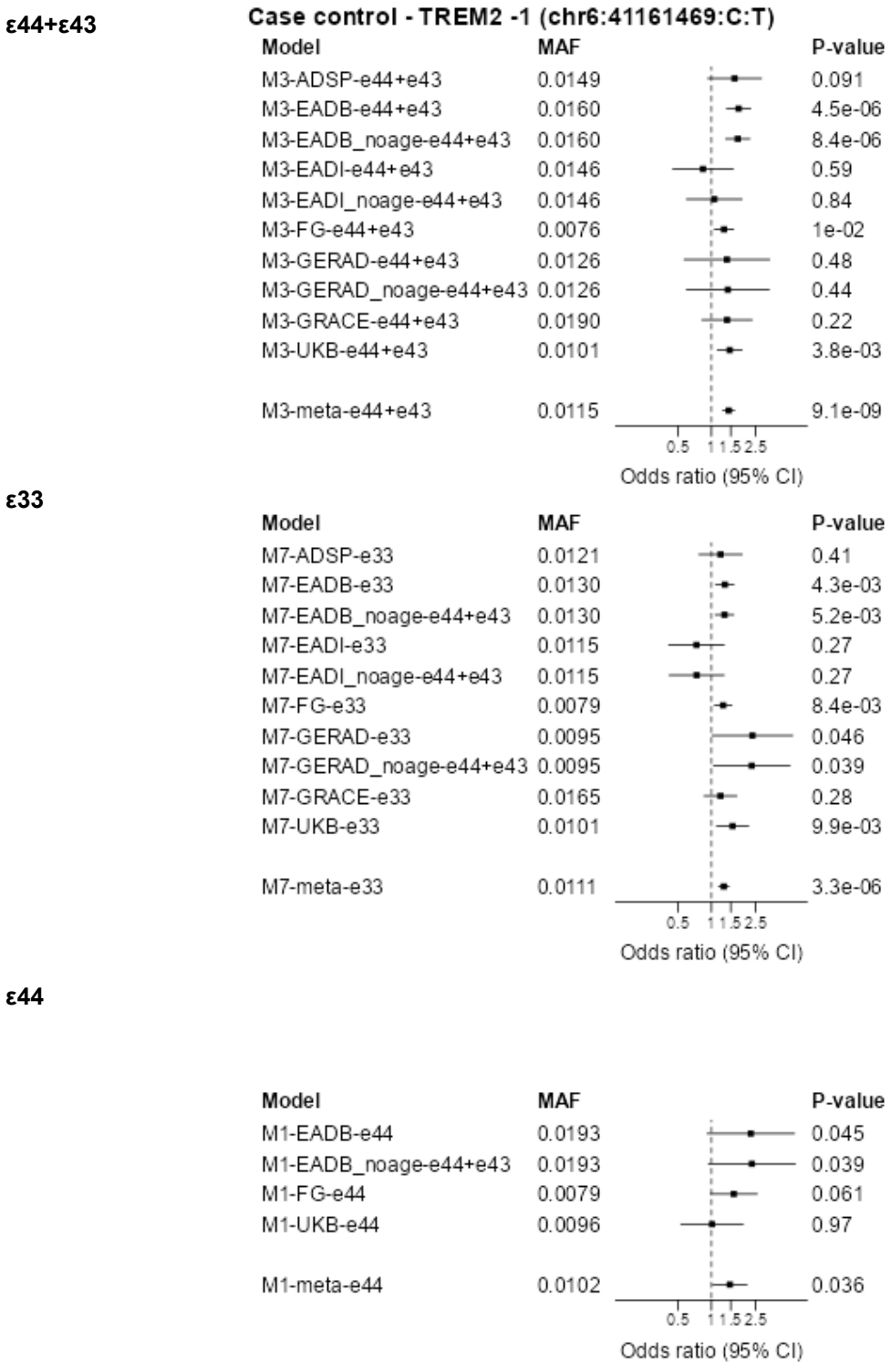
Supplementary Figure 31



Supplementary Figure 31: Forest plot across cohorts for *HLA-DRA -2.*

Forest plots across cohorts for the lead SNPs for *HLA-DRA -2* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

Supplementary Figure 32

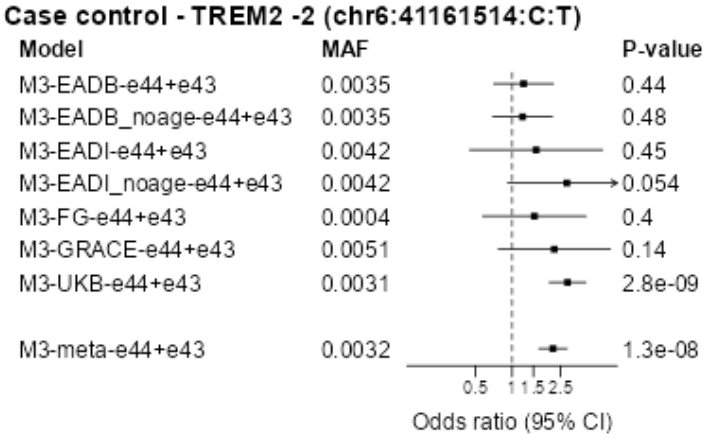


Supplementary Figure 32: Forest plot across cohorts for *TREM2 -1*

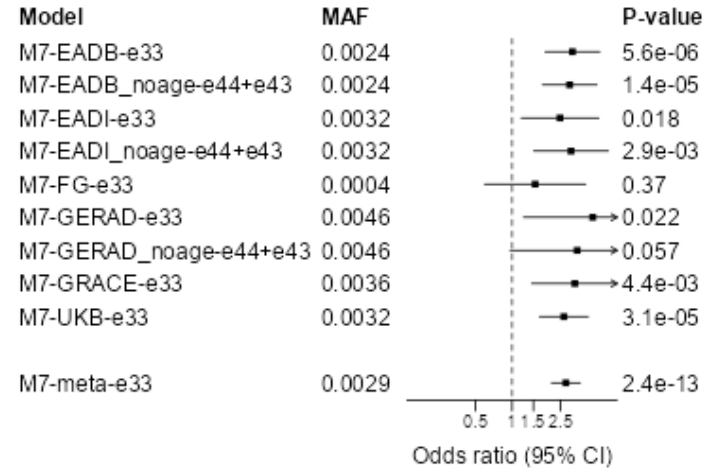
Forest plots across cohorts for the lead SNPs for *TREM2 -1* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

Supplementary Figure 33

ε44+ε43



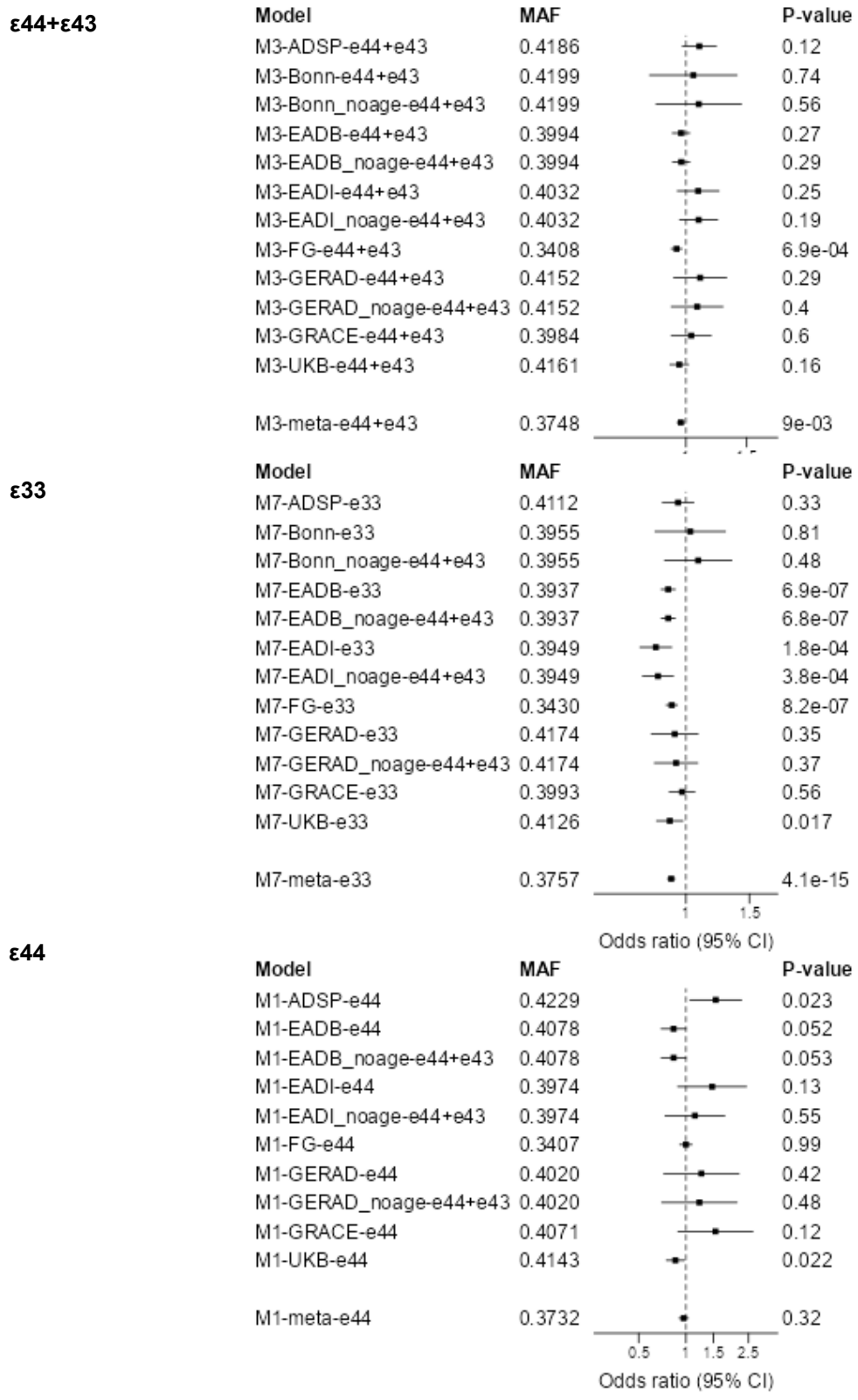
ε33



Supplementary Figure 33: Forest plot across cohorts for *TREM2 -2*

Forest plots across cohorts for the lead SNPs for *TREM2 -2* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

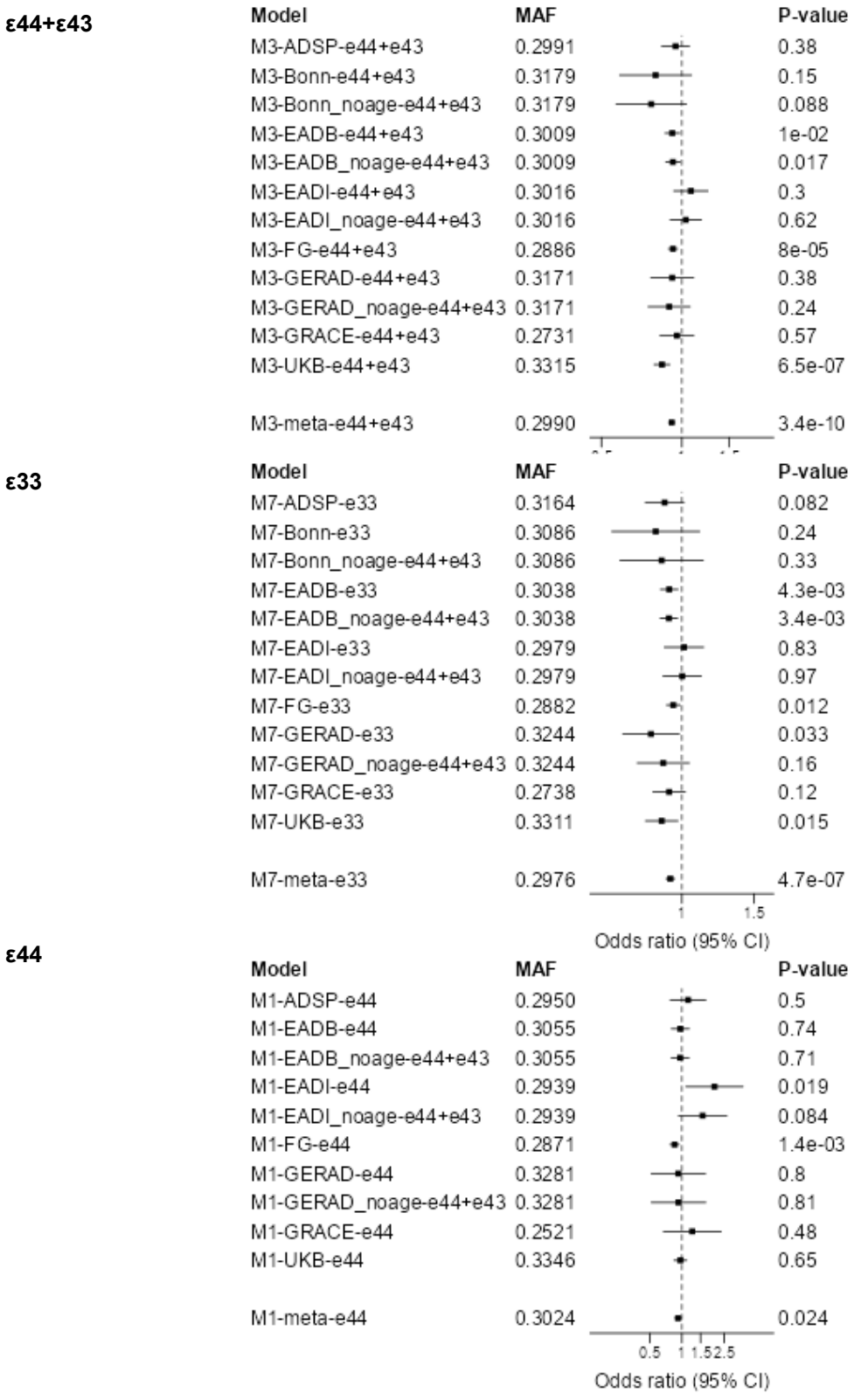
Supplementary Figure 34



Supplementary Figure 34: Forest plot across cohorts for *TMEM106B*.

Forest plots across cohorts for the lead SNPs for *TMEM106B* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

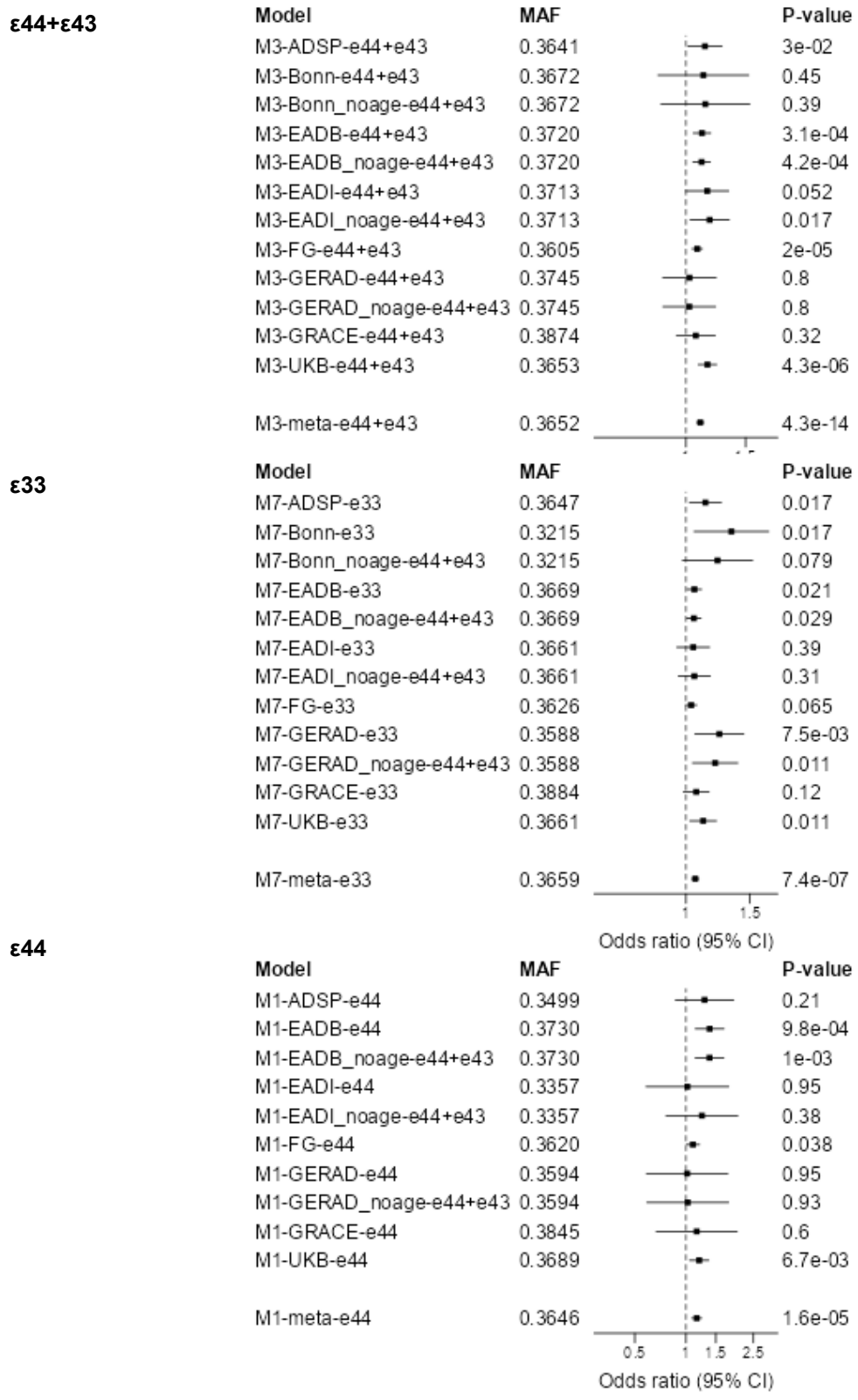
Supplementary Figure 35



Supplementary Figure 35: Forest plot across cohorts for *PLIRA*.

Forest plots across cohorts for the lead SNPs for *PLIRA* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

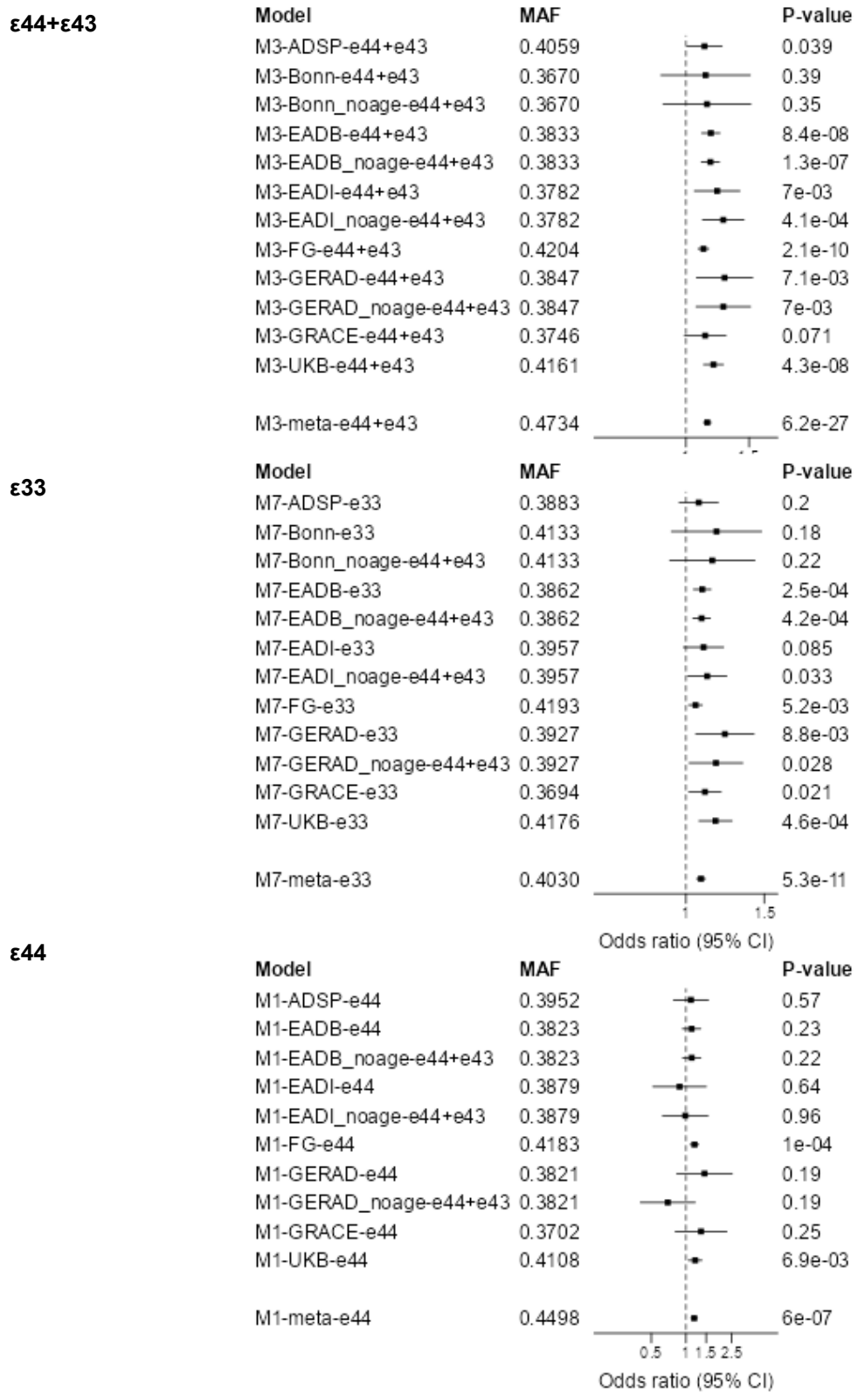
Supplementary Figure 36



Supplementary Figure 36: Forest plot across cohorts for *PTK2B*.

Forest plots across cohorts for the lead SNPs for *PTK2B* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

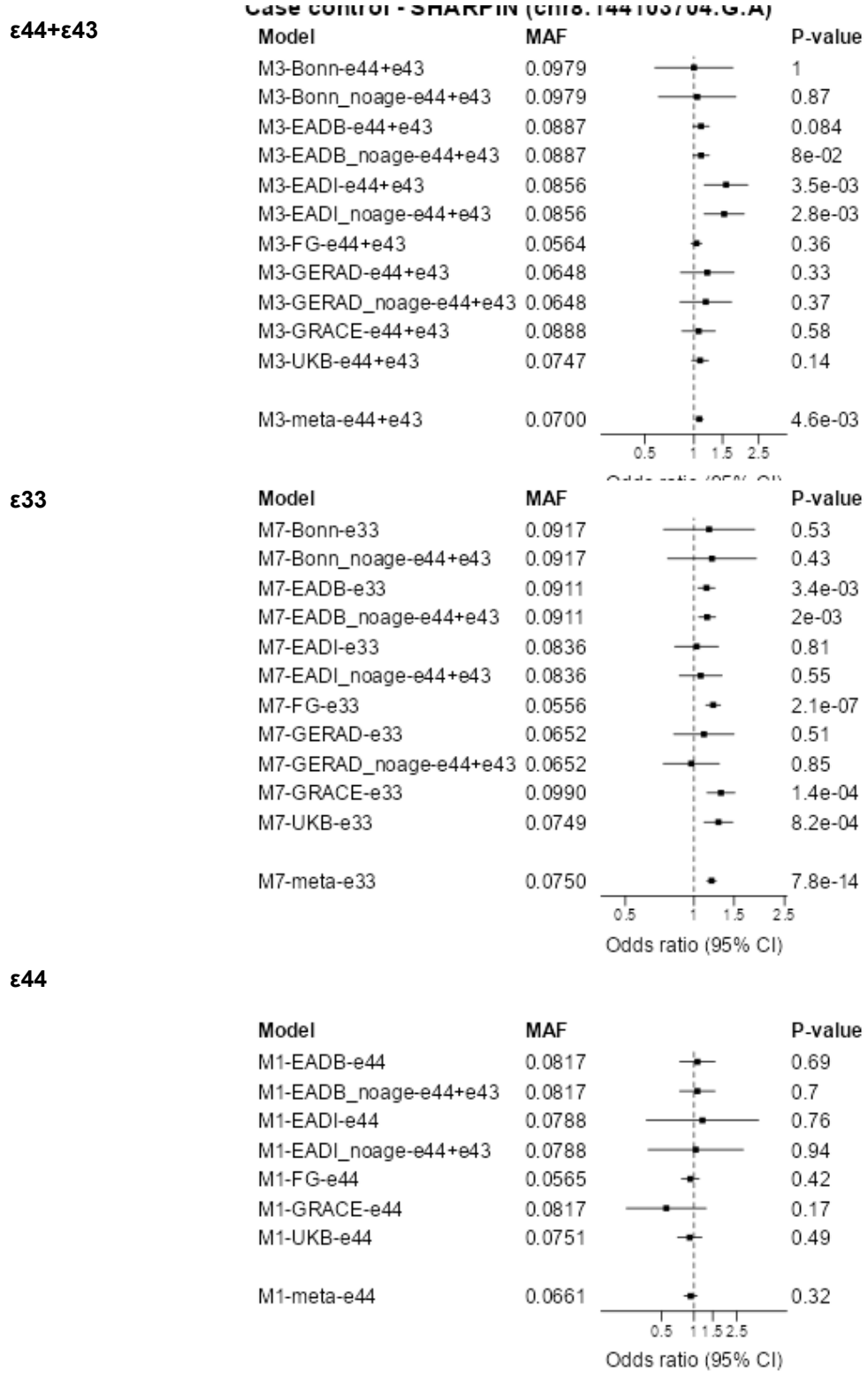
Supplementary Figure 37



Supplementary Figure 37: Forest plot across cohorts for *CLU*.

Forest plots across cohorts for the lead SNPs for *CLU* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

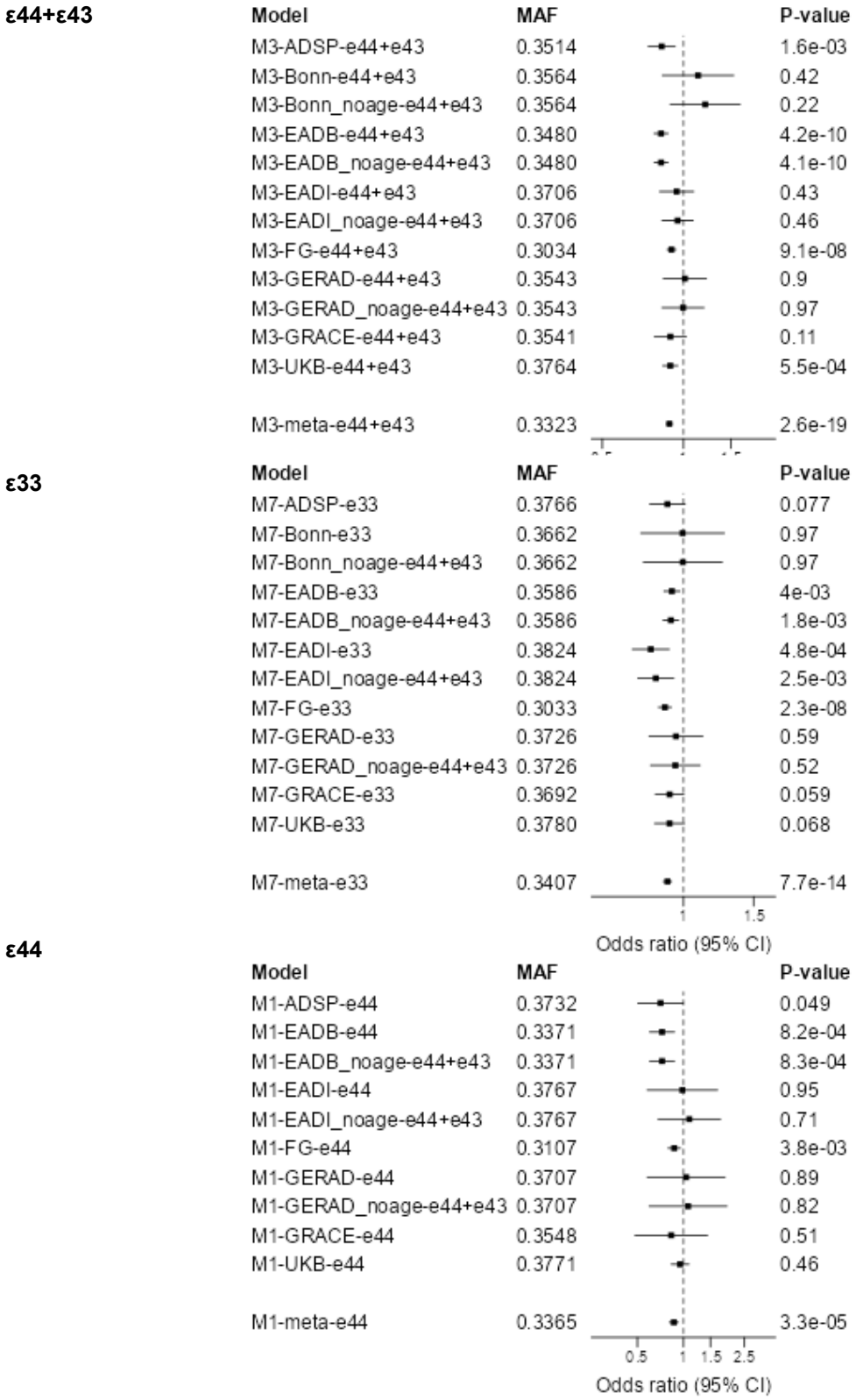
Supplementary Figure 38



Supplementary Figure 38: Forest plot across cohorts for *SHARPIN*.

Forest plots across cohorts for the lead SNPs for *SHARPIN* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

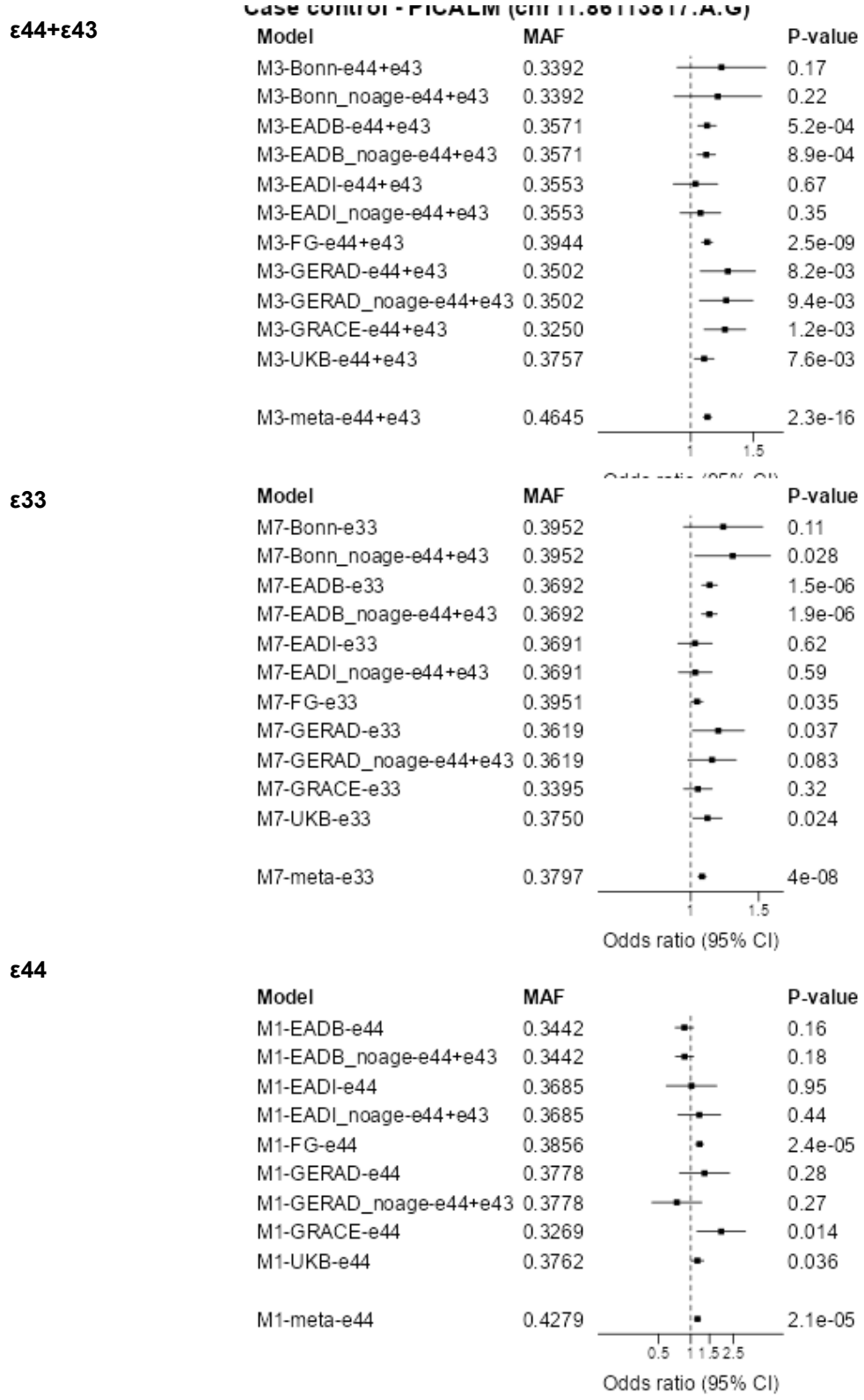
Supplementary Figure 39



Supplementary Figure 39: Forest plot across cohorts for *MS4A6A*.

Forest plots across cohorts for the lead SNPs for *MS4A6A* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

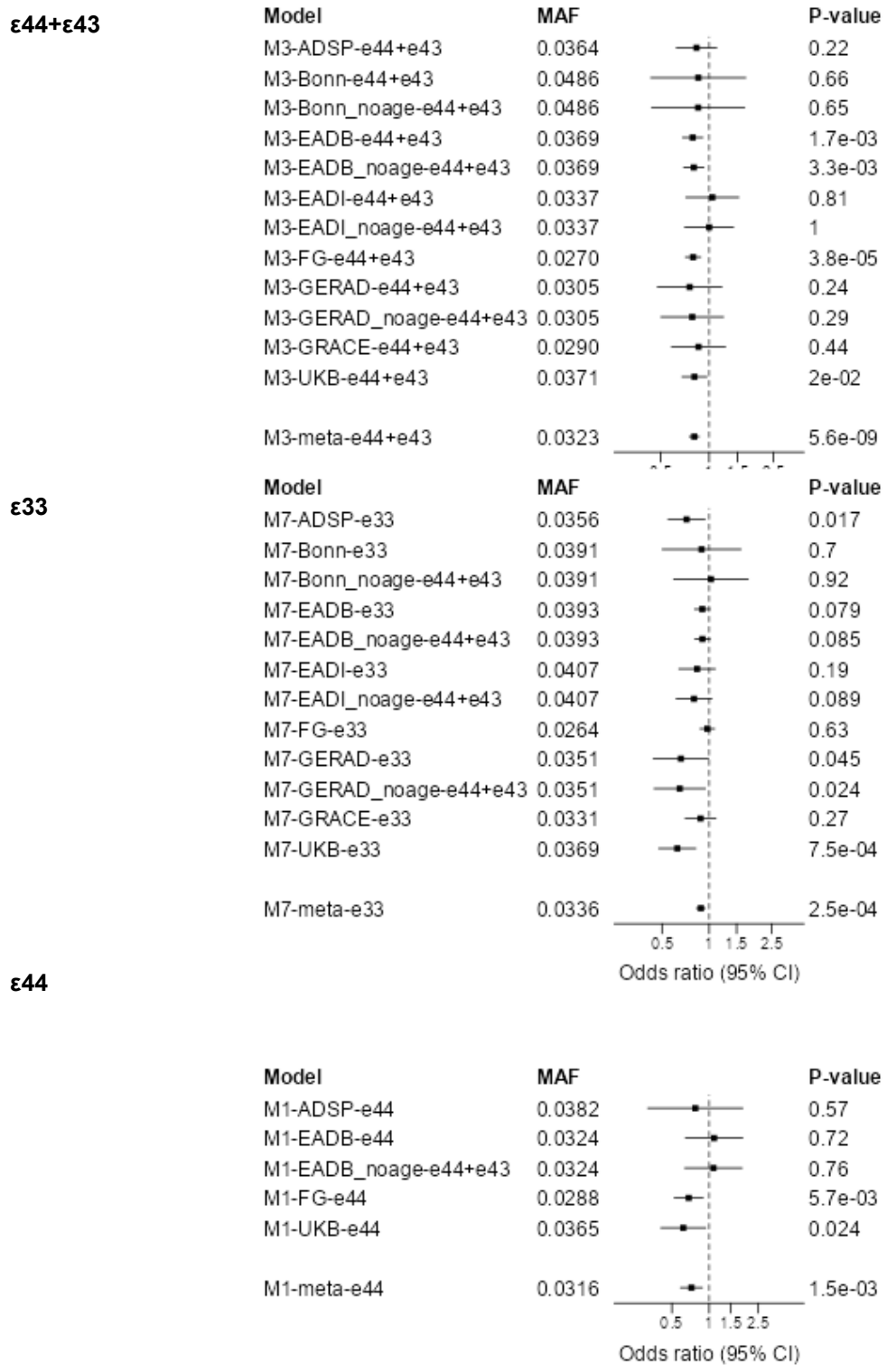
Supplementary Figure 40



Supplementary Figure 40: Forest plot across cohorts *PICALM*

Forest plots across cohorts for the lead SNPs for *PICALM* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

Supplementary Figure 41

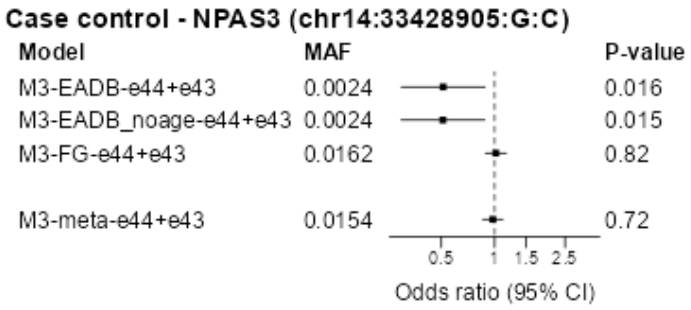


Supplementary Figure 41: Forest plot across cohorts *SORL1*.

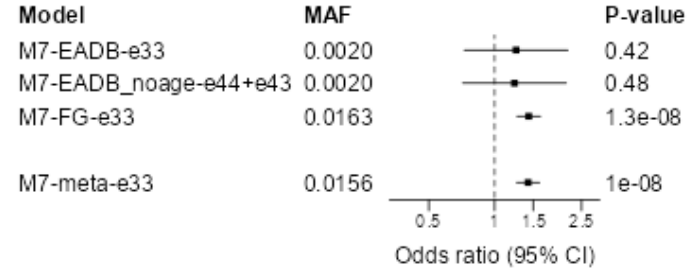
Forest plots across cohorts for the lead SNPs for *SORL1* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

Supplementary Figure 42

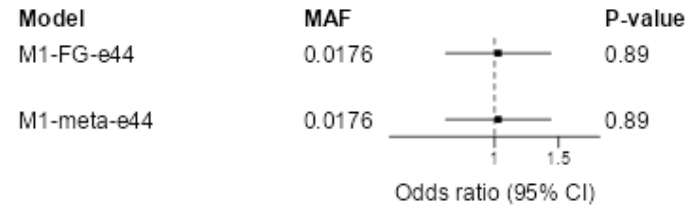
ε44+ε43



ε33



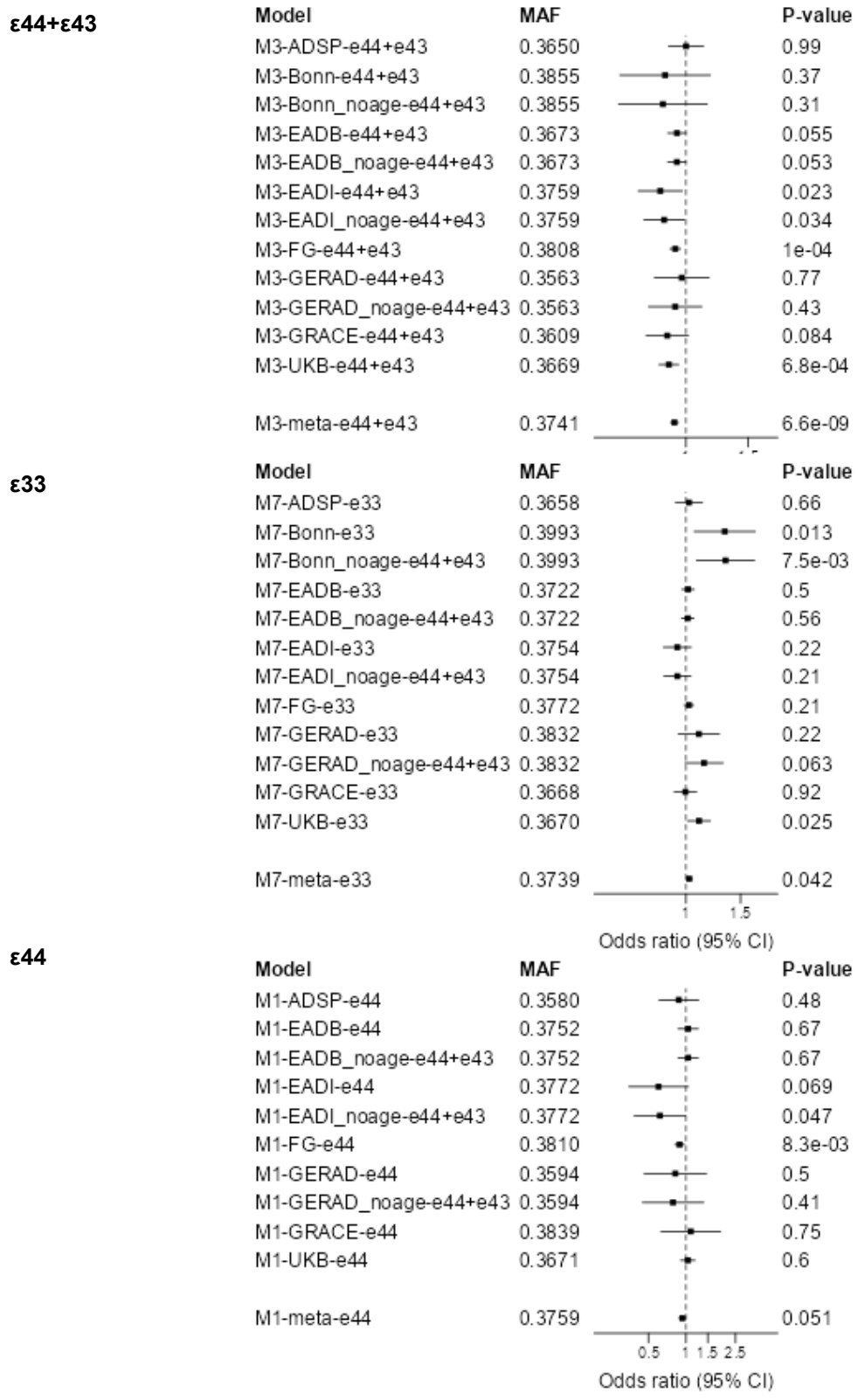
ε44



Supplementary Figure 42: Forest plot across cohorts for *NPAS3*.

Forest plots across cohorts for the lead SNPs for *NPAS3* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

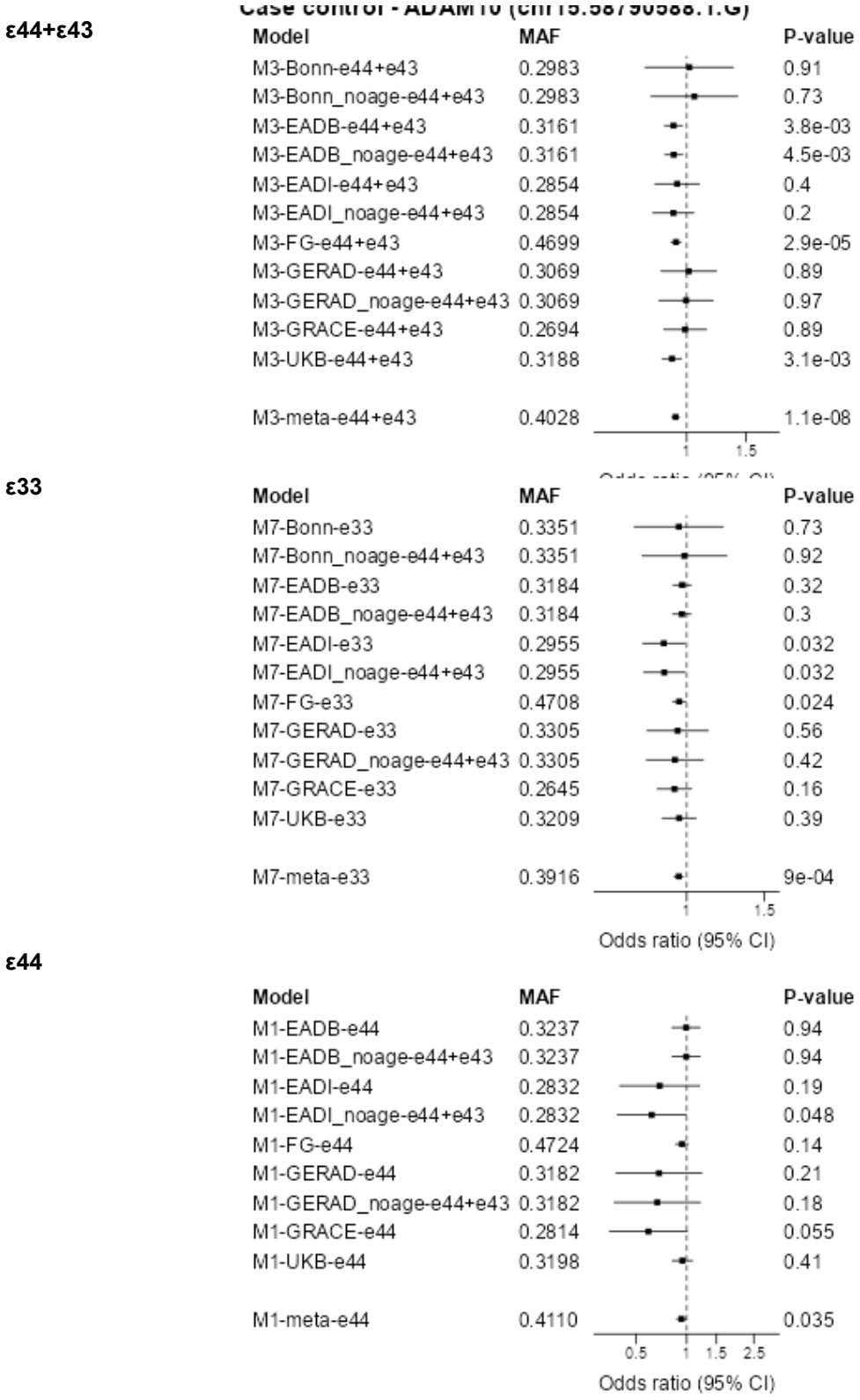
Supplementary Figure 43



Supplementary Figure 43: Forest plot across cohorts for *DDHD1*.

Forest plots across cohorts for the lead SNPs for *DDHD1* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

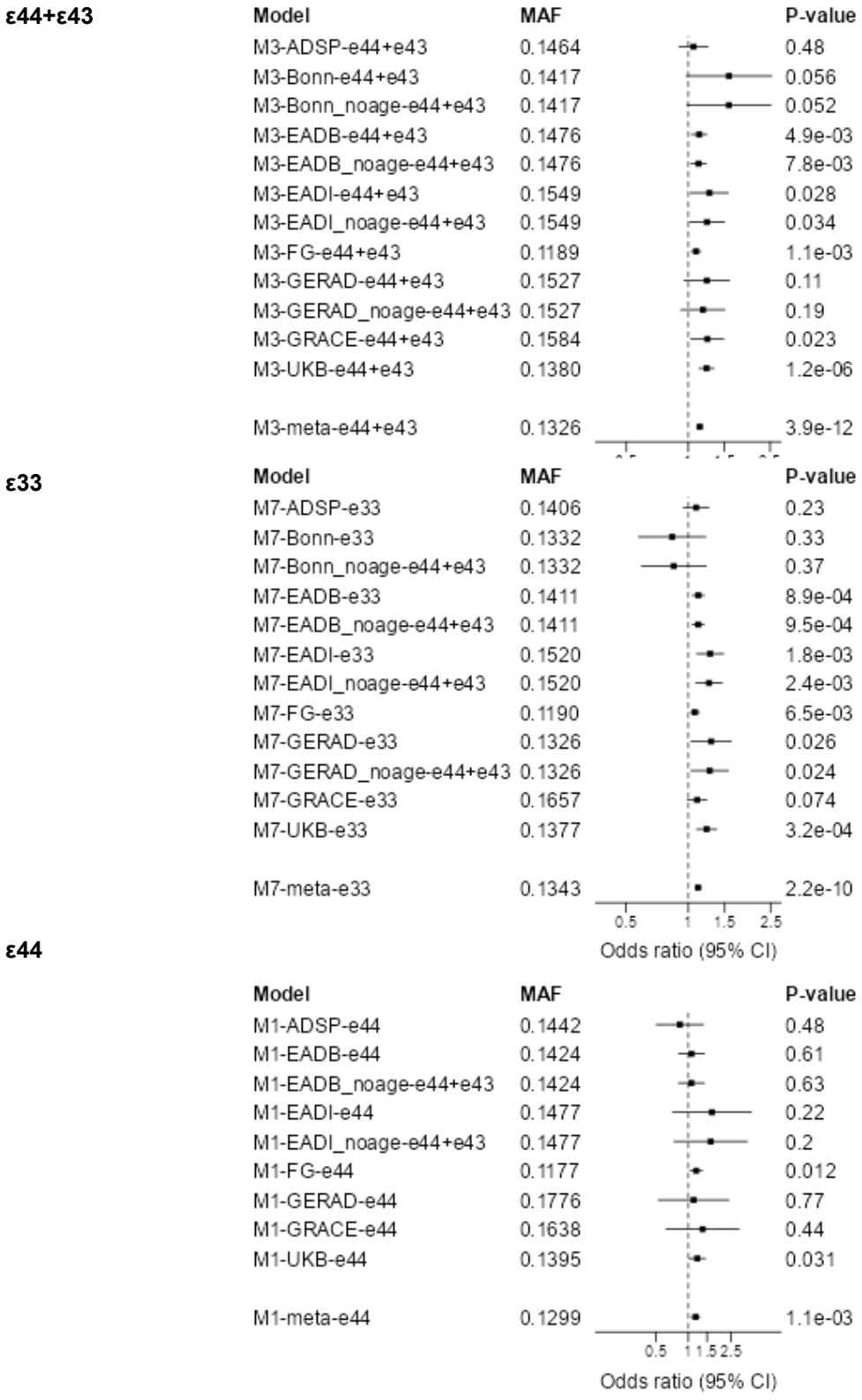
Supplementary Figure 44



Supplementary Figure 44: Forest plot across cohorts for *ADAM10*.

Forest plots across cohorts for the lead SNPs for *ADAM10* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

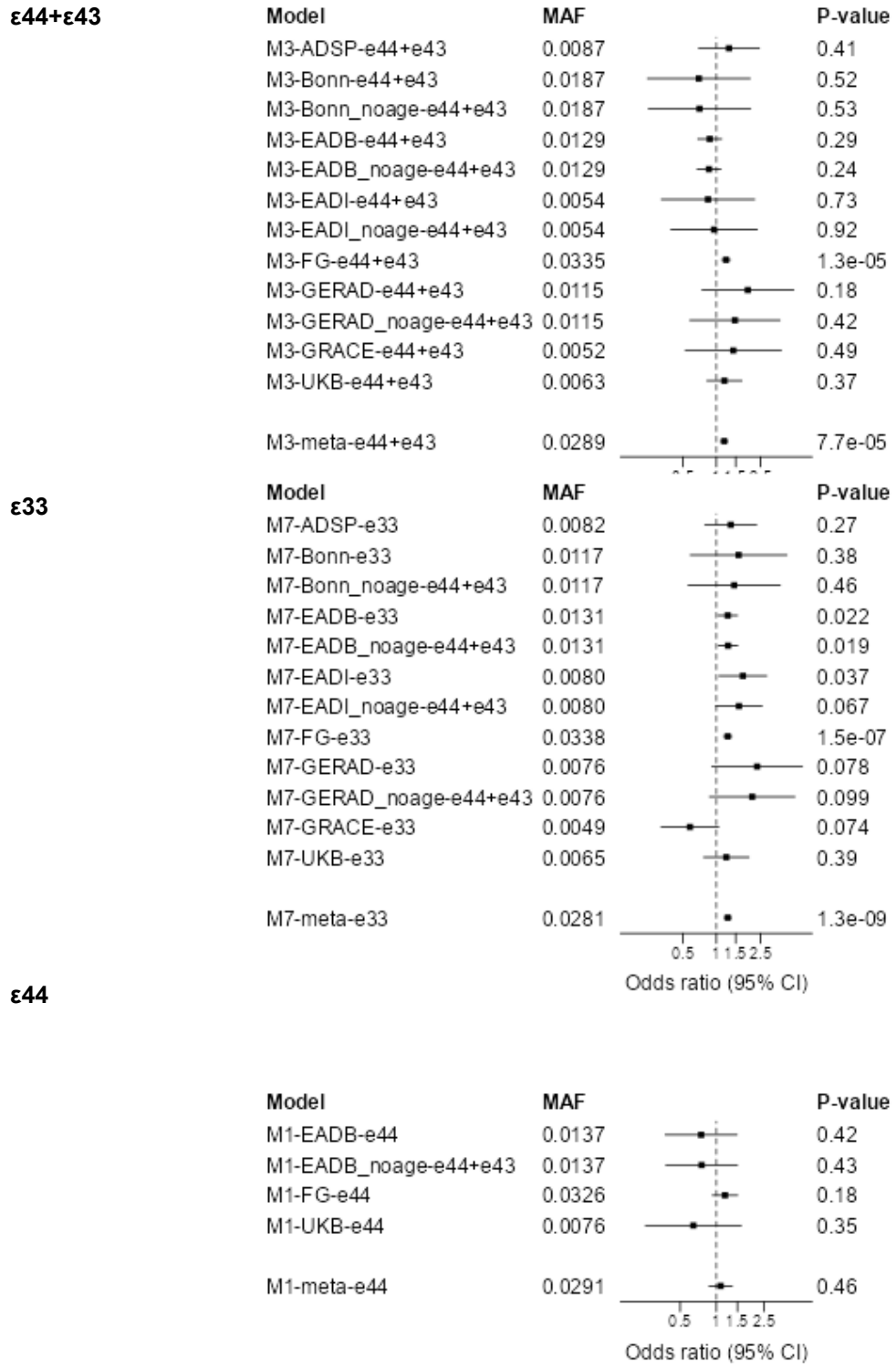
Supplementary Figure 45



Supplementary Figure 45: Forest plot across cohorts for *APH1B*.

Forest plots across cohorts for the lead SNPs for *APH1B* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

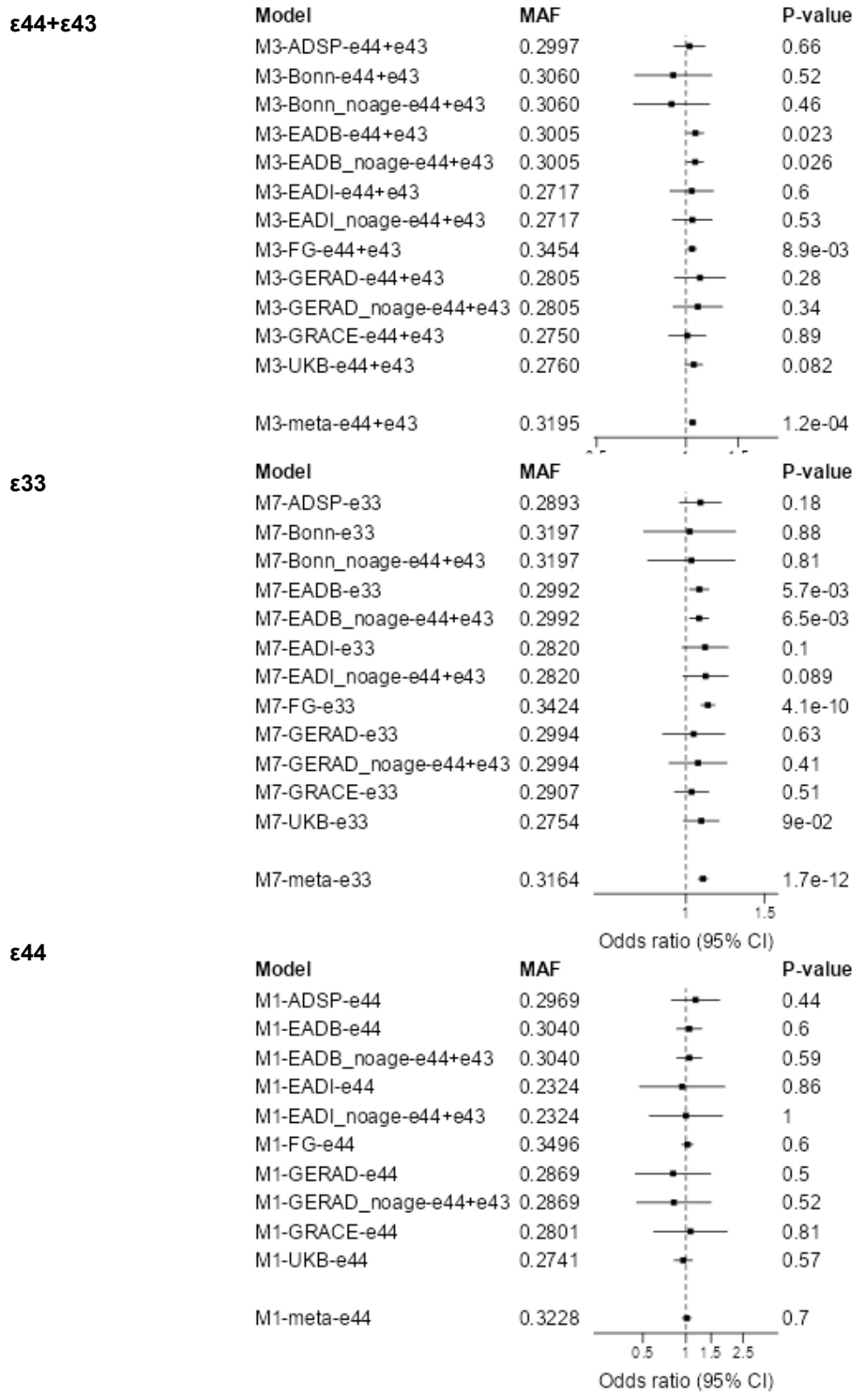
Supplementary Figure 46



Supplementary Figure 46: Forest plot across cohorts for *LINC02568.*

Forest plots across cohorts for the lead SNPs for *LINC02568* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

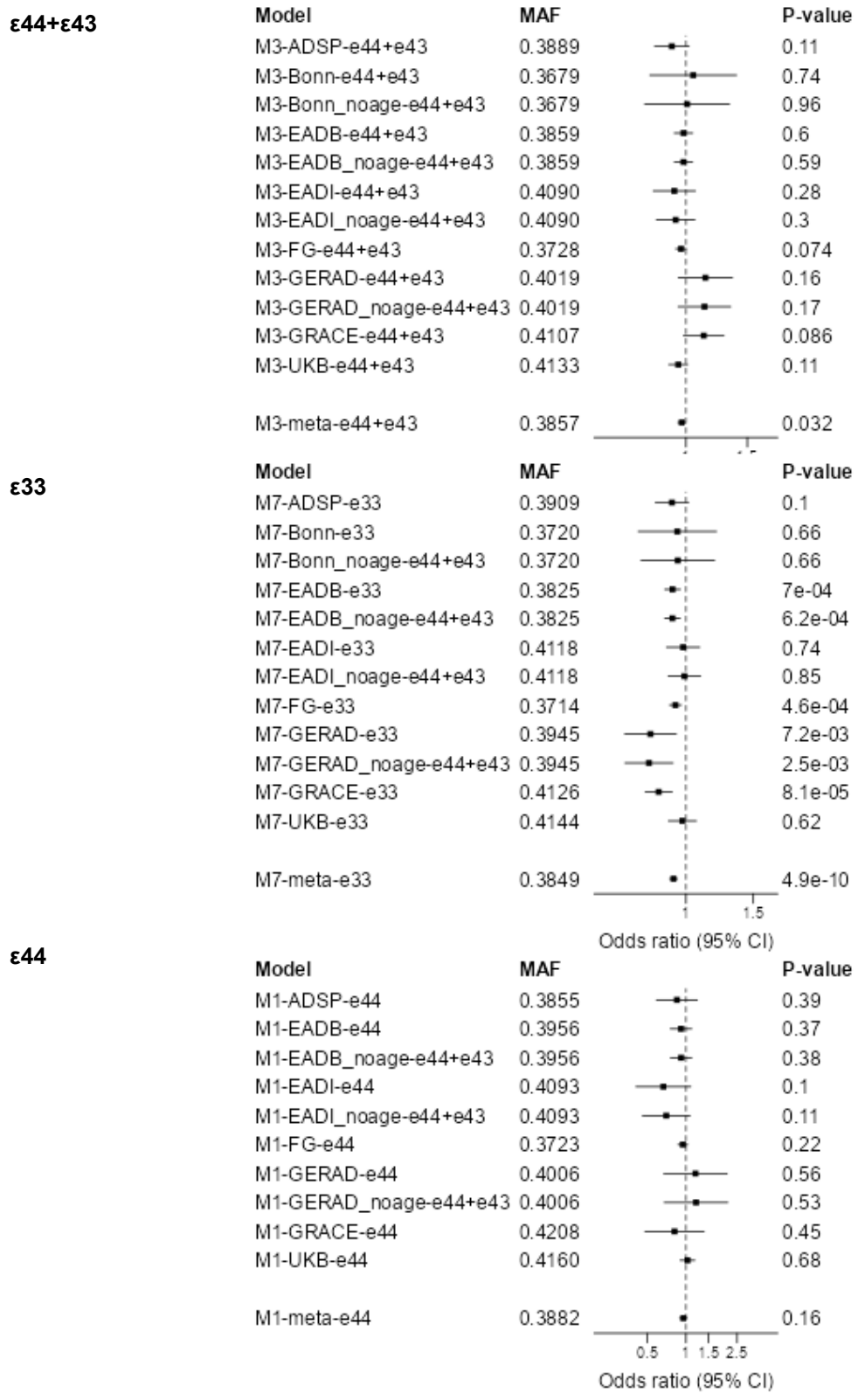
Supplementary Figure 47



Supplementary Figure 47: Forest plot across cohorts for *GRN*.

Forest plots across cohorts for the lead SNPs for *GRN* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

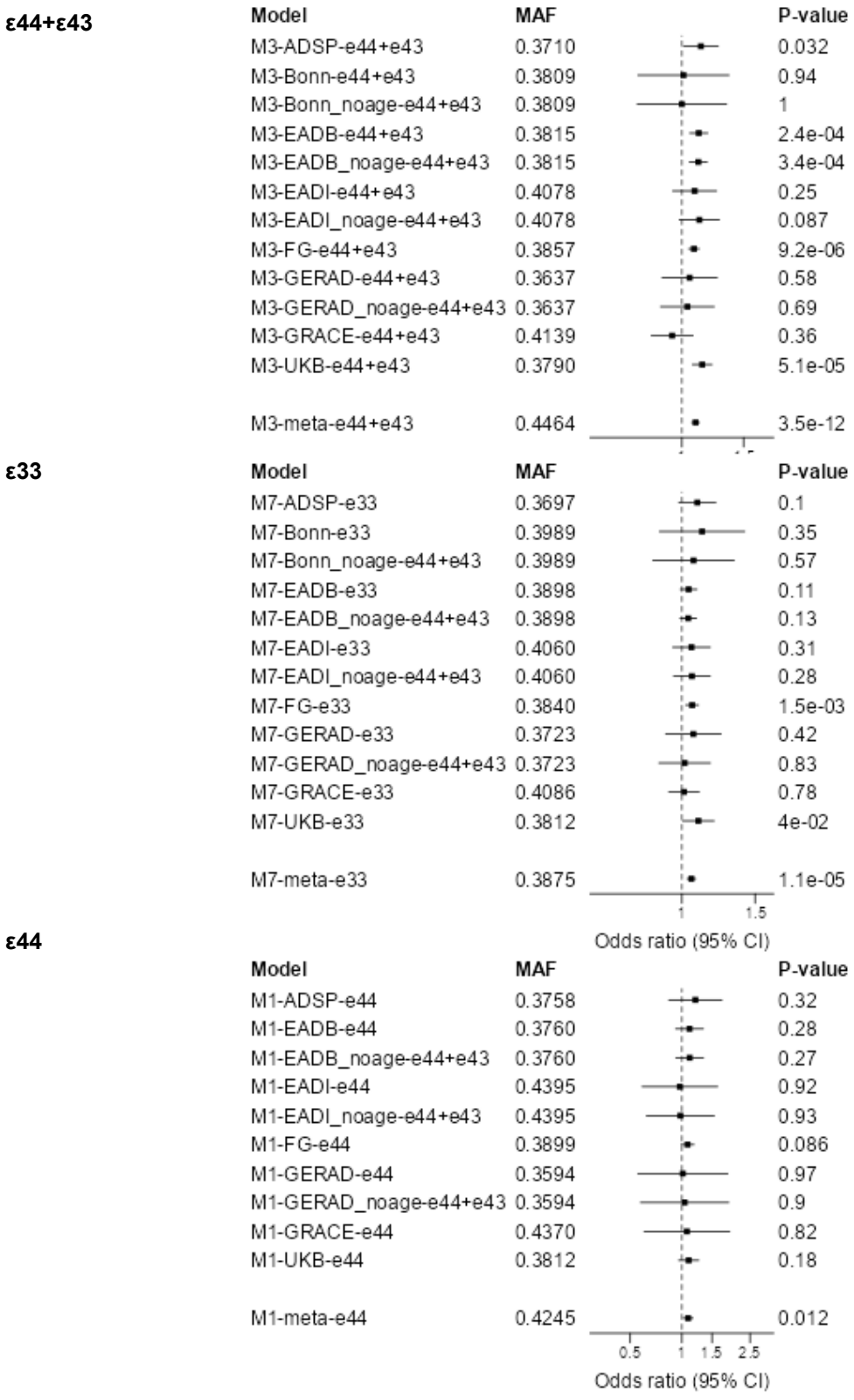
Supplementary Figure 48



Supplementary Figure 48: Forest plot across cohorts for *MAPT*.

Forest plots across cohorts for the lead SNPs for *MAPT* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

Supplementary Figure 49

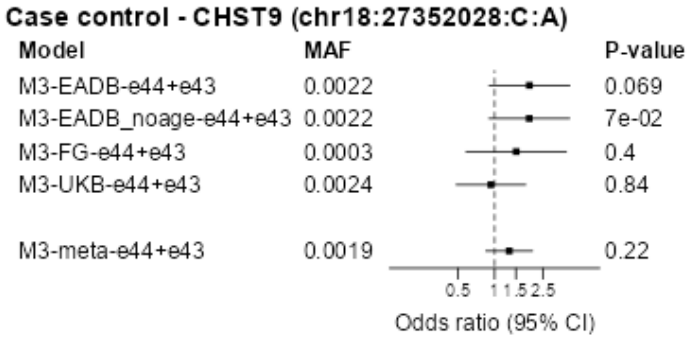


Supplementary Figure 49: Forest plot across cohorts for *ACE*.

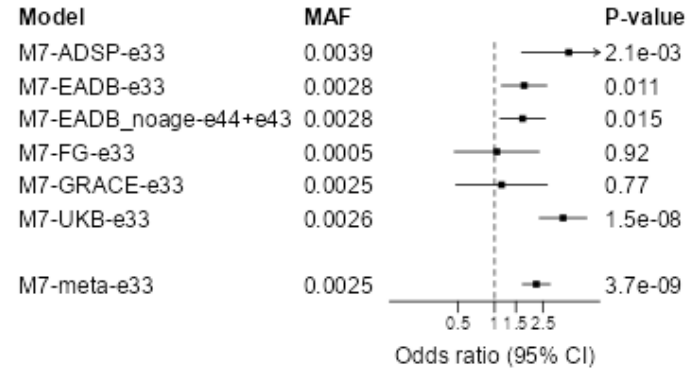
Forest plots across cohorts for the lead SNPs for *ACE* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

Supplementary Figure 50

ε44+ε43



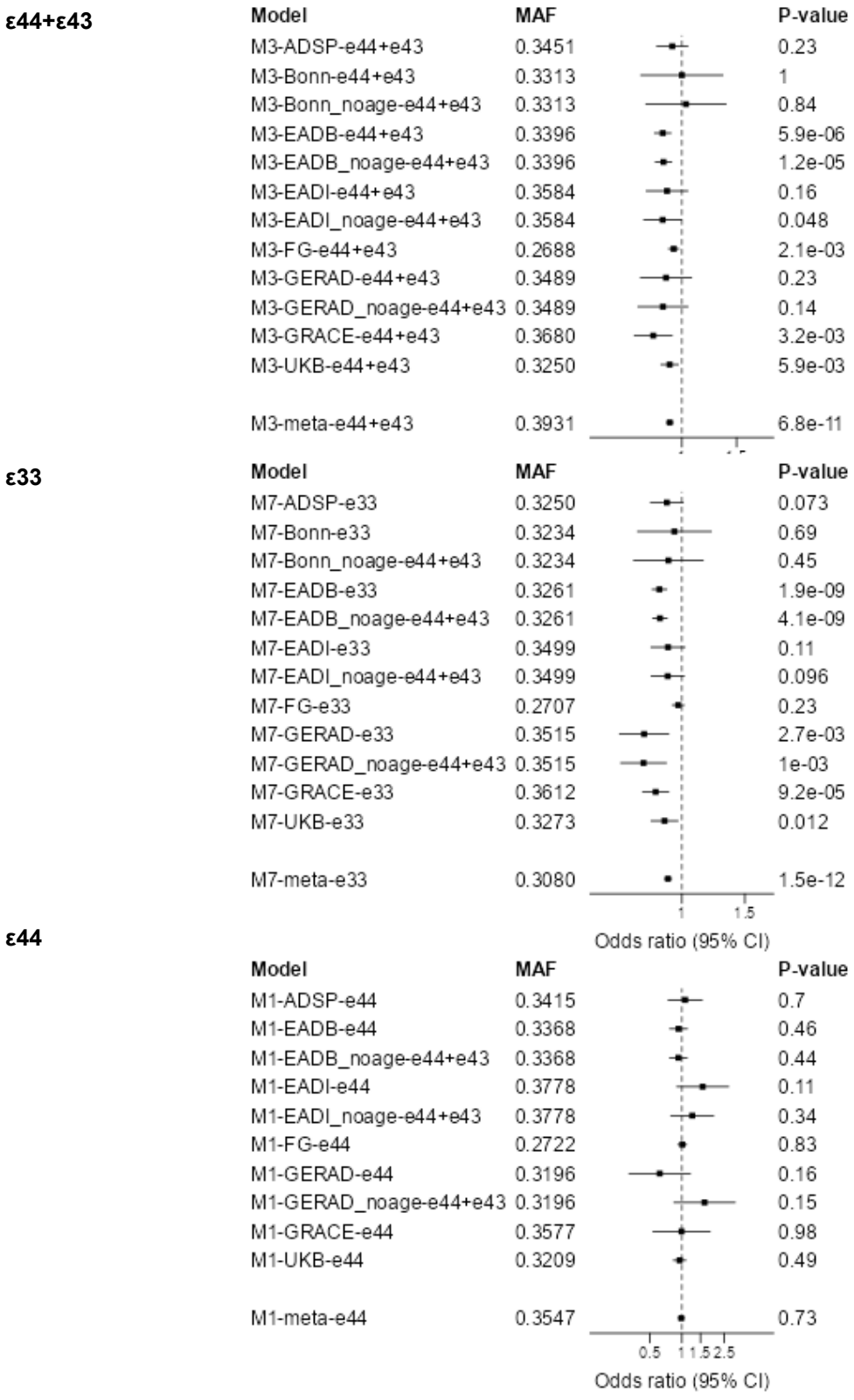
ε33



Supplementary Figure 50: Forest plot across cohorts for *CHST9*.

Forest plots across cohorts for the lead SNPs for *CHST9* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

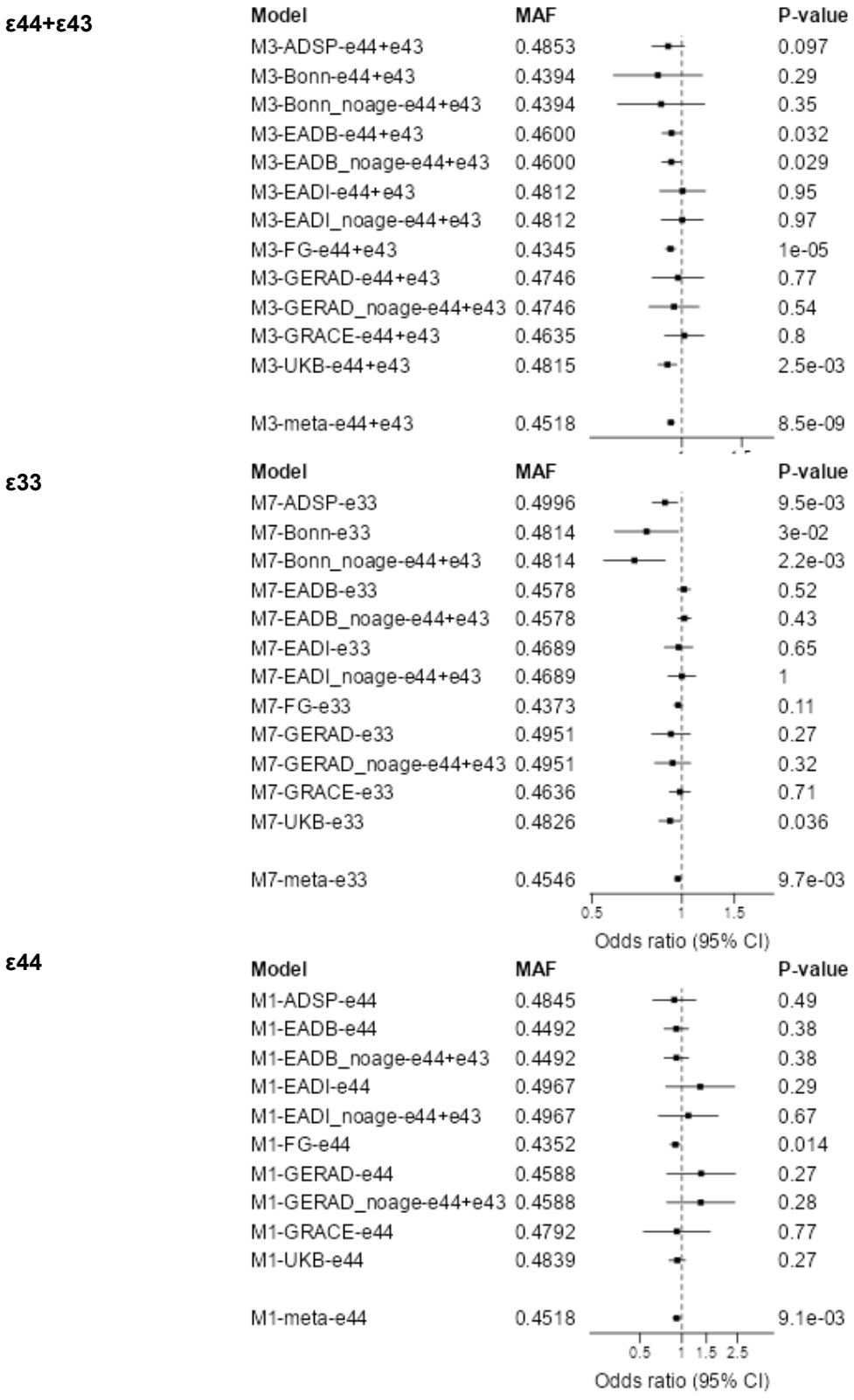
Supplementary Figure 51



Supplementary Figure 51: Forest plot across cohorts for *ABCA7*.

Forest plots across cohorts for the lead SNPs for *ABCA7* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

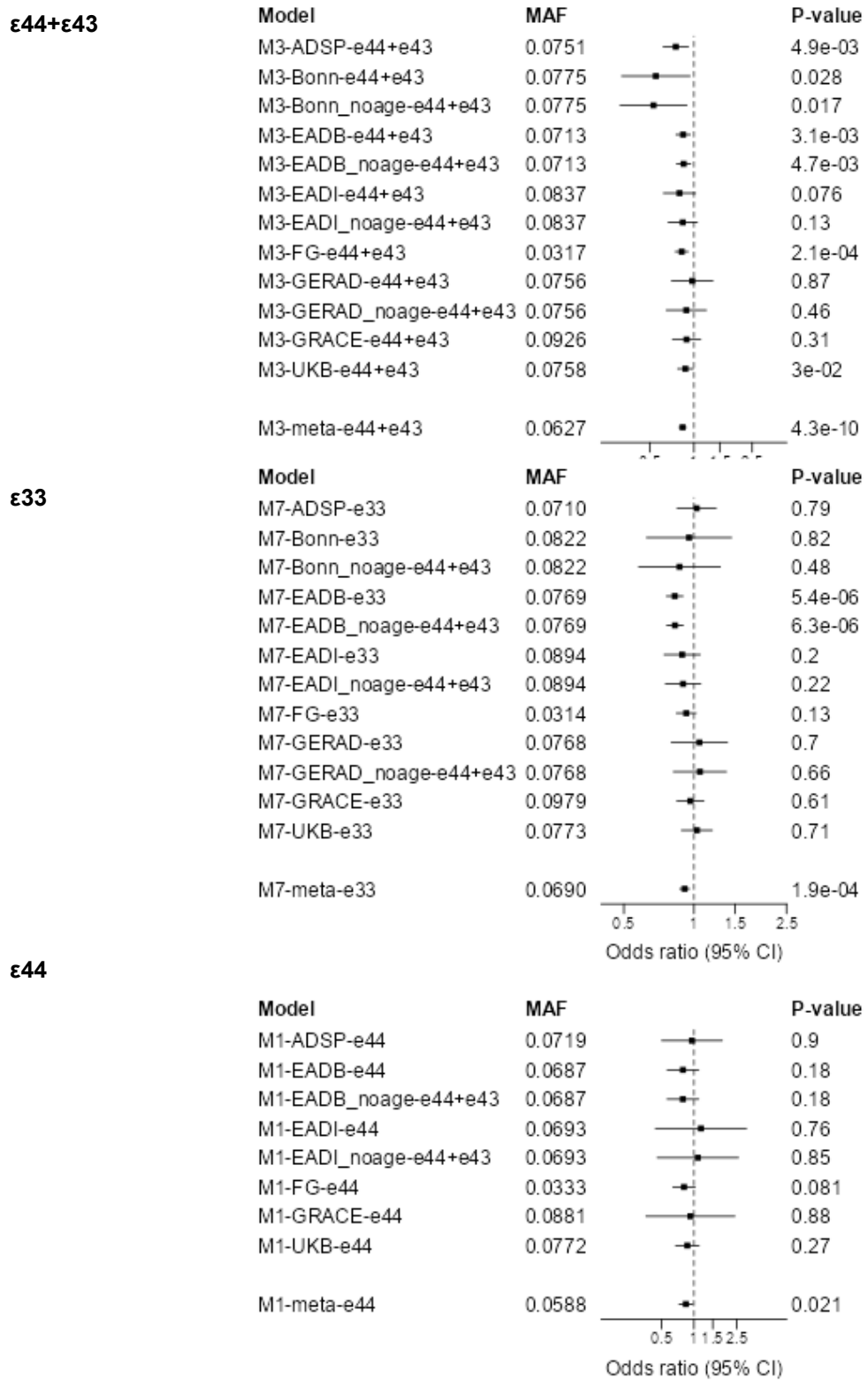
Supplementary Figure 52



Supplementary Figure 52: Forest plot across cohorts for *LILRA5*.

Forest plots across cohorts for the lead SNPs for *LILRA5* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

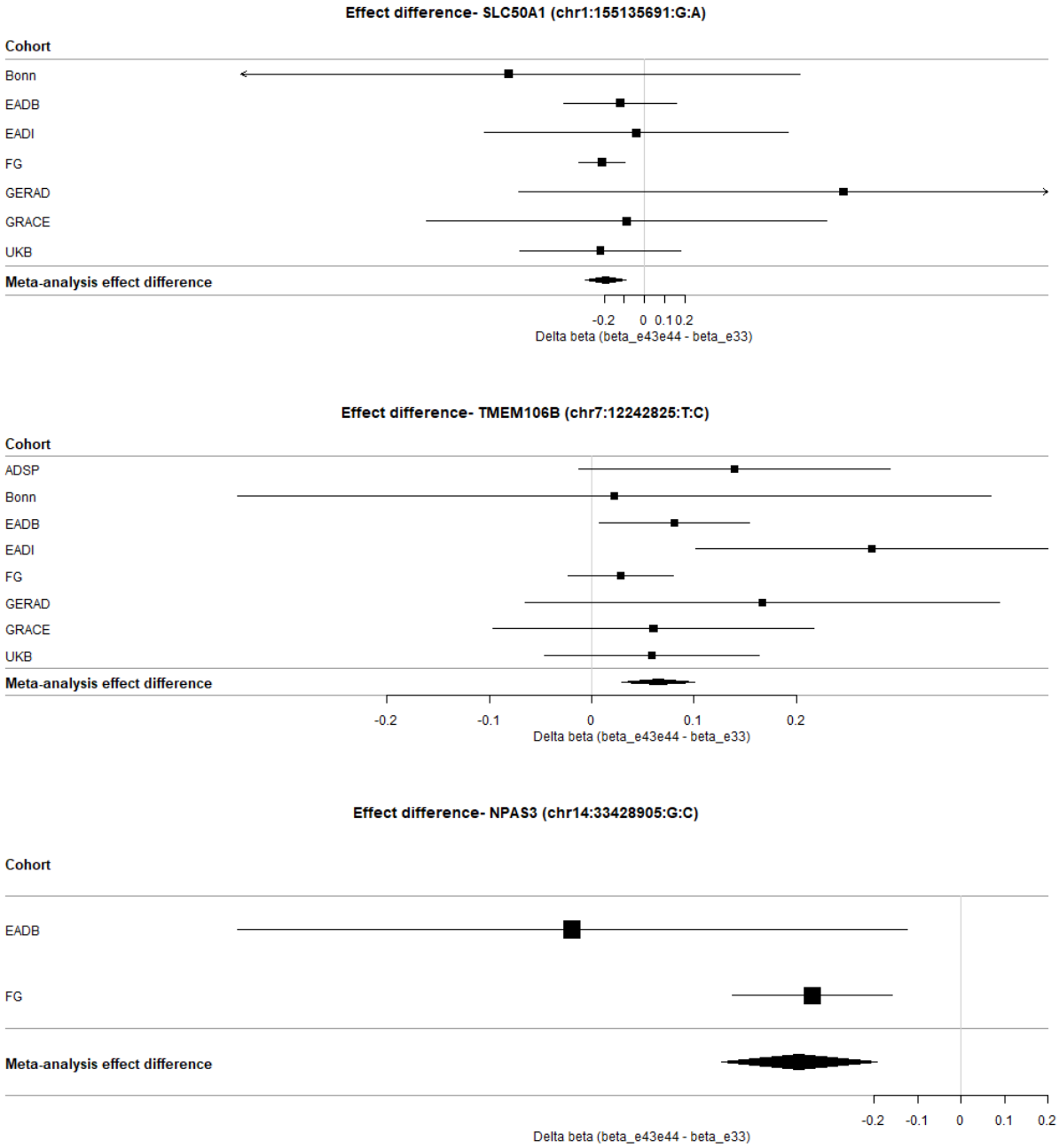
Supplementary Figure 53



Supplementary Figure 53: Forest plot across cohorts for *CASS4*

Forest plots across cohorts for the lead SNPs for *CASS4* in the three *APOE* strata ε44+ε43, ε33, and ε44. Sensitivity analyses with no age adjustment is marked with noage and are not included in the meta-analysis. The forest plot of the ε44 strata is included to illustrate the robustness across cohorts in this high-risk context.

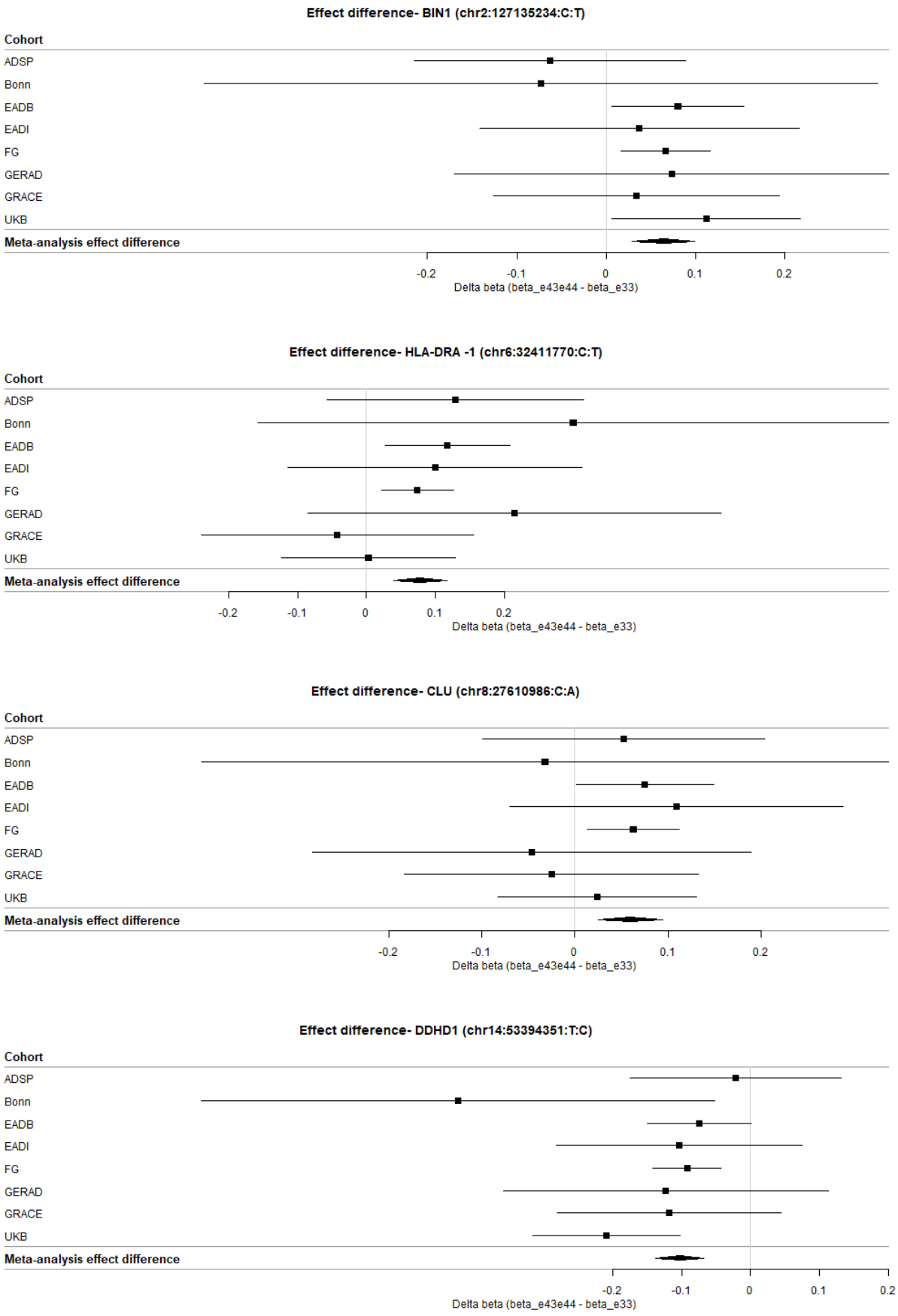
Supplementary Figure 54



Supplementary Figure 54: Forest plot for the effect difference between *APOE* strata ε44+ε43 and ε33 for loci with attenuated effect with the *APOE* ε4 allele.

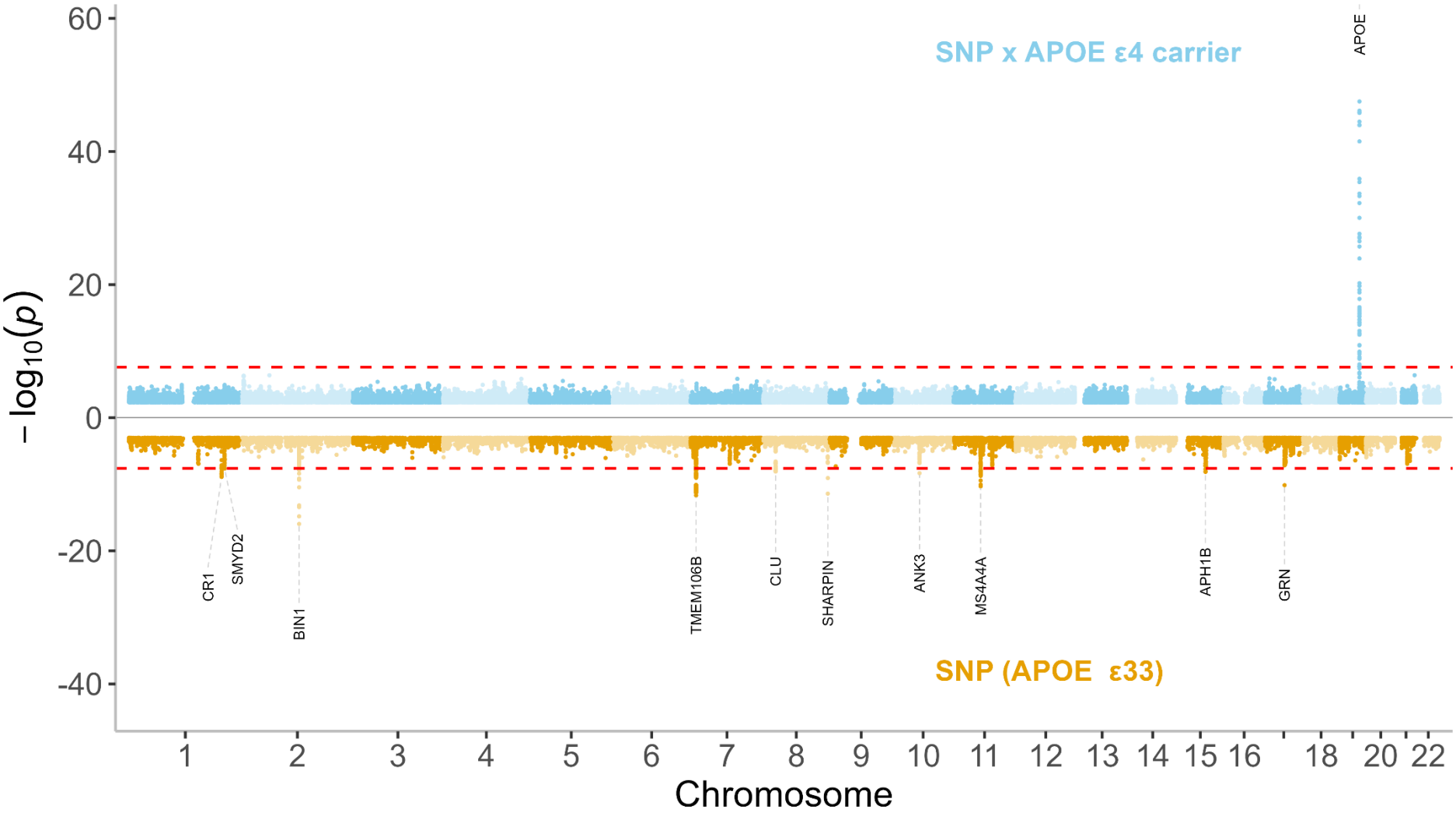
Forest plots for *SLC50A1*, *TMEM106B* and *NPAS3* of the effect difference between *APOE* strata ε44+ε43 and ε33. Note that the effect difference has been calculated with respect to the TOPMed reference allele. Only loci with dominant interaction are shown.

Supplementary Figure 55



Supplementary Figure 55: Forest plot for the effect difference between *APOE* strata ε44+ε43 and ε33 for loci with augmented effect with the *APOE* ε4 allele.

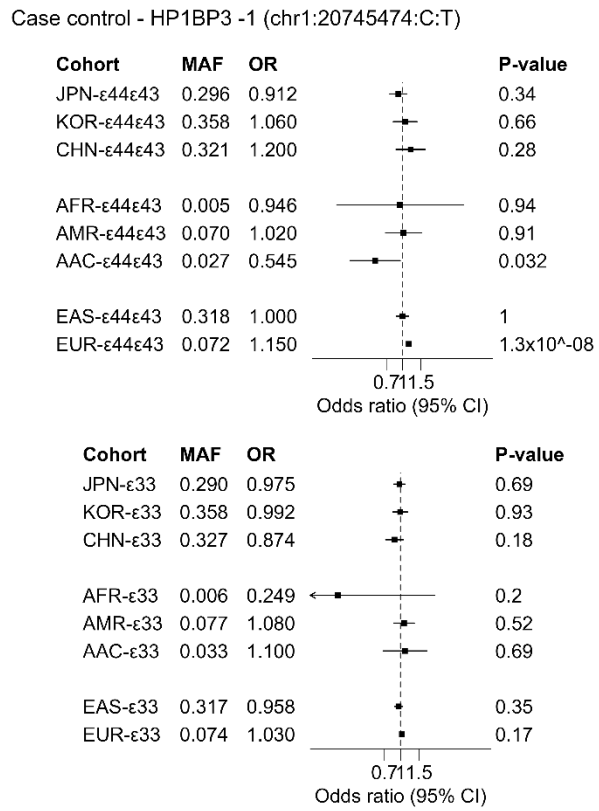
Forest plots for *BIN1*, *HLA-DRA -1*, *CLU* and *DDHD1* of the effect difference between *APOE* strata ε44+ε43 and ε33. Note that the effect difference has been calculated with respect to the TOPMed reference allele. Only loci with dominant interaction are shown.



Supplementary figure 56: Miami plot of the SNP term and interaction terms in the interaction model.

The Manhattan plot for the interaction term (SNP x *APOE* ε4 carrier) is shown in light blue in the upper part of the figure and for the SNP term (the reference level of the interaction model corresponding to the *APOE* ε33 strata) in orange in the lower part of the figure. Genome wide significant loci are annotated with the nearest gene. Two-sided raw P-values were derived from a fixed-effect meta-analysis. The red dashed lines show the genome-wide significant level ($P=2.5\times10^{-8}$). *APOE*: Apolipoprotein E gene.

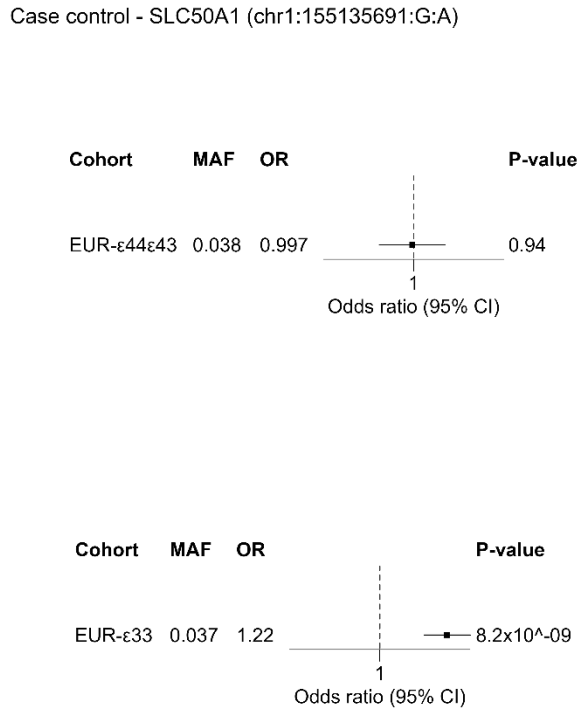
Supplementary Figure 57



Supplementary Figure 57: Evaluation of *HP1BP3* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *HP1BP3* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

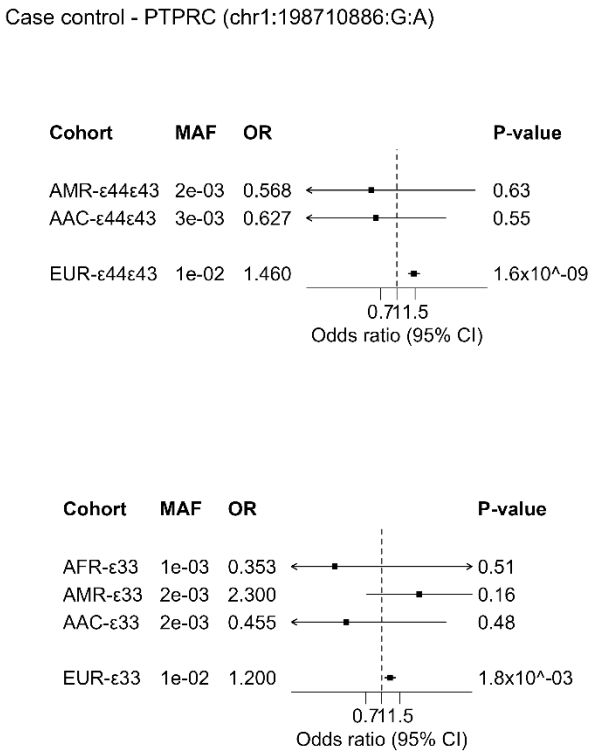
Supplementary Figure 58



Supplementary Figure 58: Evaluation of *SLC50A1* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *SLC50A1* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

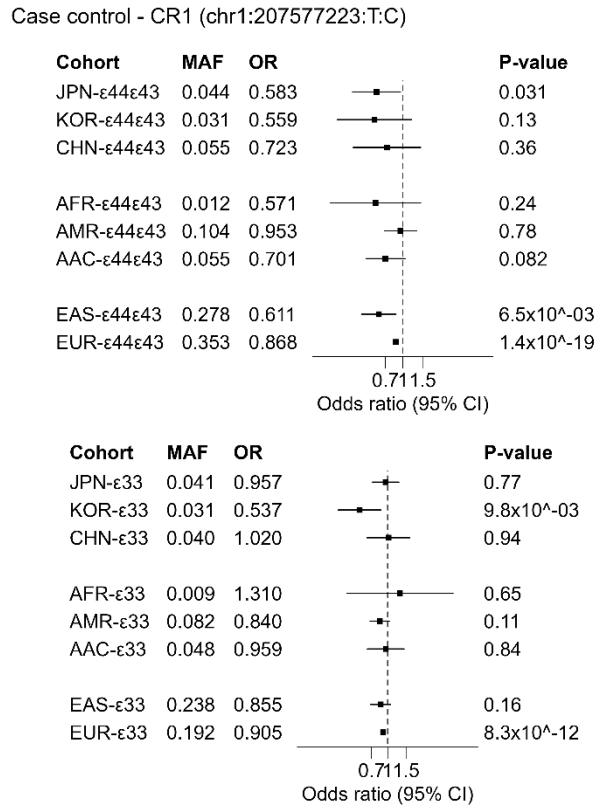
Supplementary Figure 59



Supplementary Figure 59: Evaluation of *PTPRC* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *PTPRC* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

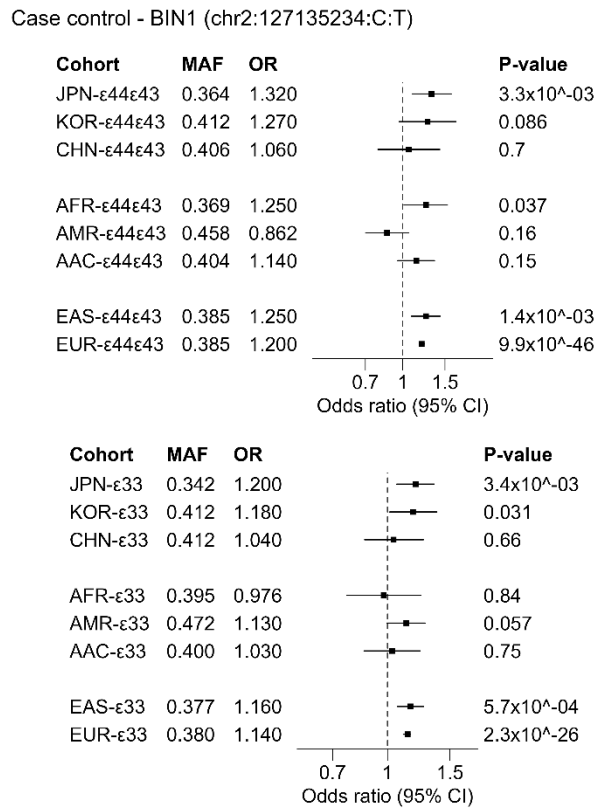
Supplementary Figure 60



Supplementary Figure 60: Evaluation of *CR1* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *CR1* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

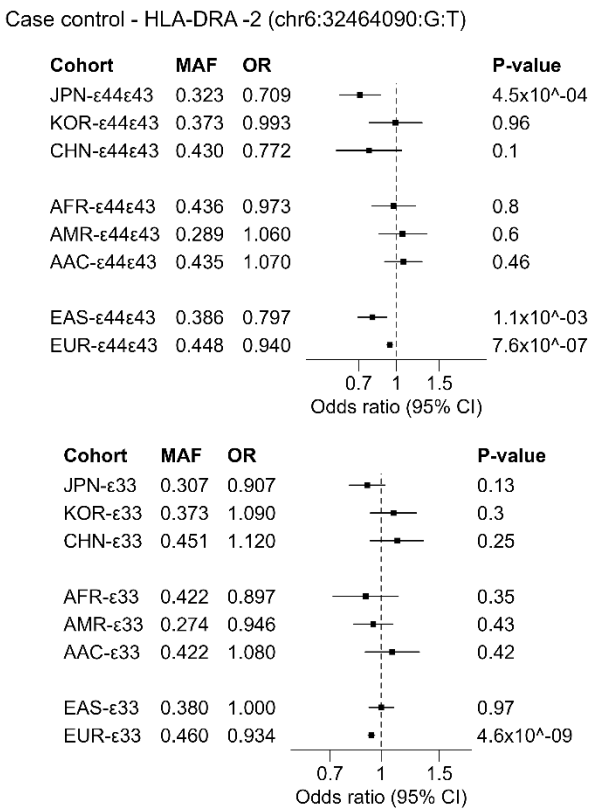
Supplementary Figure 61



Supplementary Figure 61: Evaluation of *BIN1* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *BIN1* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

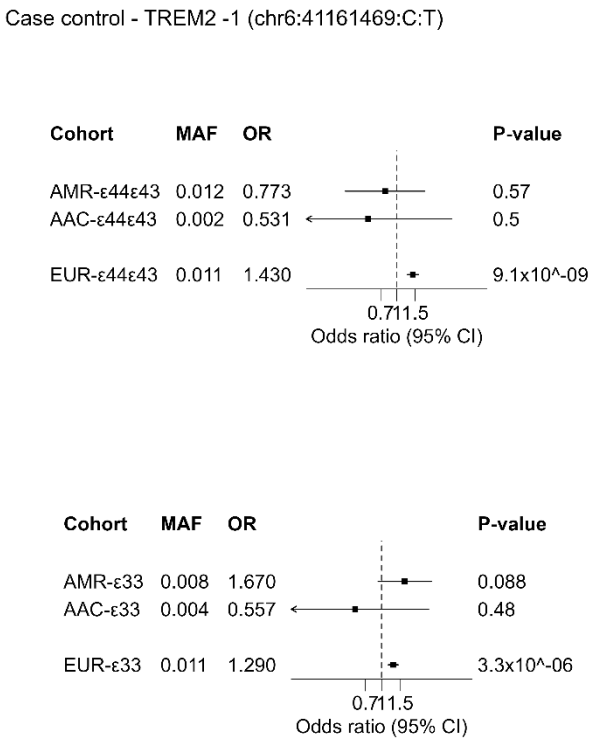
Supplementary Figure 62



Supplementary Figure 62: Evaluation of *HLA-DRA -2* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *HLA-DRA -2* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

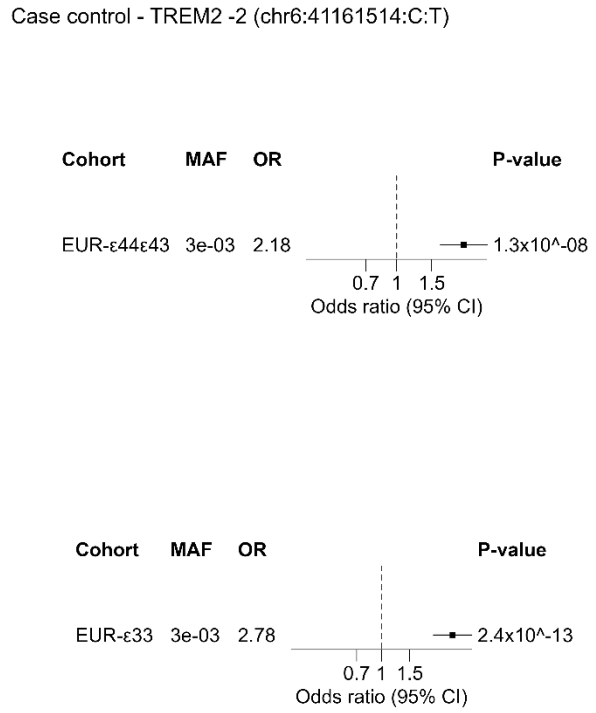
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Supplementary Figure 63: Evaluation of *TREM2 -1* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *TREM -1* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

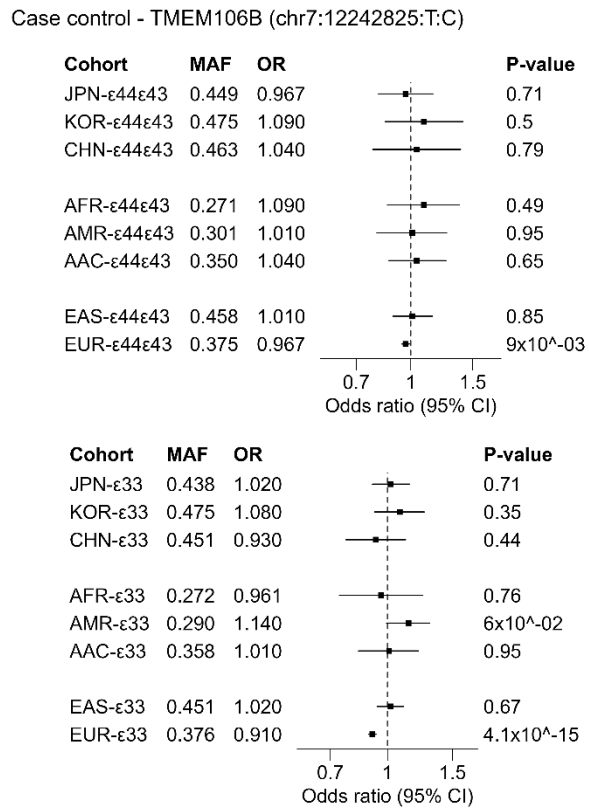
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Supplementary Figure 64: Evaluation of *TREM2 -2* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *TREM2 -2* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

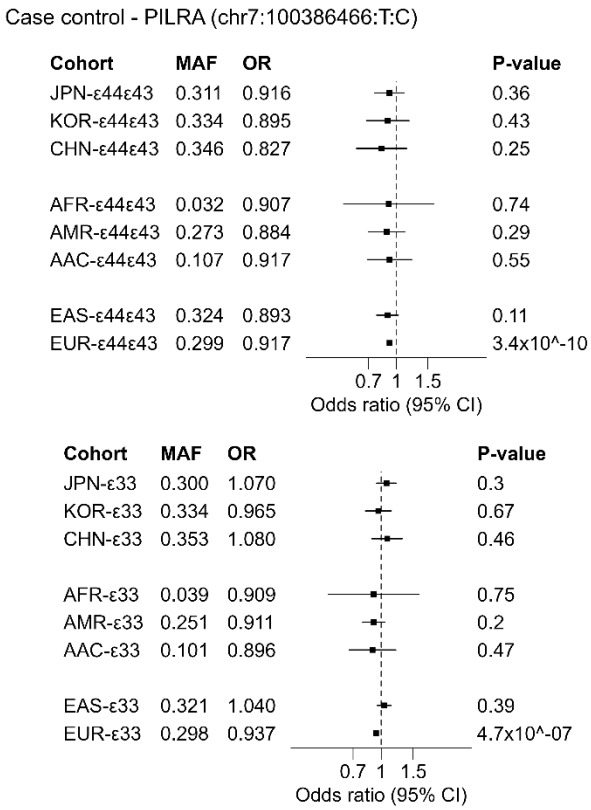
Supplementary Figure 65



Supplementary Figure 65: Evaluation of *TMEM106B* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *TMEM106B* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

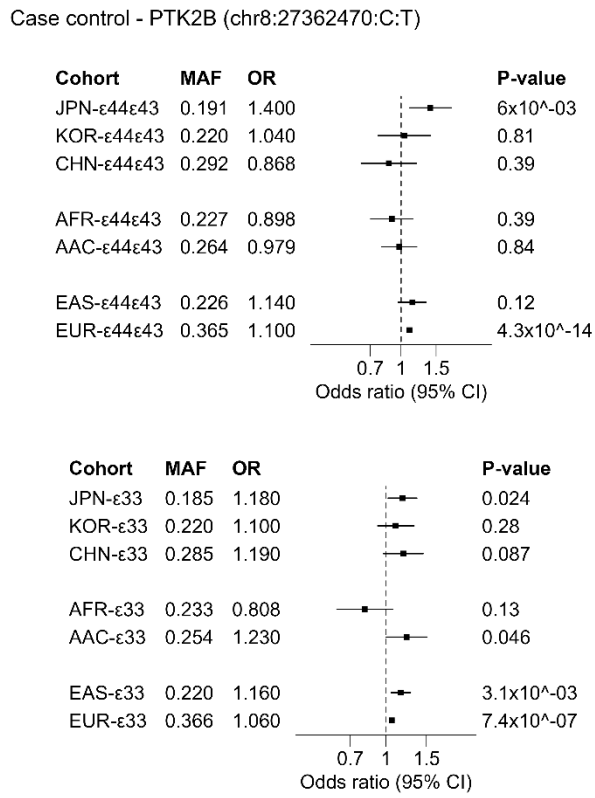
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Supplementary Figure 66: Evaluation of *PILRA* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *PILRA* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

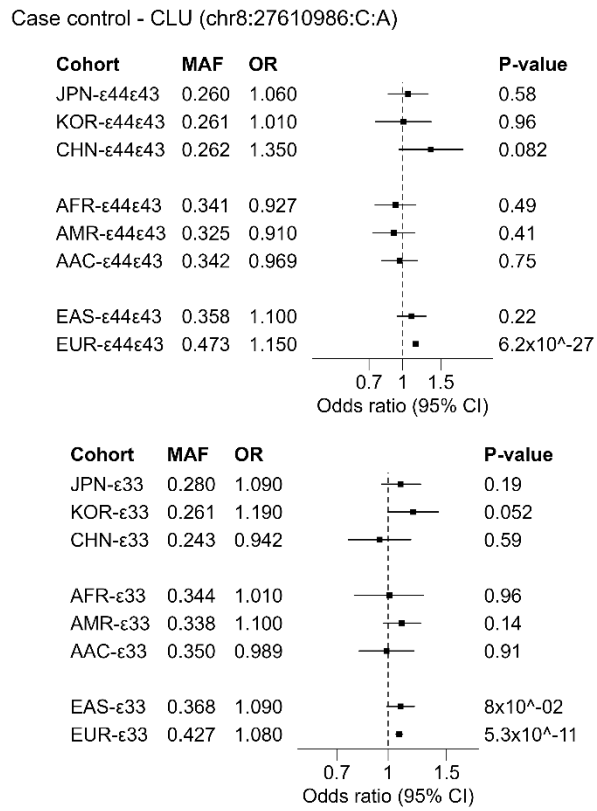
Supplementary Figure 67



Supplementary Figure 67: Evaluation of *PTK2B* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *PTK2B* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

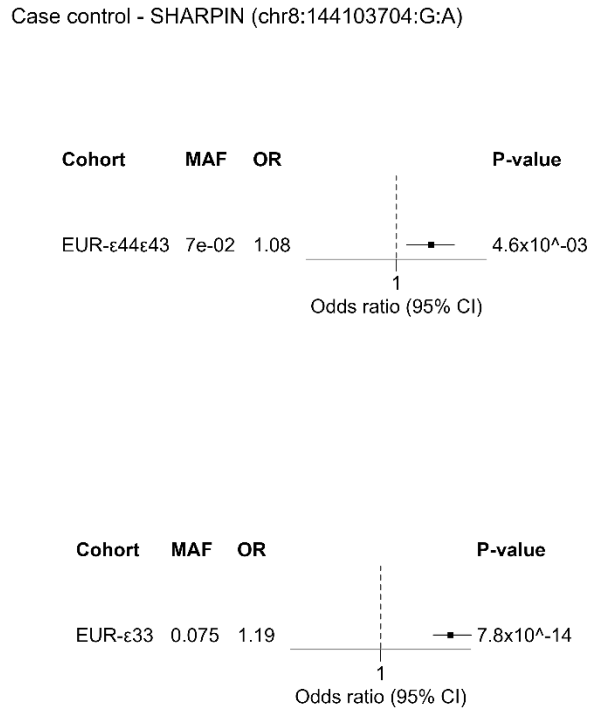
Supplementary Figure 68



Supplementary Figure 68: Evaluation of *CLU* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *CLU* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

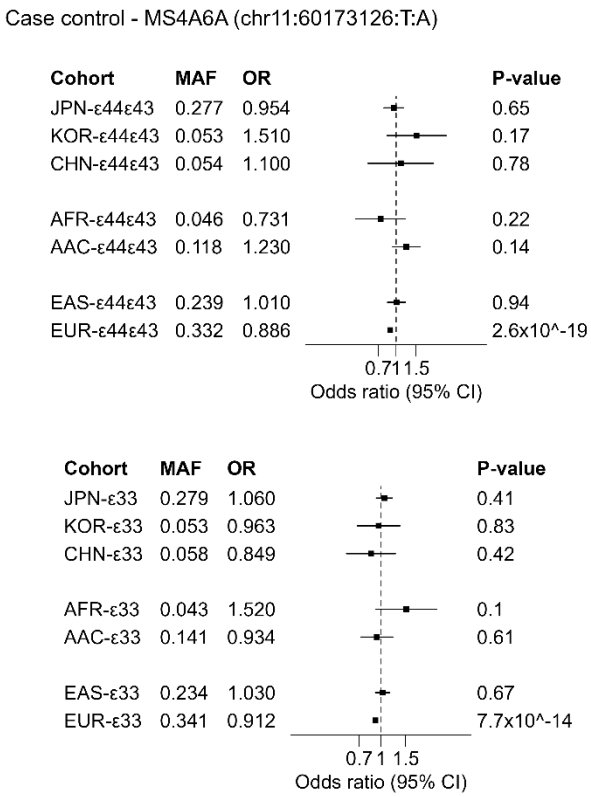
Supplementary Figure 69



Supplementary Figure 69: Evaluation of *SHARPIN* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *SHARPIN* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

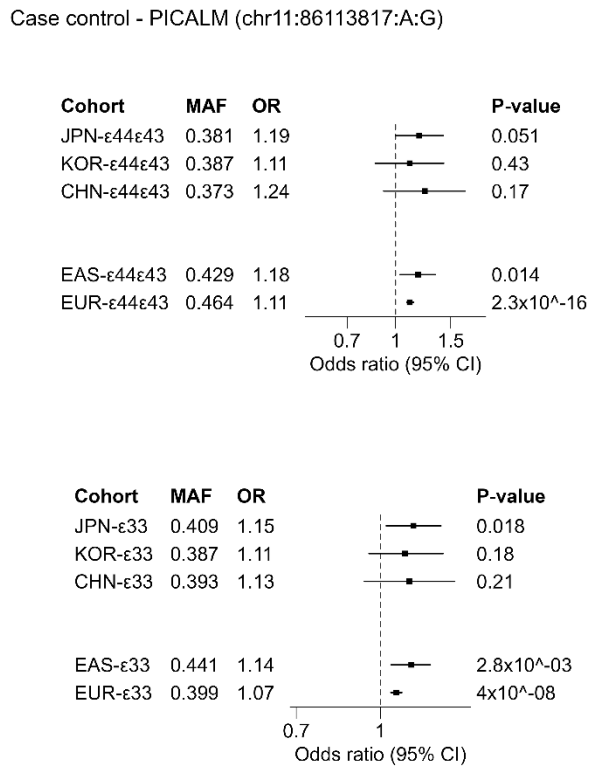
Supplementary Figure 70



Supplementary Figure 70: Evaluation of *MS4A6A* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *MS4A6A* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

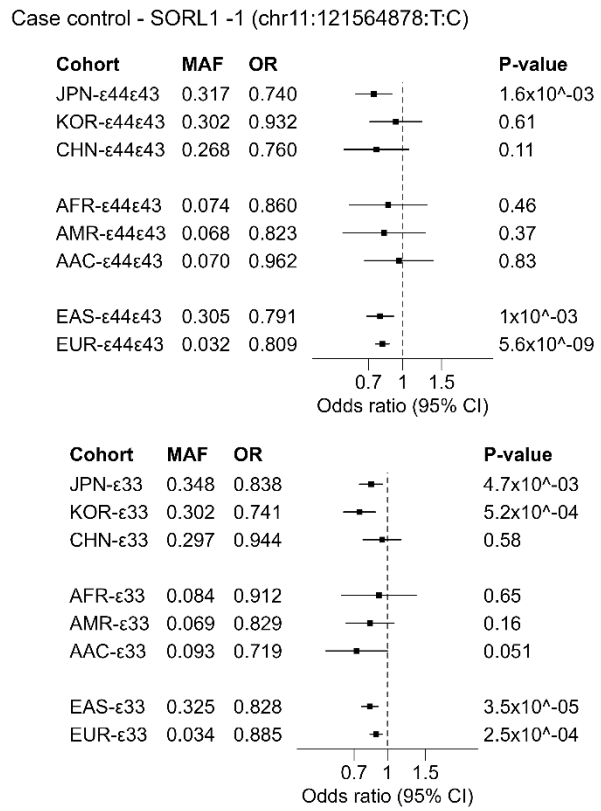
Supplementary Figure 71



Supplementary Figure 71: Evaluation of *PICALM* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *PICALM* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

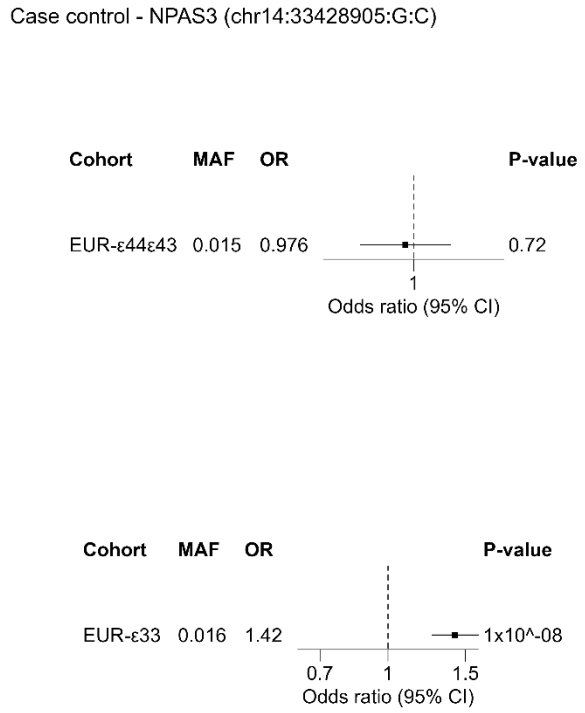
Supplementary Figure 72



Supplementary Figure 72: Evaluation of *SORL1* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *SORL1* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

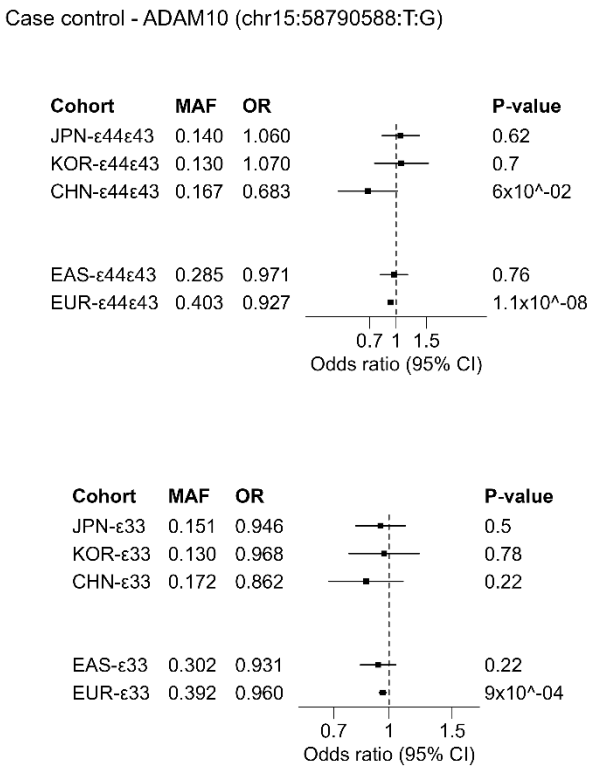
Supplementary Figure 73



Supplementary Figure 73: Evaluation of *NPAS3* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *NPAS3* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

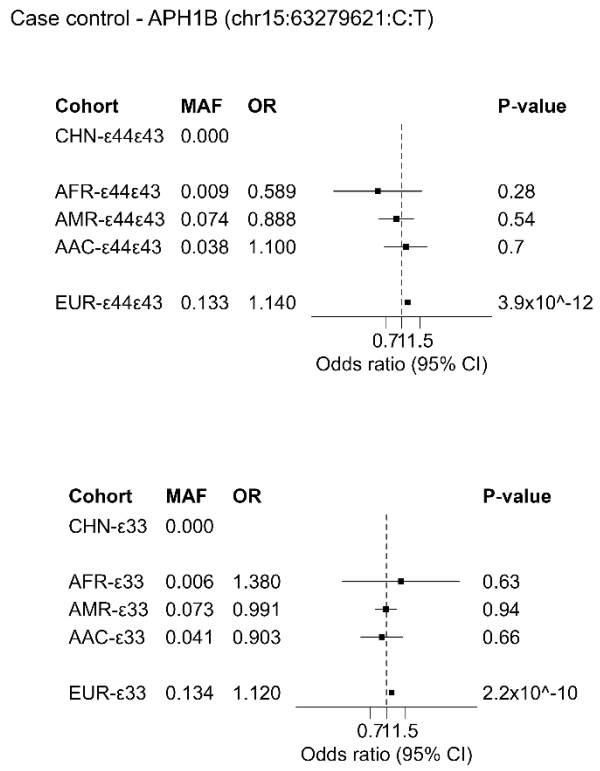
Supplementary Figure 74



Supplementary Figure 74: Evaluation of *ADAM10* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *ADAM10* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

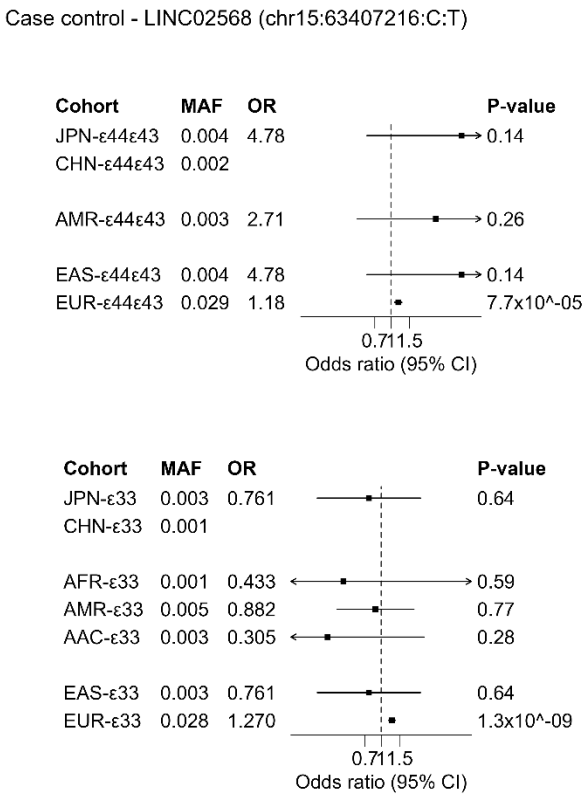
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Supplementary Figure 75: Evaluation of *APH1B* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *APH1B* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

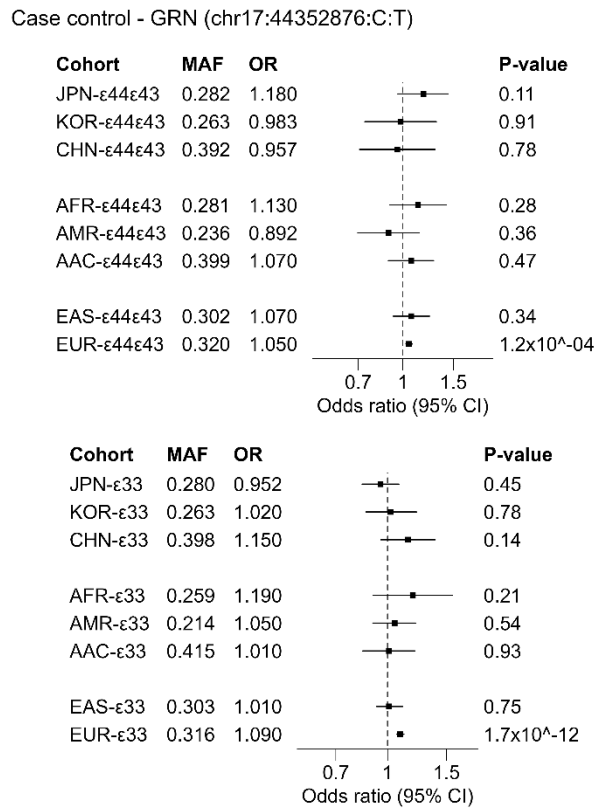
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Supplementary Figure 76: Evaluation of *LINC02568* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *LINC02568* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

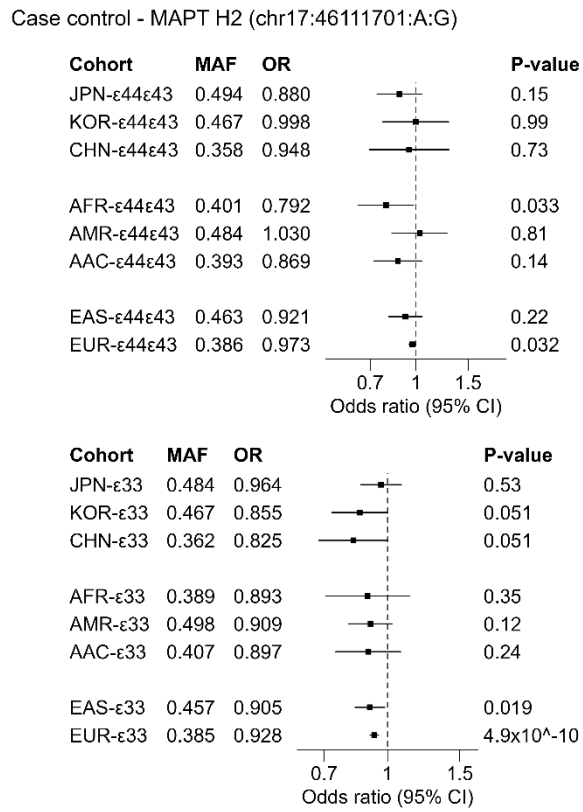
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Supplementary Figure 77: Evaluation of *GRN* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *GRN* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

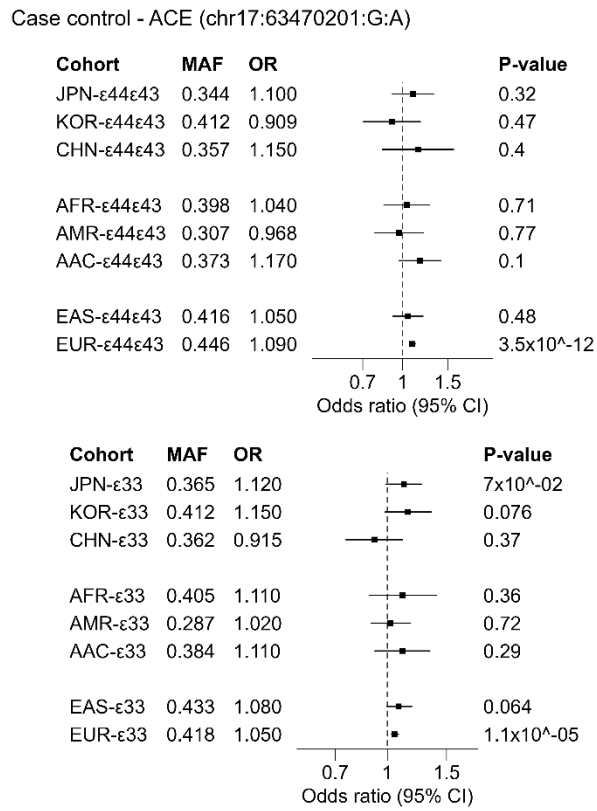
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Supplementary Figure 78: Evaluation of *MAPT* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *MAPT* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

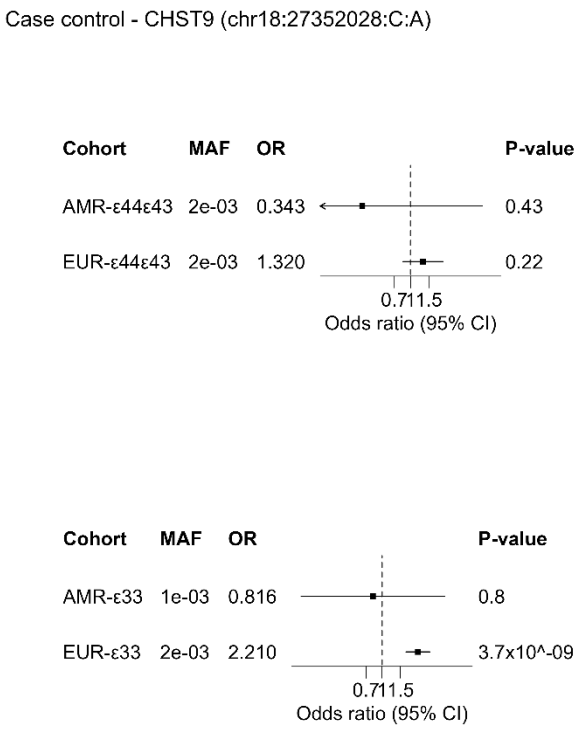
Supplementary Figure 79



Supplementary Figure 79: Evaluation of *ACE* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *ACE* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

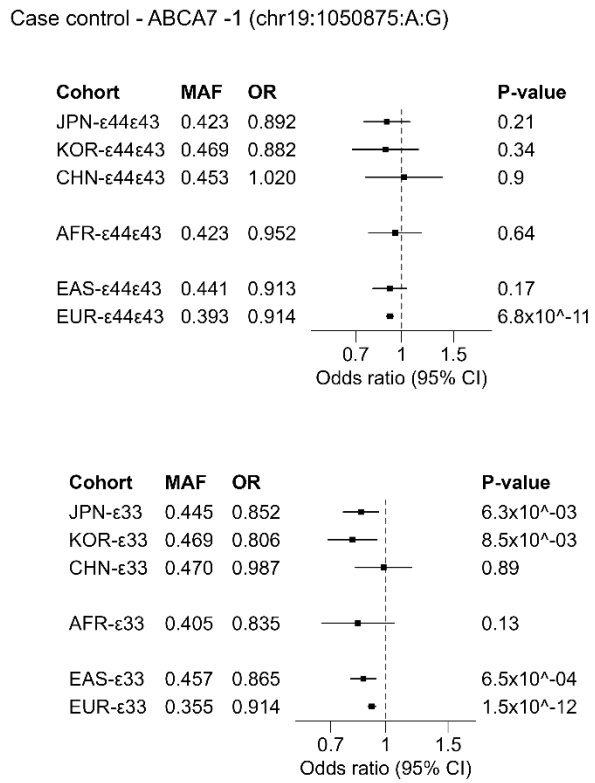
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Supplementary Figure 80: Evaluation of *CHST9* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *CHST9* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

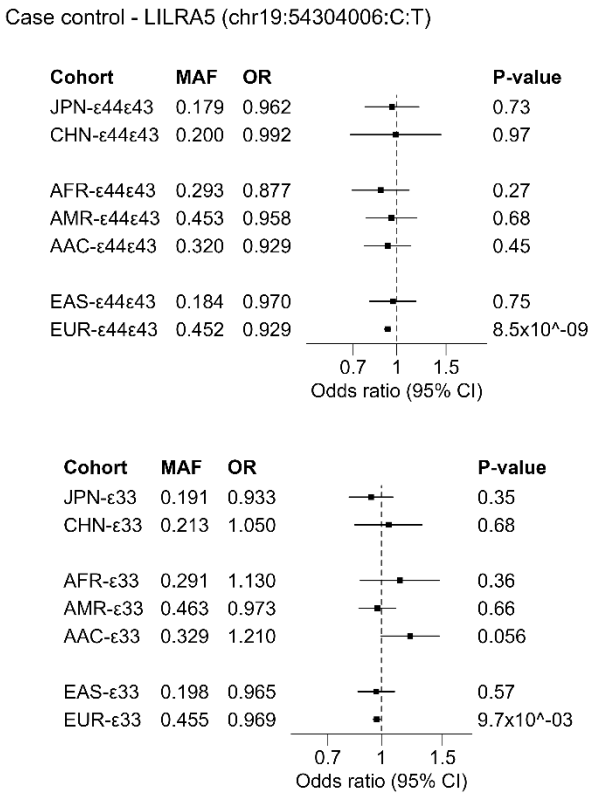
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Supplementary Figure 81: Evaluation of *ABCA7* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *ABCA7* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

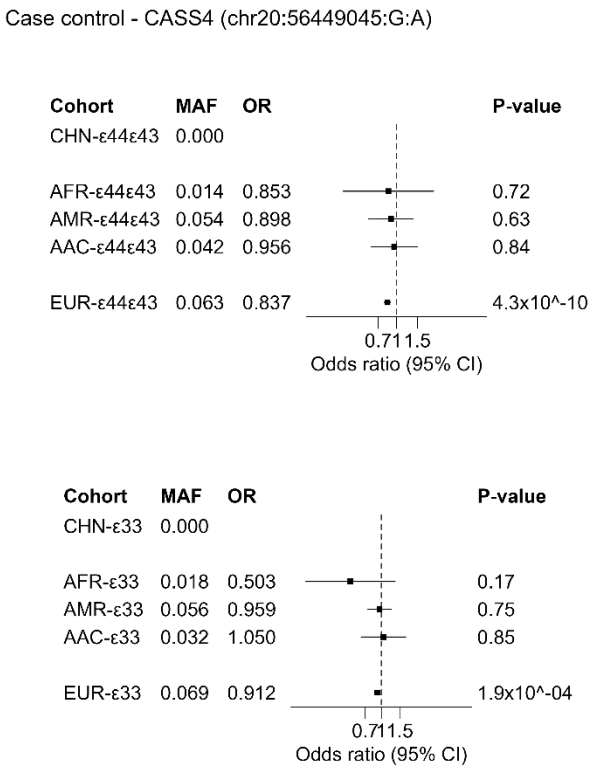
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Supplementary Figure 82: Evaluation of *LILRA5* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *LILRA5* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

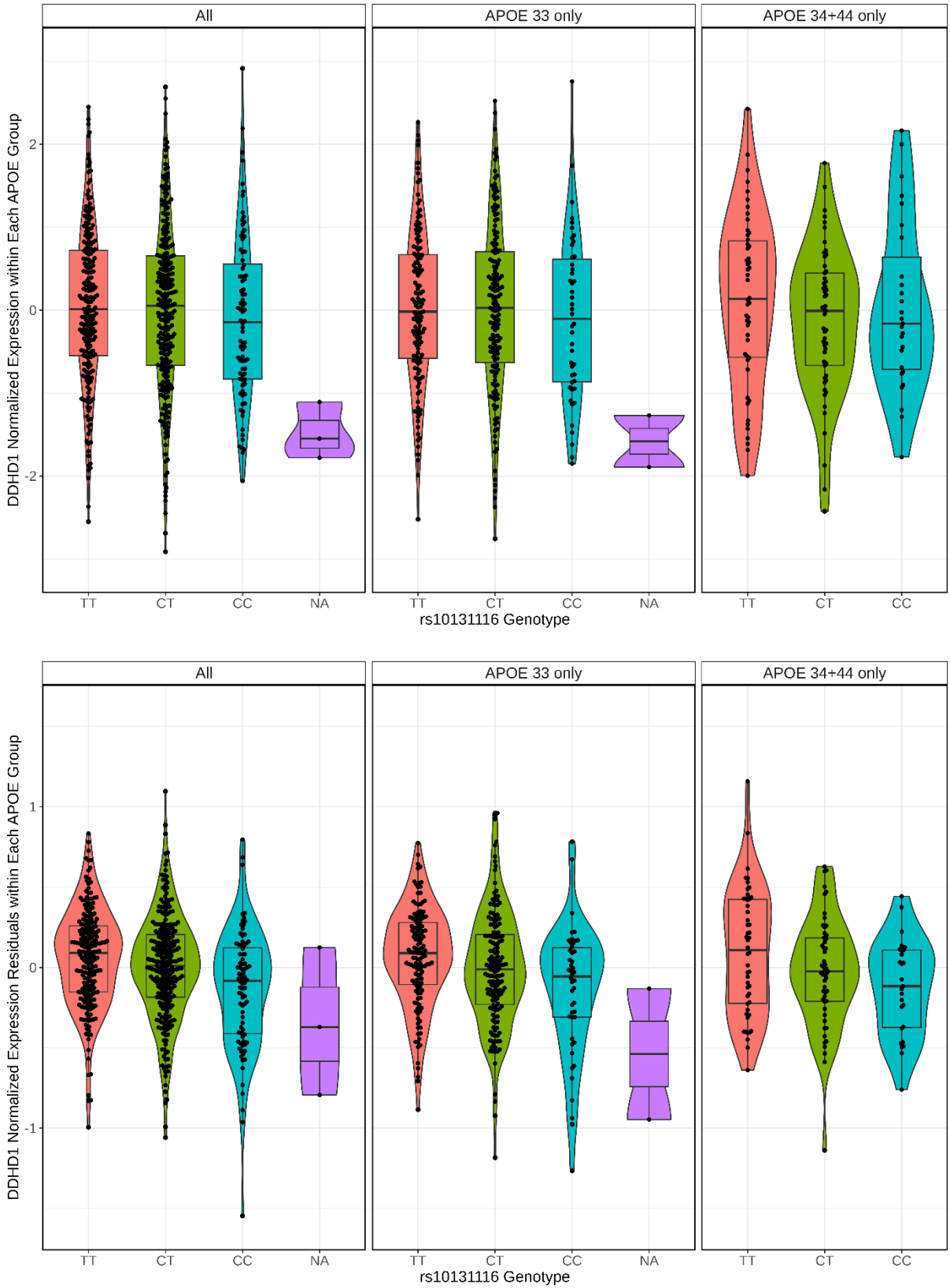
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Supplementary Figure 83: Evaluation of *CASS4* SNP across cohorts of different ancestry.

Forest plots for the lead SNP for *CASS4* across cohorts of different ancestry and fixed-effect meta-analysis estimates of the East Asian and European cohorts respectively in the two *APOE* strata ε44+ε43 and ε33. AAC: American Asian, AFR: American African, AMR: Admixed American, CHN: Hong Kong Chinese, EAS: East Asian, EUR: European, JPN: Japanese, KOR: Korean.

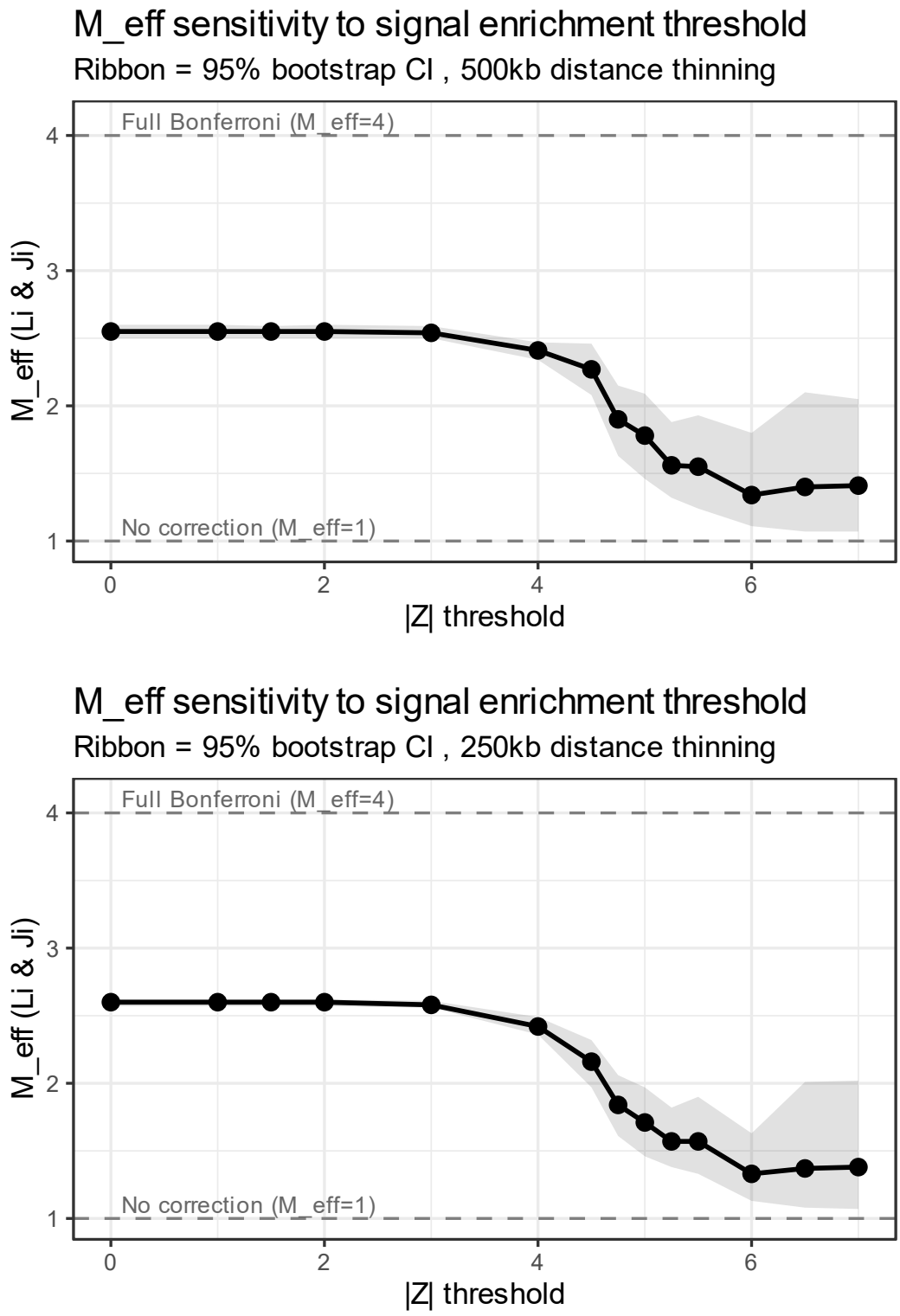
Supplementary Figure 84



Supplementary Figure 84: rs10131116 association with *DDHD1* expression

eQTL violin plots showing rs10131116 association with normalized *DDHD1* expression (top) and residuals of normalized expressions of *DDHD1* in the ROSMAP DLPFC data set shown in full dataset (left), and *APOE* ε33 strata (middle) and *APOE* ε44+ε43 strata (right).

Supplementary Figure 85



Supplementary Figure 85: M_{eff} estimation by eigenvalue decomposition of inter-strata estimated effect correlation.

Upper figure shows the effective number of independent tests (M_{eff}) estimation at different |z|-thresholds with a SNP thinning in 500 kb windows. The lower figure shows similar with a 250 kb SNP window thinning. The observed plateau M_{eff}≈1.3-1.4 for |z| > 5 is an empirical estimation of the effective number of independent tests needed to correct for in multiple testing.

APOE stratified genome-wide association analyses provide insights into the genetic etiology of Alzheimers's disease

Supplementary Note

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1. GWAS Cohort descriptions and acknowledgements

1.1 European Alzheimer & Dementia Biobank (EADB-TOPMed)

This consortium groups together 20,464 Alzheimer's disease (AD) cases and 22,244 controls after quality controls from 16 European countries (Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Portugal, Spain, Sweden, Switzerland, The Netherlands and the UK). These samples were genotyped in three independent centers (France, Germany and the Netherlands) leading to define three nodes: EADB-France, EADB-Germany and EADB-Netherlands. In addition, EADB also included Australian partners.

We thank the numerous participants, researchers, and staff from many studies who collected and contributed to the data. We thank the high performance computing service of the University of Lille. We thank all the CEA-CNRGH staff who contributed to sample preparation and genotyping for their excellent technical assistance.

This work was supported by a grant (European Alzheimer DNA BioBank, EADB) from the EU Joint Programme – Neurodegenerative Disease Research (JPND). Inserm UMR1167 is also funded by Inserm, Institut Pasteur de Lille, the Lille Métropole Communauté Urbaine, the French government's LABEX DISTALZ program (development of innovative strategies for a transdisciplinary approach to Alzheimer's disease).

EADB-France. In the France node, samples were collected from nine countries (39 centers/studies), and after quality controls (QCs), we obtained 13,867 AD cases and 15,310 controls. All these samples were genotyped at the Centre National de Recherche en Génomique Humaine (CNRGH, Evry, France).
Belgium: The participants were part of a large prospective cohort (PMID: 29589097) of Belgian AD patients and healthy elderly control individuals. The patients were ascertained at the memory clinic of Middelheim and Hoge Beuken (Hospital Network Antwerp, Belgium) and at the memory clinic of the University Hospitals of Leuven, Belgium. The control individuals were the partners of the patients or volunteers from the Belgian community. The study protocols were approved by the ethics committees of the Antwerp University Hospital and the participating neurological centers at the different hospitals of the BELNEU consortium and by the University of Antwerp.
Czech Republic: The Czech Brain Aging Study (CBAS) (PMID: 31857299) is a longitudinal memory-clinic–based study recruiting subjects at risk of dementia (subjects referred for cognitive complaints-SCD, MCI). The CBAS+ study is a cross-sectional study of patients in the early stages of dementia. All subjects signed informed consent and both studies were approved by the local ethics committee.
Denmark: The Copenhagen General Population Study (CGPS) is a prospective study of the Danish general population initiated in 2003 and still recruiting. Individuals were selected randomly based on the national Danish Civil Registration System to reflect the adult Danish population aged 20-100. Data were obtained from a self-administered questionnaire reviewed together with an investigator at the day of attendance, a physical examination, and from blood samples including DNA extraction (PMID: 33022702). The study is approved by the regional ethics committee and by the Steering Committee of the CGPS.
Finland: *The ADGEN cohort (PMID: 25807283):* clinic-based collection of AD patients from Eastern and Northern Finland examined in the Department of Neurology in Kuopio University Hospital and the Department of Neurology in Oulu University Hospital. All the patients were diagnosed with probable AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS–ADRDA). The study was approved by the ethics committee of Kuopio University Hospital, Finland (420/2016). *The FINGER study* (PMID: 25771249): a Finnish multi-domain lifestyle RCT enrolling 1,260 older adults with an increased risk of dementia from the general population. The intensive lifestyle intervention lasted for two years, and follow-up extends currently up to seven years. The FINGER study was approved by the

coordinating ethics committee of the Hospital District of Helsinki and Uusimaa (94/13/03/00/2009 and HUS/1204/2017), and all the participants gave written informed consent.
France: *The BALTAZAR multicenter (23 memory centers) prospective study* (PMID: 29458036): 1,040 participants from September 2010 to April 2015. They were classified as AD cases (n = 501) according to DSM IV-TR and NINCDS–ADRDA criteria as well as amnestic mild cognitive impairment (MCI) cases (a MCI, n = 417) and non-amnestic MCI cases (na MCI, n = 122) according to Petersen's criteria. A comprehensive battery of cognitive tests was performed, including MMSE, verbal fluency, and FCSRT. All the participants or their legal guardians gave written informed consent. The study was approved by the Paris ethics committee (CPP Ile de France IV Saint Louis Hospital). MEMENTO: a clinic-based study (PMID: 28851447) aimed at better understanding the natural history of AD, dementia, and related diseases. Between 2011 and 2014, 2,323 individuals presenting either recently diagnosed MCI or isolated cognitive complaints were enrolled in 26 memory centers in France. This study was performed in accordance with the guidelines of the Declaration of Helsinki. The MEMENTO study protocol has been approved by the local ethics committee (Comité de Protection des Personnes Sud-Ouest et Outre Mer III; approval number 2010-A01394-35). All the participants provided written informed consent. The CNRMAJ-Rouen study (PMID: 26242991): early onset AD patients (n = 870). The patients or their legal guardians provided written informed consent. This study was approved by the ethics committee of CPP Ile de France II.
Italy: The AD cases and controls were collated through Italy in different centers: Brescia, Cagliari, Florence, Milan, Rome, Pertugia, San Giovani Rotondo and Torino. AD cases were diagnosed according to DSM III-R,IV and NINCDS–ADRDA criteria. Controls were defined a minima as subjects without DMS-III-R dementia criteria and with integrity of their cognitive functions (MMS>25).
Spain: *The Dementia Genetic Spanish Consortium (DEGESCO)* is a national consortium comprising 23 research centers and hospitals across the country, that holds the institutional coverage of The Network Center for Biomedical Research in Neurodegenerative Diseases (CIBERNED). Created in 2013, DEGESCO's objective is the promotion and conduction of genetic studies aimed at understanding the genetic architecture of neurodegenerative dementias in the Spanish population and participates in coordinated actions in national and international frameworks. All DNA samples are in compliance with the Law of Biomedical Research (Law 14/2007) and the Royal Decree on Biobanks (RD 1716/2011). Patients included in the present study met clinical criteria for probable or possible disease established by the National Institute of Neurological and Communication Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA). Cognitively healthy controls were unrelated individuals who had a documented MMSE in the normal range. Contributing centers in the France node genotyping were Centro de Biología Molecular Severo Ochoa (CSIC-UAM (Madrid), the Institute Biodonostia, University of Basque Contry (EHU-UPV, San Sebastián), Institut de Biomedicina de Valencia CSIC (València), and Sant Pau Biomedical Research Institute (Barcelona).
Sweden: *Uppsala.* The Swedish AD patients were ascertained at the Memory Disorder Unit at Uppsala University Hospital. For all patients, the diagnosis was established according to the National Institute on Neurological Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) guidelines (PMID: 6610841). Healthy control subjects were recruited from the same geographic region following advertisements in local newspapers and displayed no signs of dementia upon Mini Mental State Examination (MMSE). *Karolinska Institutet, Stockholm*. AD patients were ascertained at the Memory Clinic at Karolinska University Hospital - Huddinge, Stockholm Sweden. For all patients, the diagnosis was established according to the National Institute on Neurological Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) guidelines (PMID: 6610841) and if available supported by CSF beta-amyloid and phospho-tau biomarker analyses. As controls, DNA from participants in the *Swedish National Study on Aging and Care in Kungsholmen* (SNAC-K) data was collected. The original SNAC-K population consisted of 4590 living and eligible persons who lived on the island of Kungsholmen in Central Stockholm, belonged to pre-specified age strata, and were randomly selected to take part in the study. Between 2001 and 2004, 3363 persons participated in the baseline assessment. They belonged to the age cohorts 60, 66, 72, 78, 81, 84, 87, 90, 93, and 96 years and 99 years and older. The examination consists of three parts: a nurse interview, a medical examination, and a neuropsychological testing session. Altogether, the examination takes about six hours. The participants are reexamined each time they reach the next

age cohort. All parts of the SNAC-K project have been approved by the ethical committee at Karolinska Institutet or the regional ethical review board. Informed consent was collected from all the participants or, if the person was severely cognitively impaired, from their next of kin.
The UK: MRC. The sample set comprises individuals with AD and healthy controls recruited across the MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK; Institute of Psychiatry, London, UK; University of Cambridge, Cambridge, UK. The collection of the samples was through multiple channels, including specialist NHS services and clinics, research registers and Join Dementia Research (JDR) platform. The participants were assessed at home or in research clinics along with an informant, usually a spouse, family member or close friend, who provided information about and on behalf of the individual with dementia. Established measures were used to ascertain the disease severity: Bristol activities of daily living (BADL), Clinical Dementia Rating scale (CDR), Neuropsychiatric Inventory (NPI) and Global Deterioration Scale (GlDS). Individuals with dementia completed the Addenbrooke's Cognitive Examination (ACE-r), Geriatric Depression Scale (GeDS) and National Adult Reading Test (NART) too. Control participants were recruited from GP surgeries and by means of self-referral (including existing studies and Joint Dementia Research platform). For all other recruitment, all AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the Mini Mental State Examination (MMSE) or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. Control samples were chosen to match case samples for age, gender, ethnicity and country of origin. Informed consent was obtained for all study participants, and the relevant independent ethical committees approved study protocols. SOTON, University of Southampton, Southampton, UK. All AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the MMSE or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. Nottingham and Manchester, University of Nottingham, Nottingham, UK and Manchester Brain Bank. All AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the MMSE or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. KCL, London Neurodegenerative Diseases Brain Bank. All AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the MMSE or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. PRION, All AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the MMSE or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. CFAS Wales, The Cognitive Function and Ageing Study Wales (CFAS-Wales) is a longitudinal population-based study of people aged 65 years and over in rural and urban areas of Wales that aims to investigate physical and cognitive health in older age and examine the interactions between health, social networks, activity, and participation. Individuals aged 65 years and over were randomly sampled from general medical practice lists between 2011 and 2013, stratified by age to ensure equal numbers in two age groups, 65-74 years and 75 and over. The baseline sample included 3593 older people and included those living in care homes as well as those living at home. Those who provided written consent to join the study were interviewed in their own homes by trained interviewers and could choose to have the interview conducted through the medium of either English or Welsh. Participants were followed up 2 years later. All AD cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) AD. All elderly controls were screened for dementia using the MMSE or CAMCOG, and were determined to be free from dementia. UCL-DRC. the UCL Alzheimer's disease cohort of the Dementia Research Centre (UCL - EOAD DRC) included patients seen at the Cognitive Disorders Clinics at The National Hospital for Neurology and Neurosurgery (Queen Square), or affiliated hospitals. Individuals were assessed clinically and diagnosed as having probable Alzheimer's disease based on contemporary clinical criteria in use at the time, including imaging and neuropsychological testing where appropriate.

EADB-Germany. In the German node, samples were collected from seven countries (11 centers/studies) and after QCs, we obtained 4,159 AD cases and 4,545 controls. All these samples were genotyped at Life&brain (Bonn, Germany).
Germany: *DELCODE (the multicenter DZNE-Longitudinal Cognitive Impairment and Dementia Study)*. This is an observational longitudinal memory clinic-based multicenter study in Germany comprising 400 subjects with Subjective cognitive decline (SCD), 200 mild cognitive impairment (MCI) patients, 100 AD dementia patients, 200 control subjects without subjective or objective cognitive decline, and 100 first-degree relatives of patients with a documented diagnosis of AD dementia. All patient groups (SCD, MCI, AD) are referrals, including self-referrals, to the participating memory centers. The control group and the relatives of AD dementia patients are recruited by standardized public advertisement. Ten university-based memory centers are participating, all being collaborators of local DZNE sites. All patient groups (SCD, MCI, AD) were assessed clinically at the respective memory centers before entering DELCODE. The assessments include medical history, psychiatric and neurological examination, neuropsychological testing, blood laboratory work-up, cerebrospinal fluid (CSF) biomarkers, and routine MRI, all according to the local standards. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological test battery was applied at all memory centers to measure cognitive function. German age, sex, and education-adjusted norms of the CERAD neuropsychological battery are available online (www.memoryclinic.ch). Detail description is of recruitment protocol is reported elsewhere. *The VOGEL study*: The VOGEL study is a prospective, observational, long-term follow-up study with three time points of investigation within 6–8 years. This cohort includes dementia and healthy subjects. Residents of the city of Würzburg born between 1936 and 1941 were recruited. Every participant underwent physical, psychiatric, and laboratory examinations and performed intense neuropsychological testing as well as VSEP and NIRS according to the published procedures. A total of 604 subjects were included. *The Heidelberg/Mannheim memory clinic sample*: This cohort includes 61 subjects from whom 40 MCI patients were recruited and assessed between 2012 and 2016. Some of those patients converted to dementia by AD or other dementias. *The PAGES study*: This study includes 301 subjects. AD patients were recruited at the memory clinic of the Department of Psychiatry, University of Munich, Germany. Participants in whom dementia associated with AD was diagnosed fulfilled the criteria for probable AD according to the NINCDS–ADRDA. The control group included participants who were randomly selected from the general population of Munich. Controls who had central nervous system diseases or psychotic disorders or who had first-degree relatives with psychotic disorders were excluded. *The Technische Universität München study*: This cohort includes 359 healthy, AD, and other dementias patients recruited from the Centre for Cognitive Disorders. All the participants provided written informed consent. A biobank was submitted to the ethics committee of the Technical University of Munich, School of Medicine (Munich, Germany), which raised no objections and approved the biobank (reference number 347-14*). The Göttingen Universität study*: This study includes 111 in- and outpatients with a healthy or AD dementia status from the Department of Psychiatry of the University of Göttingen. The study's ethical statement was provided locally at the Göttingen University Medical Centre. *The German Dementia Competence Network (DCN) cohort*: Individuals from the DCN cohort were recruited from 14 university hospital memory clinics across Germany between 2003 and 2005 (PMID: 19339779). The study was approved by the respective ethics committees, and written informed consent was obtained from all the participants prior to inclusion. *The German Study on Aging, Cognition, and Dementia (AgeCoDe)*: The AgeCoDe study is a general practice (GP) registry-based longitudinal study in elderly individuals that recruited patients aged 75 years and above in six German cities from 2003 to 2004 (PMID: 17848793). The study was approved by the respective ethics committees, and written informed consent was obtained from all the participants prior to inclusion.
Greece: the HELIAD study, comprising 49 AD cases and 1,150 controls. HELIAD is a population-based, multidisciplinary, collaborative study designed to estimate, in the Greek population over the age of 64 years, the prevalence and incidence of MCI, AD, other forms of dementia, and other neuropsychiatric conditions of aging and to investigate associations between nutrition and cognitive dysfunction or age-related neuropsychiatric diseases. The participants were selected through random sampling from the records of two Greek municipalities, Larissa and Marousi. All the participants signed informed consent in Greek.

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Portugal: the Lisbon study from Portugal, totalling 78 AD cases and 74 controls. This cohort was recruited in 2008–2009 to investigate the connections between oxidative stress and lipid dyshomeostasis in AD. The project includes 190 subjects and was approved by the local ethics committee, and all the participants provided written informed consent. This study includes healthy and dementia-by-AD subjects.
Spain: Those samples are part of DEGESCO. DEGESCO Centers from whom DNA samples were genotyped in the German node (1,778 cases and 470 controls) were the Alzheimer Research Center and Memory Clinic, Fundació ACE, Institut Català de Neurociències Aplicades (Barcelona), the Neurology Service at University Hospital Marqués de Valdecilla (Santander), the Alzheimer's disease and other cognitive disorders, Neurology Department, at Hospital Clínic, IDIBAPS (Barcelona), the Molecular Genetics Laboratory, at the Hospital Universitario Central de Asturias (Oviedo), and Fundació Docència i Recerca Mútua de Terrassa and Movement Disorders Unit, Department of Neurology, University Hospital Mútua de Terrassa (Barcelona).
Switzerland: Two datasets from Switzerland and Austria were combined, totaling 182 AD cases and 388 controls. The Lausanne study: This study includes 137 community-dwelling participants aged 55+ years with cognitive impairment (memory clinic patients with MCI, dementia) or normal cognition (recruited by advertisement, word of mouth). The study's ethical statement was provided locally at the Department of Psychiatry, Geneva University Centre, Switzerland. The VITA study: This is a longitudinal study of 606 individuals (Vienna, Austria) who were 75 years old in 2000, followed up every 30–90 months. This cohort includes dementia and healthy subjects. All the participants gave written informed consent. The study conformed to the latest version of the Declaration of Helsinki and was approved by the ethics committee of the City of Vienna, Austria.
EADB-Netherlands. In the Dutch node, samples were collected from six organizations in the Netherlands and after QCs, we obtained 2,438 AD cases and 2,389 controls. All these samples were genotyped at the Erasmus Medical University (Rotterdam, The Netherlands). The Medical Ethics Committee (METC) of the local institutes approved the studies. All the participants and/or their legal guardians gave written informed consent for participation in the clinical and genetic studies. Samples from the following institutes were included. 1) *Erasmus Medical Center*: most individuals were selected from population studies from the epidemiology department and accounted for most of the controls, while a smaller subset of samples originated from the neurology department, where AD was diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for AD (PMID: 21514250). 2) *The Amsterdam Dementia Cohort (ADC)* (PMID: 29562540): This cohort comprises patients who visit the memory clinic of the VU University Medical Centre, the Netherlands. The diagnosis of probable AD is based on the clinical criteria formulated by the NINCDS–ADRDA and based on the NIA–AA. Diagnosis of MCI was made according to Petersen and NIA-AA. Controls presented with subjective cognitive decline at the memory clinic, but performed within normal limits on all clinical investigations. 3) *The 100-Plus study*: This study includes Dutch-speaking individuals who (i) can provide official evidence for being aged 100 years or older, (ii) self-report to be cognitively healthy, which is confirmed by a proxy, (iii) consent to the donation of a blood sample, (iv) consent to (at least) two home visits from a researcher, and (v) consent to undergo an interview and neuropsychological test battery (PMID: 30362018). 4) *Parelsnoer Institute*: a collaboration between 8 Dutch University Medical Centers in which clinical data and biomaterials from patients suffering from chronic diseases (so called "Pearls") are collected according to harmonized protocols. The Pearl Neurodegenerative Diseases (PMID: 25551191) includes individuals diagnosed with dementia, mild cognitive impairment, and controls with subjective memory complaints. 5) *The Netherlands Brain Bank*: a non-profit organization that collects human brain tissue of donors with a variety of neurological and psychiatric disorders, but also of non-diseased donors. A clinical diagnosis of AD is based on the clinical criteria of probable AD (PMID: 6610841, PMID: 17616482). The selected AD patients for this study all received a definitive diagnosis which was based on autopsy. 6) *Maastricht University Medical Center*: a

subset of individuals that were referred to the memory clinic for cognitive complaints were included if they participated in the BioBank-Alzheimer Centrum Limburg (BB-ACL). Diagnosis of MCI was made according to the criteria of Petersen, and diagnosis of AD-type dementia was made according to the criteria of the DSM-4, and the NINCDS-ADRDA (PMID: 6610841).

Genotyping. EADB genomic DNA samples were transferred to 3 genotyping centers and samples that passed the DNA QC were genotyped with the Illumina Infinium Global Screening Array. Raw probe intensities were shared with the CNRGH, which performed the genotype calling on all samples using the same custom cluster file. During the genotyping QC process, three genotyping batches were considered: (1) 49 genotyping chips were identified as possibly problematic and thus were considered as a separate batch, (2) a batch of samples was genotyped and processed after all other samples and (3) the main batch including all other samples. Further details are available in *Bellenguez et al 2022*.

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1.2 FinnGen

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FinnGen R11 ethics statement and materials & methods

Study subjects in FinnGen provided informed consent for biobank research, based on the Finnish Biobank Act. Alternatively, separate research cohorts, collected prior the Finnish Biobank Act came into effect (in September 2013) and start of FinnGen (August 2017), were collected based on study-specific consents and later transferred to the Finnish biobanks after approval by Fimea (Finnish Medicines Agency), the National Supervisory Authority for Welfare and Health. Recruitment protocols followed the biobank protocols approved by Fimea. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS) statement number for the FinnGen study is Nr HUS/990/2017.

The FinnGen study is approved by Finnish Institute for Health and Welfare (permit numbers: THL/2031/6.02.00/2017, THL/1101/5.05.00/2017, THL/341/6.02.00/2018, THL/2222/6.02.00/2018, THL/283/6.02.00/2019, THL/1721/5.05.00/2019 and THL/1524/5.05.00/2020), Digital and population data service agency (permit numbers: VRK43431/2017-3, VRK/6909/2018-3, VRK/4415/2019-3), the Social Insurance Institution (permit numbers: KELA 58/522/2017, KELA 131/522/2018, KELA 70/522/2019, KELA 98/522/2019, KELA 134/522/2019, KELA 138/522/2019, KELA 2/522/2020, KELA 16/522/2020), Findata permit numbers THL/2364/14.02/2020, THL/4055/14.06.00/2020, THL/3433/14.06.00/2020, THL/4432/14.06/2020, THL/5189/14.06/2020, THL/5894/14.06.00/2020, THL/6619/14.06.00/2020, THL/209/14.06.00/2021, THL/688/14.06.00/2021, THL/1284/14.06.00/2021, THL/1965/14.06.00/2021,

THL/5546/14.02.00/2020, THL/2658/14.06.00/2021, THL/4235/14.06.00/2021, Statistics Finland (permit numbers: TK-53-1041-17 and TK/143/07.03.00/2020 (earlier TK-53-90-20) TK/1735/07.03.00/2021, TK/3112/07.03.00/2021) and Finnish Registry for Kidney Diseases permission/extract from the meeting minutes on 4th July 2019.
The Biobank Access Decisions for FinnGen samples and data utilized in FinnGen Data Freeze 11 include: THL Biobank BB2017_55, BB2017_111, BB2018_19, BB_2018_34, BB_2018_67, BB2018_71, BB2019_7, BB2019_8, BB2019_26, BB2020_1, BB2021_65, Finnish Red Cross Blood Service Biobank 7.12.2017, Helsinki Biobank HUS/359/2017, HUS/248/2020, HUS/430/2021 §28, §29, HUS/150/2022 §12, §13, §14, §15, §16, §17, §18, §23, §58 and §59, Auria Biobank AB17-5154 and amendment #1 (August 17 2020) and amendments BB_2021-0140, BB_2021-0156 (August 26 2021, Feb 2 2022), BB_2021-0169, BB_2021-0179, BB_2021-0161, AB20-5926 and amendment #1 (April 23 2020) and it´s modification (Sep 22 2021), BB_2022-0262, BB_2022-0256, Biobank Borealis of Northern Finland_2017_1013, 2021_5010, 2021_5018, 2021_5015, 2021_5015 Amendment, 2021_5023, 2021_5023 Amendment, 2021_5017, 2022_6001, 2022_6006 Amendment, BB22-0067, 2022_0262, Biobank of Eastern Finland 1186/2018 and amendment 22§/2020, 53§/2021, 13§/2022, 14§/2022, 15§/2022, 27§/2022, 28§/2022, 29§/2022, 33§/2022, 35§/2022, 36§/2022, 37§/2022, 39§/2022, 7§/2023, Finnish Clinical Biobank Tampere MH0004 and amendments (21.02.2020 & 06.10.2020), 8§/2021, 9§/2021, §9/2022, §10/2022, §12/2022, 13§/2022, §20/2022, §21/2022, §22/2022, §23/2022, 28§/2022, 29§/2022, 30§/2022, 31§/2022, 32§/2022, 38§/2022, 40§/2022, 42§/2022, 1§/2023, Central Finland Biobank 1-2017, BB_2021-0161, BB_2021-0169, BB_2021-0179, BB_2021-0170, BB_2022-0256, and Terveystalo Biobank STB 2018001 and amendment 25th Aug 2020, Finnish Hematological Registry and Clinical Biobank decision 18th June 2021, Arctic biobank P0844: ARC_2021_1001.

1.3 UK Biobank (UKB)

The UK Biobank is comprised of environmental, lifestyle, and genetic data for 500,000 participants. Cases and controls for this analysis were included based on similar criteria to what was used for the FinnGen cohort. AD cases included participants with an ICD10 code of F00 or G30 (UKB codes p130836 and p131036). Controls included participants that did not have an algorithmically defined AD diagnosis as assigned by UKB (UKB code p42020) or any ICD10 code of A81, F01, F02, G31, F03, or I673 (UKB codes p130136, p130838, p130840, p131038, p130842 or p41270). Controls were also filtered for participants currently over 60 years of age to approximate the age distribution of the cases. Cases and controls were filtered for Caucasian ancestry and related individuals removed.

UKB genetic data was genotyped and underwent quality control as described elsewhere (PMID: 30305743). For this manuscript, data imputed using the TOPMed reference panel was used for determining *APOE* genotype and for all subsequent analyses. Data was accessed and analysed on the UKB Research Analysis Platform (RAP) under UK Biobank application ID 33601.

1.4 GR@CE

The GR@ACE study (PMID: 31473137) recruited Alzheimer's disease (AD) patients from Fundació ACE, Institut Català de Neurociències Aplicades (Catalonia, Spain), and control individuals from three centers: Fundació ACE (Barcelona, Spain), Valme University Hospital (Seville, Spain), and the Spanish National DNA Bank–Carlos III (University of Salamanca, Spain) (http://www.bancoadn.org). At all sites, AD diagnosis was established by a multidisciplinary working group—including neurologists, neuropsychologists, and social workers—according to the DSM-IV criteria for dementia and the National Institute on Aging and Alzheimer's Association's (NIA–AA) 2011 guidelines for diagnosing AD. In our study, we considered as AD cases any individuals with dementia diagnosed with probable or possible AD at any point in their clinical course. Genotyping was conducted using the Axiom 815K

Spanish biobank array (Thermo Fisher) at the Spanish National Centre for Genotyping (CeGEN, Santiago de Compostela, Spain). The genotyping array not only is an adaptation of the Axiom biobank genotyping array but also contains rare population-specific variations observed in the Spanish population.

The Genome Research @ Fundació ACE project (GR@ACE) is supported by Grifols SA, Fundación bancaria 'La Caixa', Fundació ACE, and CIBERNED (Centro de Investigación Biomédica en Red Enfermedades Neurodegenerativas (Program 1, Alzheimer Disease to MB and AR)). A.R. and M.B. receive support from the European Union/EFPIA Innovative Medicines Initiative Joint undertaking ADAPTED and MOPEAD projects (grant numbers 115975 and 115985, respectively). M.B. and A.R. are also supported by national grants PI13/02434, PI16/01861, PI17/01474 and PI19/01240. Acción Estratégica en Salud is integrated into the Spanish National R + D + I Plan and funded by ISCIII (Instituto de Salud Carlos III)–Subdirección General de Evaluación and the Fondo Europeo de Desarrollo Regional (FEDER–'Una manera de hacer Europa'). Some control samples and data from patients included in this study were provided in part by the National DNA Bank Carlos III (www.bancoadn.org, University of Salamanca, Spain) and Hospital Universitario Virgen de Valme (Sevilla, Spain); they were processed following standard operating procedures with the appropriate approval of the Ethical and Scientific Committee.

1.5 European Alzheimer's Disease Initiative (EADI) Consortium

EADI is composed of several case-control studies and one population-based cohort, the 3C study (PMID: 14598854, PMID: 19734903). Case-control studies are comprised of AD cases and cognitively normal controls across France. The population-based cohort, the 3C study, is a prospective study of the relationship between vascular factors and dementia carried out in the three French cities Bordeaux, Montpellier and Dijon. The AD status was defined based on 12 years follow-up for Dijon participants, 14-15 years follow-up for Montpellier participants and 17-18 years follow-up for Bordeaux participants. All other non demented subjects of 3C were included as controls. All AD cases, both in the case-control studies and the 3C study, were ascertained by neurologists and the clinical diagnosis of probable AD was established according to the DSM-III-R and NINCDS-ADRDA criteria. Samples that passed DNA quality control were genotyped with Illumina Human 610-Quad BeadChips.

This work has been developed and supported by the LABEX (laboratory of excellence program investment for the future) DISTALZ grant (Development of Innovative Strategies for a Transdisciplinary approach to ALZheimer's disease) including funding from MEL (Metropole européenne de Lille), ERDF (European Regional Development Fund) and Conseil Régional Nord Pas de Calais. This work was supported by INSERM, the National Foundation for Alzheimer's disease and related disorders, the Institut Pasteur de Lille and the Centre National de Recherche en Génomique Humaine, CEA, the JPND PERADES, the Laboratory of Excellence GENMED (Medical Genomics) grant no. ANR-10-LABX-0013 managed by the National Research Agency (ANR) part of the Investment for the Future program, and the FP7 AgedBrainSysBio. The Three-City Study was performed as part of collaboration between the Institut National de la Santé et de la Recherche Médicale (Inserm), the Victor Segalen Bordeaux II University and Sanofi-Synthélabo. The Fondation pour la Recherche Médicale funded the preparation and initiation of the study. The 3C Study was also funded by the Caisse Nationale Maladie des Travailleurs Salariés, Direction Générale de la Santé, MGEN, Institut de la Longévité, Agence Française de Sécurité Sanitaire des Produits de Santé, the Aquitaine and Bourgogne Regional Councils, Agence Nationale de la Recherche, ANR supported the COGINUT and COVADIS projects. Fondation de France and the joint French Ministry of Research/INSERM "Cohortes et collections de données biologiques" programme. Lille Génopôle received an unconditional grant from Eisai. The Three-city biological bank was developed and maintained by the laboratory for genomic analysis LAG-BRC - Institut Pasteur de Lille.

1.6 Genetic and Environmental Risk in AD (GERAD) Consortium

Genetic and Environmental Risk in AD (GERAD) Consortium/Defining Genetic, Polygenic, and Environmental Risk for Alzheimer's Disease (PERADES) Consortium

The GERAD/PERADES sample comprises 3,177 Alzheimer's disease cases and 7,277 controls with available age and gender data (PMID: 19734902). Cases and elderly screened controls were recruited by the Medical Research Council (MRC) Genetic Resource for Alzheimer's disease (Cardiff University; Institute of Psychiatry, London; Cambridge University; Trinity College Dublin), the Alzheimer's Research Trust (ART) Collaboration (University of Nottingham; University of Manchester; University of Southampton; University of Bristol; Queen's University Belfast; the Oxford Project to Investigate Memory and Ageing (OPTIMA), Oxford University); Washington University, St Louis, United States; MRC PRION Unit, University College London; London and the South East Region Alzheimer's disease project (LASER-AD), University College London; Competence Network of Dementia (CND) and Department of Psychiatry, University of Bonn, Germany; the National Institute of Mental Health (NIMH) Alzheimer's disease Genetics Initiative. 6129 population controls were drawn from large existing cohorts with available GWAS data, including the 1958 British Birth Cohort (1958BC) (http://www.b58cgene.sgul.ac.uk), the KORA F4 Study and the Heinz Nixdorf Recall Study. All Alzheimer's disease cases met criteria for either probable (NINCDS-ADRDA, DSM-IV) or definite (CERAD) Alzheimer's disease. All elderly controls were screened for dementia using the MMSE or ADAS-cog, were determined to be free from dementia at neuropathological examination or had a Braak score of 2.5 or lower. Genotypes from all cases and 4617 controls were previously included in the AD GWAS by Harold and colleagues (PMID: 19734902). Genotypes for the remaining 2660 population controls were obtained from WTCCC2.

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AD Genetics Initiative. HH was supported by a grant of the Katharina-Hardt-Foundation, Bad Homburg vor der Höhe, Germany. The KORA F4 studies were financed by Helmholtz Zentrum München; German Research Center for Environmental Health; BMBF; German National Genome Research Network and the Munich Center of Health Sciences. The Heinz Nixdorf Recall cohort was funded by the Heinz Nixdorf Foundation (Dr. Jur. G.Schmidt, Chairman) and BMBF. We acknowledge use of genotype data from the 1958 Birth Cohort collection and National Blood Service, funded by the MRC and the Wellcome Trust which was genotyped by the Wellcome Trust Case Control Consortium and the Type-1 Diabetes Genetics Consortium, sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases, National Human Genome Research Institute, National Institute of Child Health and Human Development and Juvenile Diabetes Research Foundation International. The project is also supported through the following funding organisations under the aegis of JPND - www.jpnd.eu (United Kingdom, Medical Research Council (MR/L501529/1; MR/R024804/1) and Economic and Social Research Council (ES/L008238/1)) and through the Motor Neurone Disease Association. This study represents independent research part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. Prof Jens Wiltfang is supported by an Ilídio Pinho professorship and iBiMED (UID/BIM/04501/2013), at the University of Aveiro, Portugal.

1.7 Bonn studies

The Bonn group would like to thank Dr. Heike Koelsch for her scientific support.
The Bonn samples are part of the German Dementia Competence Network (DCN) and the German Research Network on Degenerative Dementia (KNDD, AgeCoDe study group), which are funded by the German Federal Ministry of Education and Research (BMBF): grants DCN: 01G10102, 01GI0420, 01GI0422, 01GI0423, 01GI0429, 01GI0431, 01GI0433, 04GI0434, 01GI0711; grants KNDD: 01GI1007A, 01GI0710, 01GI0711, 01GI0712, 01GI0713, 01GI0714, 01GI0715, 01GI0716, 01GI0717, 01ET1006B. Controls for the Bonn samples were also obtained from the Heinz Nixdorf Recall cohort that was funded by the Heinz Nixdorf Foundation (Dr. Jur. G.Schmidt, Chairman) and BMBF. Genotyping of the Bonn case-control sample was funded by the German Centre for Neurodegenerative Diseases (DZNE), Germany. Markus M Nöthen and Alfredo Ramirez are members of the German Research Foundation (DFG) cluster of excellence ImmunoSensation.

Bonn OMNI cohort: the Bonn OMNI cohort consists of AD patients and controls derived from a larger German GWAS cohort which was recruited from the following three sources: (i) the German Dementia Competence Network; (ii) the German study on Aging, Cognition, and Dementia in primary care patients (AgeCoDe); and (iii) the interdisciplinary Memory Clinic at the University Hospital of Bonn. The control sample comprised of individuals from the population-based study Heinz Nixdorf Recall (HNR) study cohort. This sample was previously used for replication in Lambert et al.[33]. *The German study on aging, cognition and dementia (AgeCoDe)*: see description above. *The German competence network cohort (DCN)*: The DCN cohort includes 1,095 patients with mild cognitive impairment (MCI) and 648 cases with mild Alzheimer's disease (AD) clinical dementia syndrome that were recruited from 14 university hospital memory clinics across Germany between 2003 and 2005[9]. Exclusion criteria were substance abuse or dependence, insufficient German language skills, multi-morbidity, comorbid condition with excess mortality, circumstances that would have made regular attendance at follow-up visits questionable and lack of an informant. The diagnosis of mild dementia according to ICD-10 criteria required a decline of cognitive ability (at least 1 SD) from a previous level in at least 2 domains as evidenced by age-corrected standardized tests, impairment in activities of daily living (i.e. B-ADL > 6), changes in personality, drive, social behavior or control of emotion but no clouding of consciousness. These changes must have persisted for at least 3 months. The etiological diagnosis of AD was assigned according to NINCDS-ADRDA criteria[8]. *Memory clinic Bonn*: The interdisciplinary Memory Clinic of the Department of Psychiatry and Department of Neurology at the University Hospital in Bonn provided further patients. Diagnoses were assigned according the NINCDS/ADRDA criteria[8] and on the basis of

clinical history, physical examination, neuropsychological testing (using the CERAD neuropsychological battery, including the MMSE), laboratory assessments, and brain imaging. *Control sample:* In the Heinz Nixdorf Recall (Risk Factors, Evaluation of Coronary Calcification, and Lifestyle) study, participants were randomly sampled in three cities in Germany. The study design has previously been described[34,35]. Briefly, 4814 participants aged 45 to 75 years were enrolled between 2000 and 2003 (t0, baseline). Cognitive performance of participants was evaluated at follow up scheduled 5 years after baseline (t1, n = 4157, 2005–2008) and then again at follow up 5 years after t1 (t2, n = 3087, 2010–2015). Controls sample was selected if participant did not present cognitive impairment as reported at the last available evaluation. Cognitive evaluation has been described extensively previously[36,37]. Herein, cognitive impairment at t1 was defined as a performance of one standard deviation (SD) below the age- and education-adjusted mean except for the clock-drawing test, where a performance ≥3 was rated as impaired (for a detailed description, see the study by Winkler et al.[36]). The study was approved by the University of Duisburg-Essen Institutional Review Board and followed established guidelines of good epidemiological practice.

1.8 The Alzheimer's Disease Sequencing Project (ADSP)

The Alzheimer's Disease Sequencing Project (ADSP) is comprised of two Alzheimer's Disease (AD) genetics consortia and three National Human Genome Research Institute (NHGRI) funded Large Scale Sequencing and Analysis Centers (LSAC). The two AD genetics consortia are the Alzheimer's Disease Genetics Consortium (ADGC) funded by NIA (U01 AG032984), and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) funded by NIA (R01 AG033193), the National Heart, Lung, and Blood Institute (NHLBI), other National Institute of Health (NIH) institutes and other foreign governmental and non-governmental organizations. The Discovery Phase analysis of sequence data is supported through UF1AG047133 (to Drs. Schellenberg, Farrer, Pericak-Vance, Mayeux, and Haines); U01AG049505 to Dr. Seshadri; U01AG049506 to Dr. Boerwinkle; U01AG049507 to Dr. Wijsman; and U01AG049508 to Dr. Goate and the Discovery Extension Phase analysis is supported through U01AG052411 to Dr. Goate, U01AG052410 to Dr. Pericak-Vance and U01 AG052409 to Drs. Seshadri and Fornage.

Sequencing for the Follow Up Study (FUS) is supported through U01AG057659 (to Drs. PericakVance, Mayeux, and Vardarajan) and U01AG062943 (to Drs. Pericak-Vance and Mayeux). Data generation and harmonization in the Follow-up Phase is supported by U54AG052427 (to Drs. Schellenberg and Wang). The FUS Phase analysis of sequence data is supported through U01AG058589 (to Drs. Destefano, Boerwinkle, De Jager, Fornage, Seshadri, and Wijsman), U01AG058654 (to Drs. Haines, Bush, Farrer, Martin, and Pericak-Vance), U01AG058635 (to Dr. Goate), RF1AG058066 (to Drs. Haines, Pericak-Vance, and Scott), RF1AG057519 (to Drs. Farrer and Jun), R01AG048927 (to Dr. Farrer), and RF1AG054074 (to Drs. Pericak-Vance and Beecham).

The ADGC cohorts include: Adult Changes in Thought (ACT) (U01 AG006781, U19 AG066567), the Alzheimer's Disease Research Centers (ADRC) (P30 AG062429, P30 AG066468, P30 AG062421, P30 AG066509, P30 AG066514, P30 AG066530, P30 AG066507, P30 AG066444, P30 AG066518, P30 AG066512, P30 AG066462, P30 AG072979, P30 AG072972, P30 AG072976, P30 AG072975, P30 AG072978, P30 AG072977, P30 AG066519, P30 AG062677, P30 AG079280, P30 AG062422, P30 AG066511, P30 AG072946, P30 AG062715, P30 AG072973, P30 AG066506, P30 AG066508, P30 AG066515, P30 AG072947, P30 AG072931, P30 AG066546, P20 AG068024, P20 AG068053, P20 AG068077, P20 AG068082, P30 AG072958, P30 AG072959), the Chicago Health and Aging Project (CHAP) (R01 AG11101, RC4

AG039085, K23 AG030944), Indiana Memory and Aging Study (IMAS) (R01 AG019771), Indianapolis Ibadan (R01 AG009956, P30 AG010133), the Memory and Aging Project (MAP) (R01 AG17917), Mayo Clinic (MAYO) (R01 AG032990, U01 AG046139, R01 NS080820, RF1 AG051504, P50 AG016574), Mayo Parkinson's Disease controls (NS039764, NS071674, 5RC2HG005605), University of Miami (R01 AG027944, R01 AG028786, R01 AG019085, IIRG09133827, A2011048), the Multi-Institutional Research in Alzheimer's Genetic Epidemiology Study (MIRAGE) (R01 AG09029, R01 AG025259), the National Centralized Repository for Alzheimer's Disease and Related Dementias (NCRAD) (U24 AG021886), the National Institute on Aging Late Onset Alzheimer's Disease Family Study (NIA- LOAD) (U24 AG056270), the Religious Orders Study (ROS) (P30 AG10161, R01 AG15819), the Texas Alzheimer's Research and Care Consortium (TARCC) (funded by the Darrell K Royal Texas Alzheimer's Initiative), Vanderbilt University/Case Western Reserve University (VAN/CWRU) (R01 AG019757, R01 AG021547, R01 AG027944, R01 AG028786, P01 NS026630, and Alzheimer's Association), the Washington Heights-Inwood Columbia Aging Project (WHICAP) (RF1 AG054023), the University of Washington Families (VA Research Merit Grant, NIA: P50AG005136, R01AG041797, NINDS: R01NS069719), the Columbia University Hispanic Estudio Familiar de Influencia Genetica de Alzheimer (EFIGA) (RF1 AG015473), the University of Toronto (UT) (funded by Wellcome Trust, Medical Research Council, Canadian Institutes of Health Research), and Genetic Differences (GD) (R01 AG007584). The CHARGE cohorts are supported in part by National Heart, Lung, and Blood Institute (NHLBI) infrastructure grant HL105756 (Psaty), RC2HL102419 (Boerwinkle) and the neurology working group is supported by the National Institute on Aging (NIA) R01 grant AG033193.

The CHARGE cohorts participating in the ADSP include the following: Austrian Stroke Prevention Study (ASPS), ASPS-Family study, and the Prospective Dementia Registry-Austria (ASPS/PRODEM-Aus), the Atherosclerosis Risk in Communities (ARIC) Study, the Cardiovascular Health Study (CHS), the Erasmus Rucphen Family Study (ERF), the Framingham Heart Study (FHS), and the Rotterdam Study (RS). ASPS is funded by the Austrian Science Fond (FWF) grant number P20545-P05 and P13180 and the Medical University of Graz. The ASPS-Fam is funded by the Austrian Science Fund (FWF) project I904), the EU Joint Programme – Neurodegenerative Disease Research (JPND) in frame of the BRIDGET project (Austria, Ministry of Science) and the Medical University of Graz and the Steiermärkische Krankenanstalten Gesellschaft. PRODEM-Austria is supported by the Austrian Research Promotion agency (FFG) (Project No. 827462) and by the Austrian National Bank (Anniversary Fund, project 15435. ARIC research is carried out as a collaborative study supported by NHLBI contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). Neurocognitive data in ARIC is collected by U01 2U01HL096812, 2U01HL096814, 2U01HL096899, 2U01HL096902, 2U01HL096917 from the NIH (NHLBI, NINDS, NIA and NIDCD), and with previous brain MRI examinations funded by R01-HL70825 from the NHLBI. CHS research was supported by contracts HHSN268201200036C, HHSN268200800007C, N01HC55222, N01HC85079, N01HC85080, N01HC85081, N01HC85082, N01HC85083, N01HC85086, and grants U01HL080295 and U01HL130114 from the NHLBI with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided by R01AG023629, R01AG15928, and R01AG20098 from the NIA. FHS research is supported by NHLBI contracts N01-HC-25195 and HHSN268201500001I. This study was also supported by additional grants from the NIA (R01s AG054076, AG049607 and AG033040 and NINDS (R01 NS017950). The ERF study as a part of EUROSPAN (European

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1.9 Japanese GWAS Cohorts

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J-ADNI

504 samples (139 ADs, 220 MCIs, and 145 controls) J-ADNI enrolled cognitively unimpaired participants, participants with late MCI, and patients with mild AD dementia using criteria consistent with those of the North American ADNI (Weiner et a. Alzheimers Dement. 2017;13(4):e1-e85).

J-ADNI was supported by the following grants: Translational Research Promotion Project from the New Energy and Industrial Technology Development Organization of Japan; Research on Dementia, Health Labor Sciences Research Grant; Life Science Database Integration Project of Japan Science and Technology Agency; Research Association of Biotechnology (contributed by Astellas Pharma Inc., Bristol-Myers Squibb, Daiichi-Sankyo, Eisai, Eli Lilly and Company, Merck-Banyu, Mitsubishi Tanabe Pharma, Pfizer Inc., Shionogi & Co., Ltd., Sumitomo Dainippon, and Takeda Pharmaceutical Company), Japan, and a grant from an anonymous Foundation.

Clinical cohort (CL)

Probable AD cases were ascertained on the basis of the criteria of the National Institute of Neurological and Communicative Disorders, and Stroke-Alzheimer's Disease and Related Disorders (NINCDS/ADRDA). The Mini-Mental State Examination, Clinical Dementia Rating, and/or Function Assessment Staging were primarily used for evaluation of cognitive impairment. Elders living in an unassisted manner in the local community with no signs of dementia were used as controls.

Neuropathological cohort (NP)

565 samples (207 cases and 358 controls) In this cohort, 358 control donors had little pathological findings associated with AD and 212 case donors had those consistent with AD. All AD patients were neuropathologically diagnosed by senile plaque and neurofibrillary tangle. No neuropathological features of other neurodegenerative disorders such as dementia with Lewy body disease, frontotemporal lobal degeneration, and Parkinson's disease, were observed. Control individuals did not show the typical neuropathological hallmarks of AD. As no clinical diagnosis is provided in this cohort, the term case or control is used in this study.

1.10 GARD

The Gwangju Alzheimer's & Related Dementias (GARD) cohort is a longitudinal, single center study based in Gwangju, Republic of Korea, designed to develop clinical, imaging, genetic, and other biomarkers for the early detection and progression tracking of dementia, primarily Alzheimer's disease. Participants aged 60 years or older were recruited from the local community. The study includes standardized clinical evaluations, neuropsychological testing (Seoul Neuropsychological Screening

Battery), 3T MRI imaging, and optional ^{18}F-Florbetaben amyloid PET scans. All procedures were approved by the Institutional Review Board of Chosun University Hospital (CHOSUN 2013-12-018-070), and written informed consent was obtained from all participants or their legal representatives.

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1.11 HK Chinese

Participants in HK Chinese cohort were recruited from the Prince of Wales Hospital, Haven of Hope Christian Service, and Community CareAge Foundation. Patients with AD were diagnosed according to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). This study was approved by the Clinical Research & Ethics Committees of the Joint Chinese University of Hong Kong–New Territories East Cluster for the Prince of Wales Hospital (CREC ref. no. 2015.461) and the Human Participants Research Panel of the Hong Kong University of Science and Technology (CRP#180 and CRP#225). All participants provided written informed consent for both study enrolment and sample collection.

2 eQTL analysis datasets

ROSMAP RNAseq and WGS datasets

The data available in the AD Knowledge Portal would not be possible without the participation of research volunteers and the contribution of data by collaborating researchers. The results published here are in whole or in part based on data obtained from the AD Knowledge Portal (https://adknowledgeportal.org). Study data were provided by the Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago. Data collection was supported through funding by NIA grants P30AG10161, R01AG15819, R01AG17917, U01AG46152, U01AG046170, U01AG046139, and U01AG61356. Additional phenotypic data can be requested at www.radc.rush.edu.

3 Supplementary discussion

Limitations of the study

In most datasets AD case status was based on medical records and an ICD based definition and in one cohort the use of Alzheimer's disease medication was additionally included to define AD status. This may have induced a misclassification bias, and may potentially lead to identification of loci that are not related to true AD or may, due to the underdiagnosis of AD in general, lead to conservative estimates in the cohorts. The first issue is to some extend mitigated by using a meta-analysis setup where cohorts with different AD definitions were used and the requirement that a signal needed to be present in multiple cohorts.

Furthermore, we have excluded the *APOE* ε42 strata from all analyses and this exclusion may have induced an ascertainment bias, and the identified interactions between a genetic variant and *APOE* genotypes may not extend to individuals in the *APOE* ε42 strata. Also, we have a

considerable residual population stratification which may also have induced a bias in the analyses.

Influence of age

Because late-onset AD is strongly associated with age, we adjusted all analyses for age. To ensure that bias due to heterogeneity in selection processes of cases and controls across studies was not a major challenge, we performed sensitivity analyses of the eight main cohorts where age was not adjusted. Similar findings were observed when comparing analyses with and without age adjustment. Despite differences in age distributions between cases and controls and between *APOE* strata, they were not of substantial size to influence the main observations.

The signals that were augmented in the *APOE* ε33 strata (and thus attenuated in ε44+ε43), *SLC50A1*, *TMEM106B*, *NPAS3* and *SHARPIN*, might be influenced by the effect of statistical power and age differences discussed above. For example, *TMEM106B* associates with the tauopathy-endophenotype which has a later mean onset compared to the *APOE*-related-AD endophenotype[1]. Because the ε33 strata display a higher mean age the observed interaction could be driven by this mean age difference. On the other hand, a clear attenuation of the effect on risk of AD in an *APOE* ε4 allele context was observed. Future mechanistic studies would be important to further scrutinize this finding, and to substantiate if the *APOE* ε4 allele biologically interacts with the tauopathy-endophenotype. Similar considerations are valid for *SLC50A1* and *SHARPIN*. Conversely, *NPAS3* has been reported to modify *reelin* expression and *reelin* binds to both the VLDL- and APOER2-receptors to which apoE is also a ligand. It is known that the apoE4 isoform has a higher binding affinity to these receptors[2,3]. Hence, in this situation it may be plausible that the *APOE* ε4 allele confers a protective effect on AD risk conferred by *NPAS3* and the reeling pathway.

Interaction analysis

Interaction analysis is notoriously difficult to perform convincingly as it constitutes an extra level of complexity compared to a normal association study. It is however of clear importance to determine if the observed differences across *APOE* strata with some certainty can be judged true. Our approach was to use several layers of evidence to claim an interaction.

We used two complementary approaches to test for SNP x *APOE* interactions: a genome-wide SNP x *APOE* ε4 carrier interaction GWAS meta-analysis and a stratified effect comparison. The SNP x *APOE* ε4 carrier interaction GWAS is standard for testing gene-gene or gene-environment interactions as the different terms in the model are evaluated under the same statistical framework with a proper variance structure and correlation modeling. However, the methodology requires high statistical power, and the interpretation of the results can be challenging. The stratified effect comparison difference method requires less statistical power, has a clear interpretation and allows for direct visualization of the stratified effects. However, it assumes independence between the strata, does not formally model the interaction term in a single framework, may identify differences driven by power asymmetry between strata, and has multiple testing considerations. Performing both complementary interaction strategies allows a more nuanced interpretation.

To address the limitation in the stratified effect comparison approach, we only considered the lead variants in the loci that reached genome wide significance in either the ε33 or the ε44+ε43 strata. This was to avoid data dredging and only to consider genetic variants which had sufficient statistical power. For each lead variant we have provided the Forest plot of the

effect on risk for each stratum. This allows scrutinization of tendencies across *APOE* strata and visual inspection of confidence interval overlaps and stepwise effects as a function of number of ε4 alleles. We did not use a simple t-test to test for overlapping confidence intervals because we have performed a meta-analysis across several cohorts with different diagnostic criteria, different cohort types (case-control vs biobanks), different allele frequencies and potential differences between strata due to relatedness. Hence, using different fixed- and mixed-effect models to investigate the possible interactions between *APOE* ε4 and lead variants seem appropriate. Further, the Forest plots showing the effect difference between ε44+ε43 and ε33 strata indicate that a possible bias due to relatedness between strata in some of the cohorts is minimal. Unfortunately, the SNP x *APOE* ε4 carrier interaction GWAS meta-analysis was underpowered to find significant interactions, but for a few SNPs the interaction GWAS results support at a suggestive level the main *DDHD1* finding

The *APOE* ε33 and ε44+ε43 strata are comparable in power, however we cannot exclude that some of the observed differences among these two strata could be explained by differences in power. A difference in statistical power would however mostly affect the confidence interval size and therefore the p-value, whereas the effect size (beta) should remain relatively stable. In contrast, and in support of our interaction analysis strategy, we consistently observe large shifts in the effect size when an interaction is present between a lead variant and *APOE* ε4 carrier status.

In the main dominant stratified effect comparison analysis where the effect difference and SE are calculated within each cohort, the dataset only contains 8 rows – one from each of the cohorts. In the additive tests and the dominant-sensitivity test, the datasets contain 18 and 24 rows – one for each cohort+strata. This difference leads to the higher observed heterogeneity.

Although we find significant stratified effect comparison differences, the analysis is affected by limited statistical power even when using eight cohorts. This can for example be seen in the patterns for the *TMEM106B*, *GRN* and *MAPT* loci only being significant in the *APOE* ε33 strata. They are all known to associate with the tauopathy dementia endophenotype, but only *TMEM106B* has a significant stratified effect comparison test. However, the tests for *GRN* and *MAPT* show a similar trend and will possibly become significant if statistical power is increased.

Summary data-based Mendelian Randomization (SMR)

STAG3 has previously been reported in SMR in previous studies using non-stratified summary GWAS data[4,5]. In our study, it was only significant in the ε44+ε43 stratum, however there was a non-significant signal in the ε33 stratum indicating some shared effects between the strata. The *LRRC37A*, *ARL17B* and *LRRC37A2* are novel findings all located in the *MAPT* locus. The novel loci nominated by the stratified *APOE* meta-analyses were not present in the MetaBrain dataset for testing and would need further investigation to determine whether the expression of these genes influences disease risk.

References for Supplementary discussion

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EADB

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185. Abbvie, Chicago, IL, USA.
186. Astra Zeneca, Cambridge, UK.
187. Bayer AG, Leverkusen, Germany.
188. Biogen, Cambridge, MA, USA.
189. Boehringer Ingelheim, Ingelheim am Rhein, Germany.
190. Bristol Myers Squibb, New York, NY, USA.
191. Genentech, San Francisco, CA, USA.
192. GlaxoSmithKline, Collegeville, PA, USA.
193. Merck, Kenilworth, NJ, USA.
194. Pfizer, New York, NY, USA.
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203. Finnish Red Cross Blood Service / Finnish Hematology Registry and Clinical Biobank, Helsinki, Finland.
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226. Tampere University, Tampere, Finland.
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