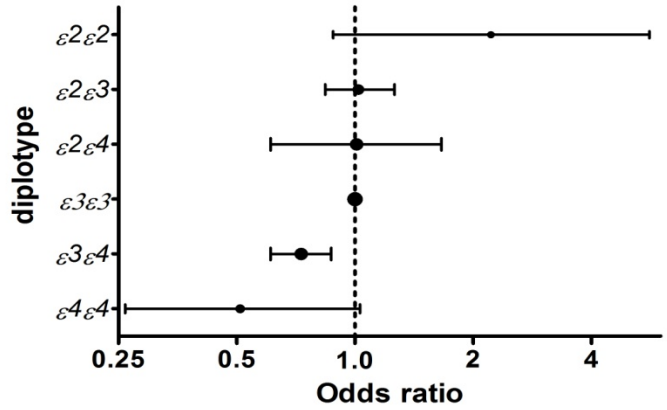
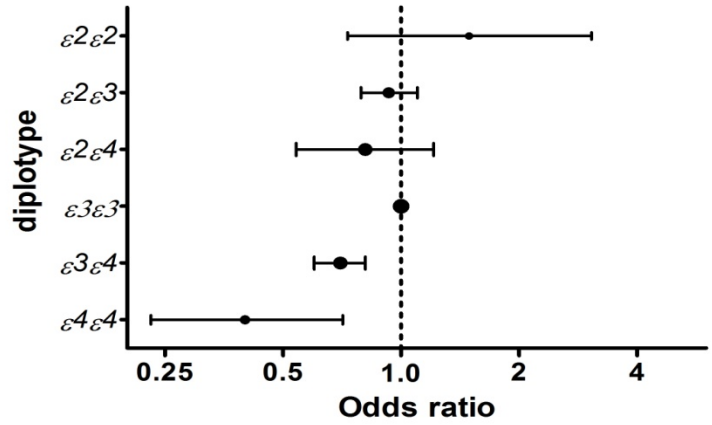
a. Males only




| | N | Odds ratio (95%CI) | P |
|---|---|---|---|
| ε2ε2 | 39 | 2.22(0.88-5.62) | 0.09 |
| ε2ε3 | 824 | 1.02(0.84-1.26) | 0.80 |
| ε2ε4 | 129 | 1.01(0.61-1.66) | 0.97 |
| ε3ε3 | 3868 | 1.00 (reference) | |
| ε3ε4 | 1274 | 0.73(0.61-0.87) | 0.001 |
| ε4ε4 | 94 | 0.51(0.26-1.03) | 0.06 |

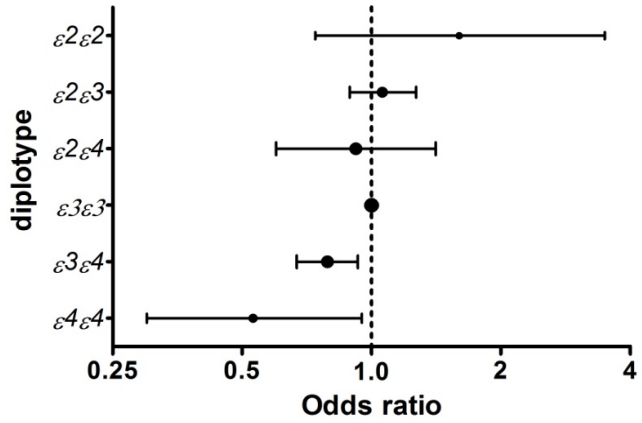
b. Females only




| | N | Odds ratio (95%CI) | P |
|---|---|---|---|
| ε2ε2 | 74 | 1.49(0.73-3.06) | 0.27 |
| ε2ε3 | 1379 | 0.93(0.79-1.10) | 0.40 |
| ε2ε4 | 235 | 0.81(0.54-1.21) | 0.30 |
| ε3ε3 | 6432 | 1.00 (reference) | |
| ε3ε4 | 1982 | 0.70(0.60-0.81) | $2.87 \times 10^{-6}$ |
| ε4ε4 | 149 | 0.40(0.23-0.71) | 0.002 |

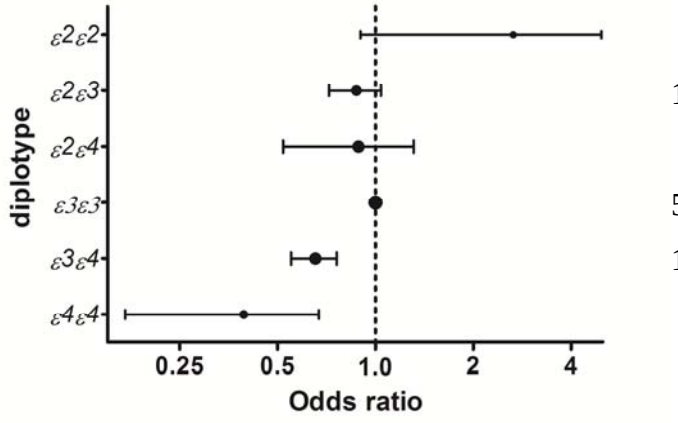
**Supp. Figure S1.** Analysis of *APOE* diplotype and late AMD in males (a) and females (b) only. Late AMD includes categories GA, NV and GANV. Odds ratios against the reference (*ε3ε3*), 95% confidence intervals and P values were adjusted for age-group within each study and for smoking status (ever versus never smoker) and sample sizes (N) are presented for each group.

a. Never smokers only



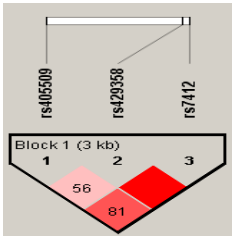

| | N | Odds ratio (95%CI) | P |
|---|---|---|---|
| ε2ε2 | 52 | 1.60(0.74-3.49) | 0.24 |
| ε2ε3 | 1053 | 1.06(0.89-1.27) | 0.52 |
| ε2ε4 | 179 | 0.92(0.60-1.41) | 0.70 |
| ε3ε3 | 4879 | 1.00 (reference) | |
| ε3ε4 | 1469 | 0.79(0.67-0.93) | 0.005 |
| ε4ε4 | 126 | 0.53(0.30-0.95) | 0.03 |

b. Ever smokers only




| | N | Odds ratio (95%CI) | P |
|---|---|---|---|
| ε2ε2 | 61 | 2.11 (0.90-4.95) | 0.09 |
| ε2ε3 | 1150 | 0.86(0.72-1.04) | 0.13 |
| ε2ε4 | 185 | 0.83(0.52-1.31) | 0.41 |
| ε3ε3 | 5421 | 1.00 (reference) | |
| ε3ε4 | 1787 | 0.65(0.55-0.76) | $1.10 \times 10^{-7}$ |
| ε4ε4 | 117 | 0.34(0.17-0.67) | 0.002 |

**Supp. Figure S2.** Analysis of *APOE* diplotype and late AMD in never smokers (a) and ever smokers (b) only. Late AMD includes categories GA, NV and GANV. Odds ratios against the reference (*ε3ε3*), 95% confidence intervals and P values were adjusted for age-group and sex within each study and sample sizes (N) are presented for each group.




| SNP | Position | HWE P value | % Genotyped | MAF |
|---|---|---|---|---|
| rs405509 | 45,408,586 | 0.60 | 37.8 | 0.461 |
| rs429358 | 45,411,691 | 0.85 | 100 | 0.124 |
| rs7412 | 45,412,329 | 0.58 | 100 | 0.084 |

**Supp. Figure S3.** Linkage disequilibrium values represented as D' between SNPs. Hardy-Weinberg equilibrium (HWE) P values are presented for combined cases and controls with percentage of samples genotyped and associated minor allele frequencies (MAF).

**Supp. Table S1. Frequency of *APOE* haplotypes by study**

| | Control | | | | | | | late AMD | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | No. | *ε2* | %(*ε2*) | *ε3* | %(*ε3*) | *ε4* | %(*ε4*) | No. | *ε2* | %(*ε2*) | *ε3* | %(*ε3*) | *ε4* | %(*ε4*) |
| Belfast | 872 | 67 | 0.077 | 690 | 0.791 | 115 | 0.132 | 900 | 70 | 0.078 | 731 | 0.812 | 99 | 0.110 |
| Regensburg | 1106 | 78 | 0.071 | 887 | 0.802 | 141 | 0.127 | 1278 | 131 | 0.103 | 1019 | 0.797 | 128 | 0.100 |
| Portland | 544 | 43 | 0.079 | 425 | 0.781 | 76 | 0.140 | 1292 | 128 | 0.099 | 1030 | 0.797 | 134 | 0.104 |
| Rotterdam | 7610 | 647 | 0.085 | 5751 | 0.756 | 1212 | 0.159 | 206 | 23 | 0.112 | 167 | 0.811 | 16 | 0.078 |
| AREDS | 398 | 43 | 0.108 | 301 | 0.756 | 54 | 0.136 | 1278 | 128 | 0.100 | 1021 | 0.799 | 129 | 0.101 |
| Melbourne | 212 | 18 | 0.085 | 150 | 0.708 | 44 | 0.208 | 326 | 32 | 0.098 | 250 | 0.767 | 44 | 0.135 |
| Philadelphia | 758 | 51 | 0.067 | 600 | 0.792 | 107 | 0.141 | 732 | 52 | 0.071 | 608 | 0.831 | 72 | 0.098 |
| WHI-SE | 2566 | 196 | 0.076 | 2003 | 0.781 | 367 | 0.143 | 96 | 6 | 0.063 | 81 | 0.844 | 9 | 0.094 |
| Edinburgh | 358 | 32 | 0.089 | 292 | 0.816 | 34 | 0.095 | 382 | 32 | 0.084 | 302 | 0.791 | 48 | 0.126 |
| Southampton | 916 | 73 | 0.080 | 712 | 0.777 | 131 | 0.143 | 570 | 48 | 0.084 | 471 | 0.826 | 51 | 0.089 |
| Los Angeles | 284 | 26 | 0.092 | 229 | 0.806 | 29 | 0.102 | 1166 | 116 | 0.099 | 970 | 0.832 | 80 | 0.069 |
| EUREYE | 3870 | 260 | 0.067 | 3166 | 0.818 | 444 | 0.115 | 280 | 22 | 0.079 | 233 | 0.832 | 25 | 0.089 |
| Michigan | 506 | 40 | 0.079 | 407 | 0.804 | 59 | 0.117 | 864 | 78 | 0.090 | 695 | 0.804 | 91 | 0.105 |
| Cambridge | 834 | 70 | 0.084 | 630 | 0.755 | 134 | 0.161 | 1622 | 154 | 0.095 | 1309 | 0.807 | 159 | 0.098 |
| London | 412 | 40 | 0.097 | 319 | 0.774 | 53 | 0.129 | 1796 | 173 | 0.096 | 1443 | 0.803 | 180 | 0.100 |
| Pool haplotype frequency | | | 0.079 | | 0.783 | | 0.135 | | | 0.092 | | 0.809 | | 0.099 |

Late AMD is composed of geographic atrophic (GA) and neovascular AMD (NV) or both GA and NV together (GANV).

**Supp. Table S2. Frequency of *APOE* diplotype by status and AMD sub-phenotype**

| Phenotype | *APOε2* (%) | *APOε3* (%) | *APOε4* (%) | *ε2ε2* (%) | *ε2ε3* (%) | *ε2ε4* (%) | *ε3ε3* (%) | *ε3ε4* (%) | *ε4ε4* (%) | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| Control | 1684 (7.9) | 16562 (78.0) | 3000 (14.1) | 59 (0.6) | 1326 (12.5) | 240 (2.3) | 6445 (60.7) | 2346 (22.1) | 207 (1.9) | 10623 |
| eAMD | 685 (8.3) | 6703 (80.9) | 898 (10.8) | 31 (0.7) | 565 (13.6) | 58 (1.4) | 2709 (65.4) | 720 (17.4) | 60 (1.4) | 4143 |
| GA | 277 (10.1) | 2215 (80.8) | 248 (9.1) | 11 (0.8) | 223 (16.3) | 32 (2.3) | 893 (65.2) | 206 (15.0) | 5 (0.4) | 1370 |
| NV | 693 (8.8) | 6358 (80.8) | 819 (10.4) | 36 (0.9) | 549 (13.9) | 72 (1.8) | 2568 (65.2) | 673 (17.1) | 37 (0.9) | 3935 |
| GANV | 223 (10.2) | 1757 (80.7) | 198 (9.1) | 9 (0.8) | 171 (15.7) | 34 (3.1) | 718 (65.9) | 150 (13.8) | 7 (0.6) | 1089 |
| Total | 3562 (8.4) | 33595 (79.4) | 5163 (12.2) | 146 (0.7) | 2834 (13.4) | 436 (2.1) | 13333 (63.0) | 4095 (19.4) | 316 (1.5) | 21160 |

AMD is commonly divided into early (eAMD) and late AMD. Late AMD is subdivided into geographic atrophic (GA) and neovascular AMD (NV) or both GA and NV together (GANV).

**Supp. Table S3. Genotyping quality control metrics.**

| Study | Sample failure rate (%) | SNP genotype rate (%) | | | Duplicate concordance (%) | | | HWE P value | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | rs405509 | rs429358 | rs7412 | rs405509 | rs429358 | rs7412 | rs405509 | rs429358 | rs7412 |
| Belfast | 0.9 | NA | 98.0 | 98.5 | NA | 100.0 | 100.0 | NA | 0.05 | 0.15 |
| Regensburg | 0.0 | 100.0 | 99.6 | 98.4 | 100.0 | 100.0 | 100.0 | 0.45 | 0.84 | 0.32 |
| Portland | 1.2 | NA | 99.0 | 97.0 | NA | 100.0 | 100.0 | NA | 0.56 | 1.00 |
| Rotterdam | 0.0 | 85.6 | 100.0 | 100.0 | NA | NA | NA | 1.00 | 0.92 | 0.82 |
| AREDS | 0.1 | NA | 100.0 | 99.5 | NA | 100.0 | 100.0 | NA | 0.51 | 0.28 |
| Melbourne | 2.2 | NA | 100.0 | 100.0 | NA | 100.0 | 100.0 | NA | 0.41 | 0.46 |
| Philadelphia | 0.0 | 100.0 | 100.0 | 100.0 | NA | NA | NA | 0.93 | 0.78 | 0.55 |
| WHI-SE | 0.6 | NA | 99.4 | 99.4 | NA | 100.0 | 100.0 | NA | 0.67 | 0.26 |
| Edinburgh | 2.6 | NA | 97.8 | 96.8 | NA | 100.0 | 100.0 | NA | 0.14 | 0.16 |
| Southampton | 0.1 | 98.6 | 99.4 | 99.0 | NA | NA | NA | 0.03 | 1.00 | 0.84 |
| Los Angeles | 7.0 | NA | 100.0 | 100.0 | NA | NA | NA | NA | 0.34 | 1.00 |
| EUREYE | 0.5 | NA | 97.9 | 97.7 | NA | 100.0 | 100.0 | NA | 0.07 | 0.97 |
| Michigan | 0.0 | 99.5 | 91.2 | 96.6 | 100.0 | NA | NA | 1.00 | 0.55 | 0.54 |
| Cambridge | 1.7 | NA | 98.6 | 99.0 | NA | NA | NA | NA | 0.37 | 0.81 |
| London | 0.0 | NA | 99.9 | 99.8 | NA | 100.0 | 100.0 | NA | 1.00 | 0.66 |