Supplementary Figures

Circulating LDL cholesterol before dementia onset is associated with higher AD neuropathology burden independent of *APOE*

Authors

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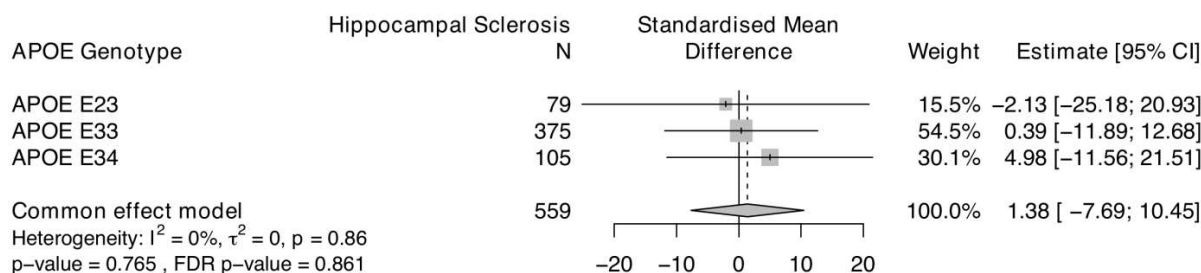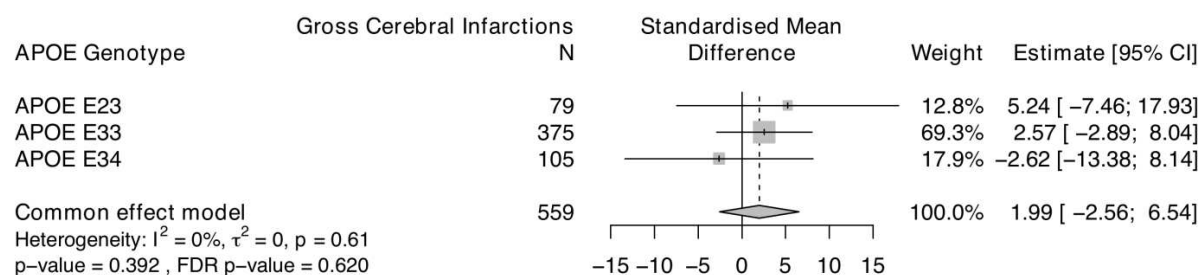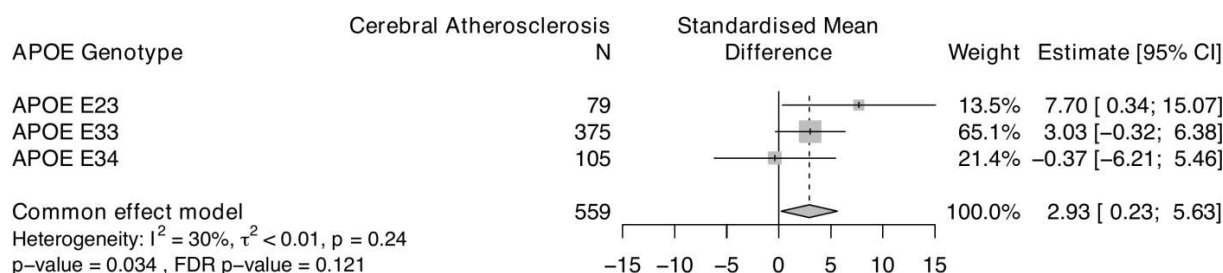[3]Department of Neurology, Emory University School of Medicine, Atlanta, GA 30322, USA

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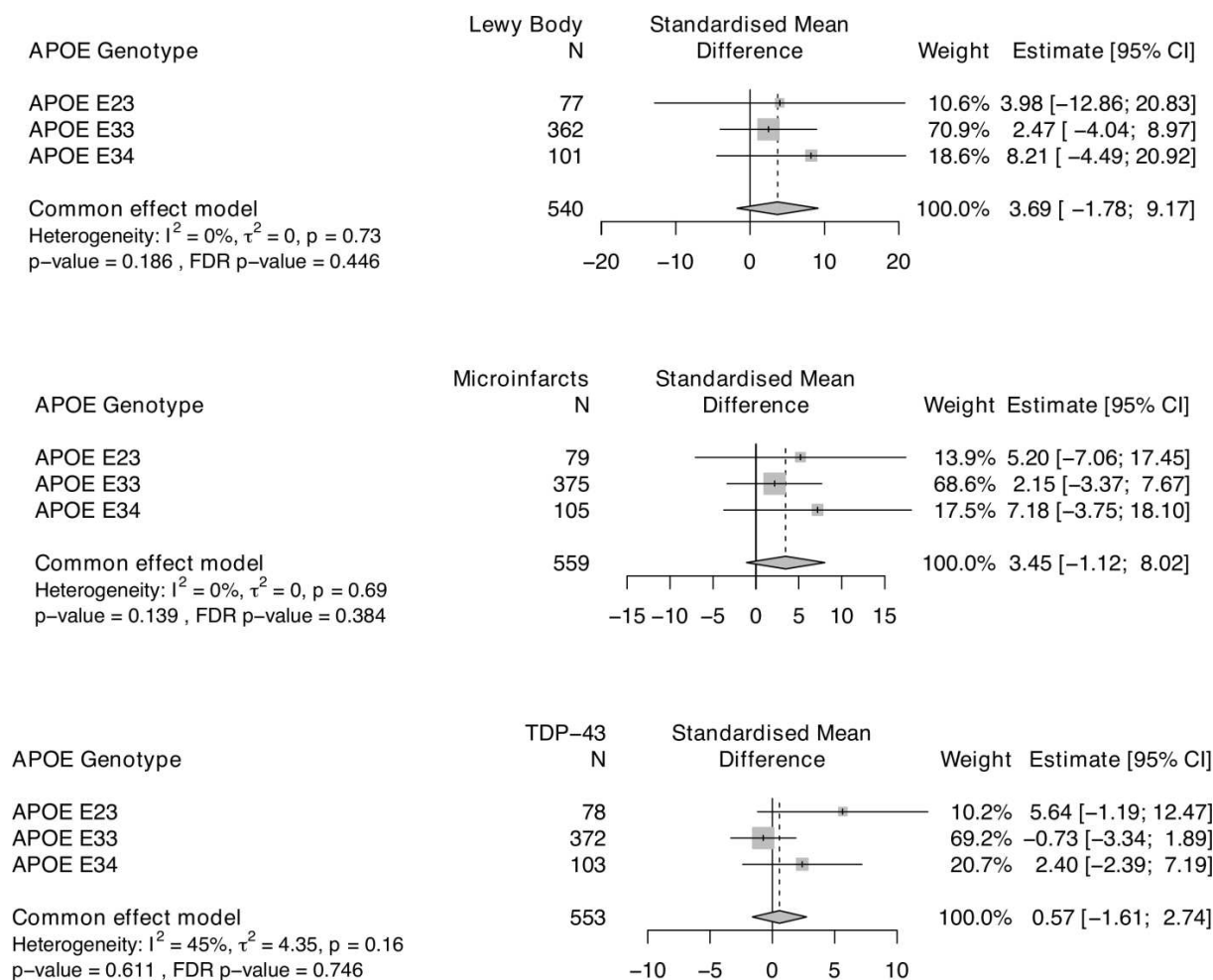
J Neurol Neurosurg Psychiatry

Supplementary Figure 1. Results for non-significant association testing between longitudinally measured LDL-C and neuropathologies in individuals with NCI or MCI at baseline with censoring of LDL-C for a diagnosis of either dementia. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis shown by in the forest plot, and the nominal p-value and FDR p-values are given. Results of each *APOE* genotype are shown with their sample size, standardized mean difference estimate (small vertical black line), the 95% confidence interval (CI) of the standardized mean difference estimate (horizontal black line), and their relative contribution to the meta-analysis (gray shaded box around the standardized mean difference estimate). The result of the fixed-effect meta-analysis is shown as a vertical dotted line and the 95% CI as a diamond. Measures of the heterogeneity between groups are given, I^2, and the residual heterogenity, tau^2, and estimated p-value are given. The standardized mean difference may be considered as the difference in the neuropathology score per unit of blood lipid measured.

The Relationship between LDL–C and Neuropathology

Supplementary Figure 1 – part 1 of 2

The Relationship between LDL–C and Neuropathology

APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	77		10.6%	3.98 [−12.86; 20.83]
APOE E33	362		70.9%	2.47 [−4.04; 8.97]
APOE E34	101		18.6%	8.21 [−4.49; 20.92]
Common effect model	540		100.0%	3.69 [−1.78; 9.17]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.73$
p–value = 0.186 , FDR p–value = 0.446

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	79		13.9%	5.20 [−7.06; 17.45]
APOE E33	375		68.6%	2.15 [−3.37; 7.67]
APOE E34	105		17.5%	7.18 [−3.75; 18.10]
Common effect model	559		100.0%	3.45 [−1.12; 8.02]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.69$
p–value = 0.139 , FDR p–value = 0.384

APOE Genotype	TDP–43 N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	78		10.2%	5.64 [−1.19; 12.47]
APOE E33	372		69.2%	−0.73 [−3.34; 1.89]
APOE E34	103		20.7%	2.40 [−2.39; 7.19]
Common effect model	553		100.0%	0.57 [−1.61; 2.74]

Heterogeneity: $I^2 = 45\%$, $\tau^2 = 4.35$, $p = 0.16$
p–value = 0.611 , FDR p–value = 0.746

Supplementary Figure 1 – part 2 of 2

Supplementary Figure 2. Results for significant association testing between longitudinally measured HDL-C and neuropathologies in individuals with NCI or MCI at baseline with censoring of LDL-C for a diagnosis of either dementia. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis and is shown in by forest plot following the same layout as described in Supplementary Figure 1.

The Relationship between HDL–C and Neuropathology

APOE Genotype	Hippocampal Sclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	79		18.2%	7.68 [−3.87; 19.23]
APOE E33	375		44.8%	10.54 [3.18; 17.89]
APOE E34	105		37.0%	1.40 [−6.69; 9.49]
Common effect model	559		100.0%	6.63 [1.71; 11.55]

Heterogeneity: $I^2 = 27\%$, $\tau^2 = 9.68$, p = 0.26
p–value = 0.008 , FDR p–value = 0.043

APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	77		12.5%	−7.23 [−15.71; 1.25]
APOE E33	362		63.2%	−3.97 [−7.74; −0.20]
APOE E34	101		24.3%	−6.40 [−12.48; −0.32]
Common effect model	540		100.0%	−4.97 [−7.96; −1.97]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.69
p–value = 0.001 , FDR p–value = 0.020
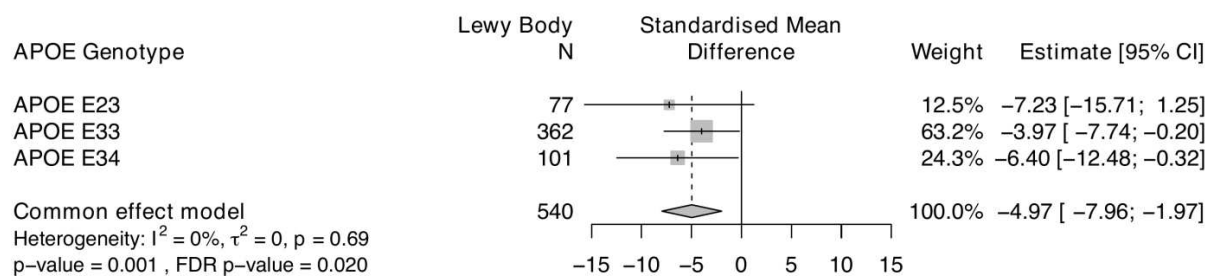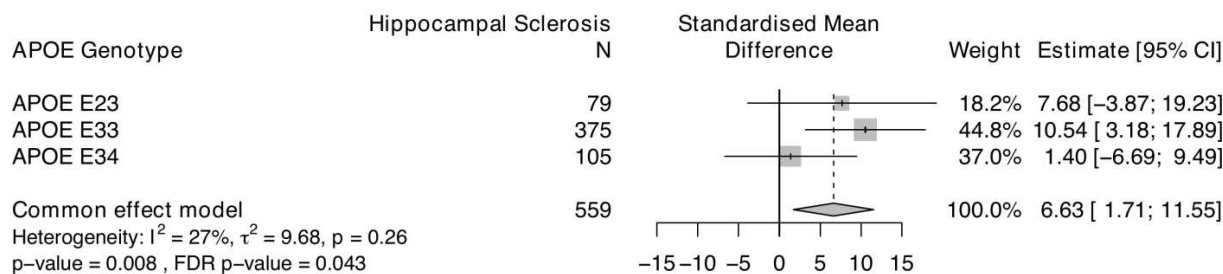
Supplementary Figure 2

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Supplementary Figure 3. Results for non-significant association testing between longitudinally measured HDL-C and neuropathologies in individuals with NCI or MCI at baseline with censoring of HDL-C for a diagnosis of either dementia. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis and is shown in by forest plot following the same layout as described in Supplementary Figure 1.
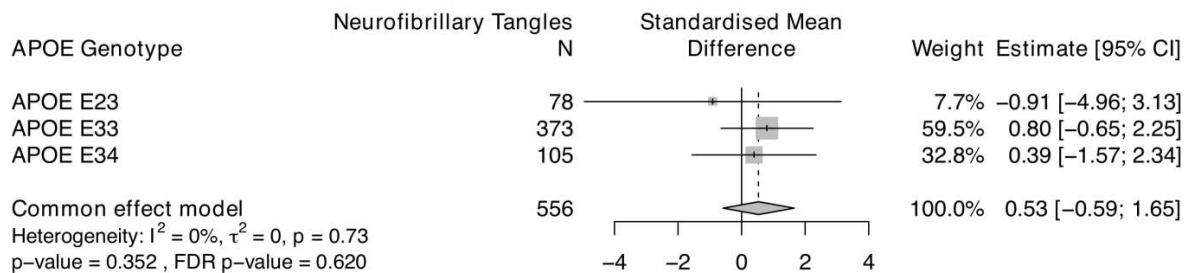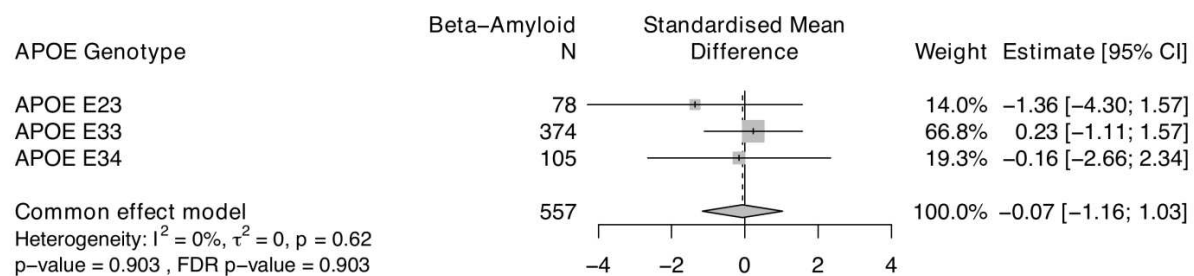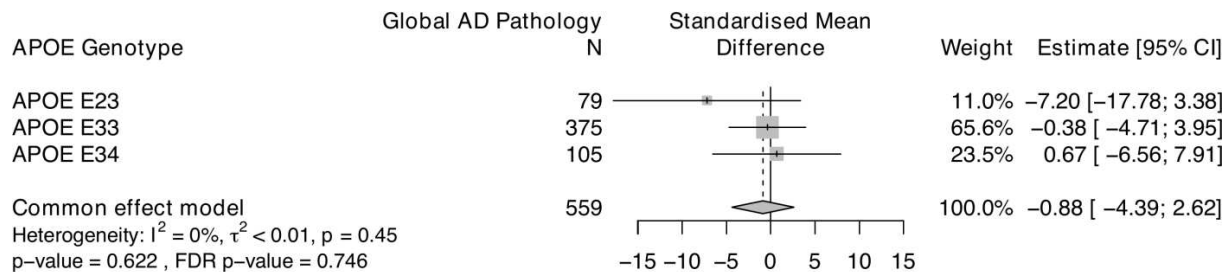
The Relationship between HDL–C and Neuropathology

Supplementary Figure 3 – part 1 of 4
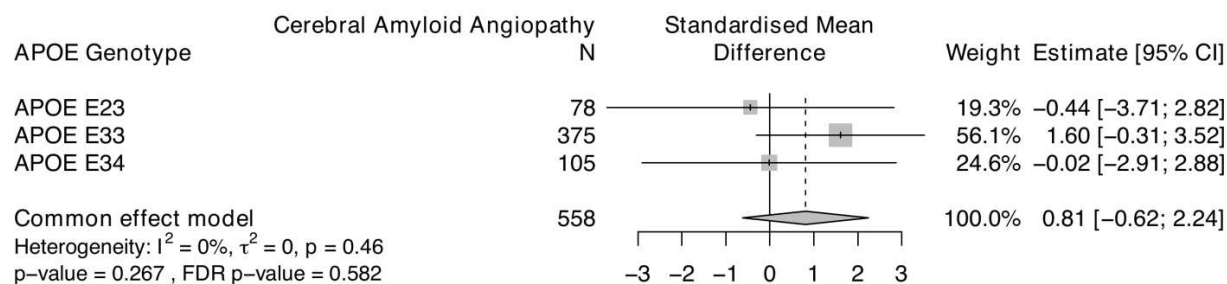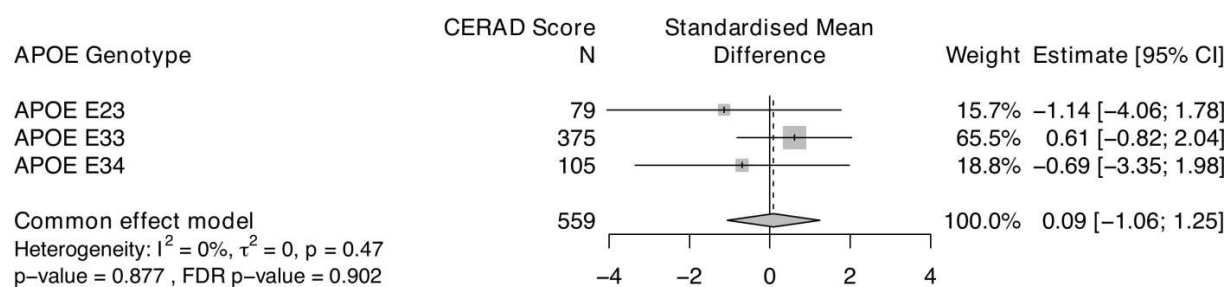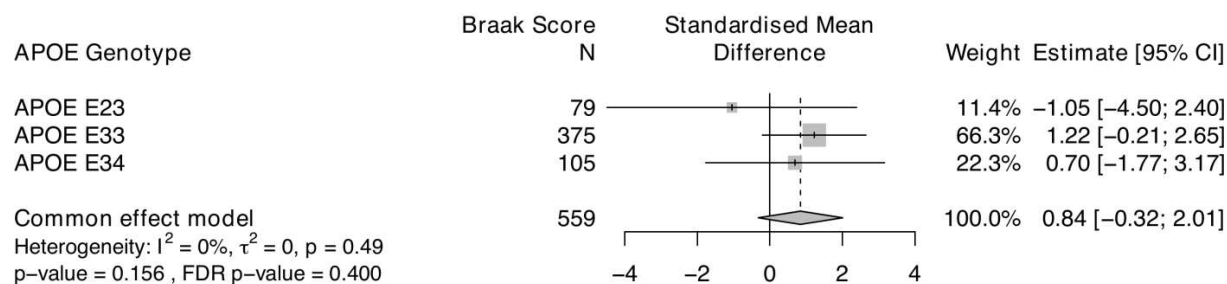
The Relationship between HDL–C and Neuropathology

APOE Genotype	Braak Score N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	79		11.4%	−1.05 [−4.50; 2.40]
APOE E33	375		66.3%	1.22 [−0.21; 2.65]
APOE E34	105		22.3%	0.70 [−1.77; 3.17]
Common effect model	559		100.0%	0.84 [−0.32; 2.01]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.49
p–value = 0.156 , FDR p–value = 0.400

APOE Genotype	CERAD Score N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	79		15.7%	−1.14 [−4.06; 1.78]
APOE E33	375		65.5%	0.61 [−0.82; 2.04]
APOE E34	105		18.8%	−0.69 [−3.35; 1.98]
Common effect model	559		100.0%	0.09 [−1.06; 1.25]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.47
p–value = 0.877 , FDR p–value = 0.902

APOE Genotype	Cerebral Amyloid Angiopathy N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	78		19.3%	−0.44 [−3.71; 2.82]
APOE E33	375		56.1%	1.60 [−0.31; 3.52]
APOE E34	105		24.6%	−0.02 [−2.91; 2.88]
Common effect model	558		100.0%	0.81 [−0.62; 2.24]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.46
p–value = 0.267 , FDR p–value = 0.582

Supplementary Figure 3 – part 2 of 4

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The Relationship between HDL–C and Neuropathology

APOE Genotype	Cerebral Atherosclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	79		14.9%	1.00 [−2.88; 4.88]
APOE E33	375		56.2%	0.07 [−1.93; 2.07]
APOE E34	105		28.9%	2.23 [−0.56; 5.02]
Common effect model	559		100.0%	0.84 [−0.66; 2.33]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.03$, $p = 0.47$
p–value = 0.275 , FDR p–value = 0.582

APOE Genotype	Gross Cerebral Infarctions N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	79		15.2%	−0.43 [−6.99; 6.13]
APOE E33	375		60.9%	−0.69 [−3.97; 2.59]
APOE E34	105		23.9%	−2.70 [−7.94; 2.54]
Common effect model	559		100.0%	−1.13 [−3.69; 1.43]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.80$
p–value = 0.386 , FDR p–value = 0.620

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	79		16.9%	−3.06 [−9.33; 3.21]
APOE E33	375		60.2%	−0.74 [−4.07; 2.58]
APOE E34	105		22.9%	3.22 [−2.16; 8.61]
Common effect model	559		100.0%	−0.23 [−2.80; 2.35]

Heterogeneity: $I^2 = 18\%$, $\tau^2 < 0.01$, $p = 0.29$
p–value = 0.864 , FDR p–value = 0.902

Supplementary Figure 3 – part 3 of 4

The Relationship between HDL–C and Neuropathology

APOE Genotype	TDP–43 N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	78		11.8%	−0.17 [−3.72; 3.39]
APOE E33	372		59.9%	0.30 [−1.27; 1.88]
APOE E34	103		28.4%	2.87 [0.58; 5.16]
Common effect model	553		100.0%	0.97 [−0.24; 2.19]

Heterogeneity: $I^2 = 46\%$, $\tau^2 = 1.25$, $p = 0.16$
p–value = 0.117 , FDR p–value = 0.352

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Supplementary Figure 4. Results for association testing between longitudinally measured TG and neuropathologies in individuals with NCI or MCI at baseline with censoring of TG for a diagnosis of either dementia. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis and is shown in by forest plot following the same layout as described in Supplementary Figure 1.
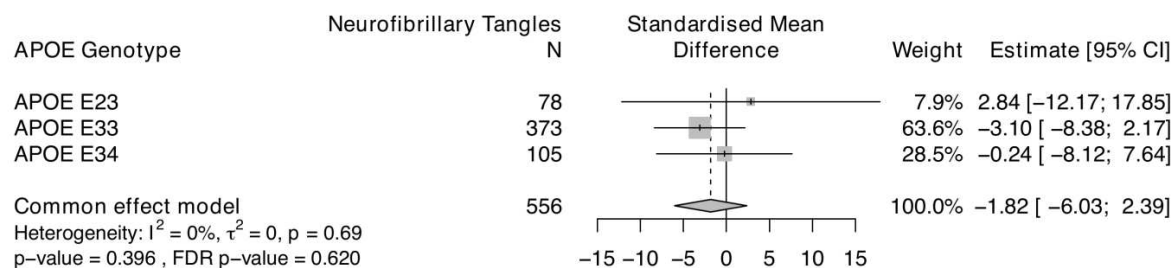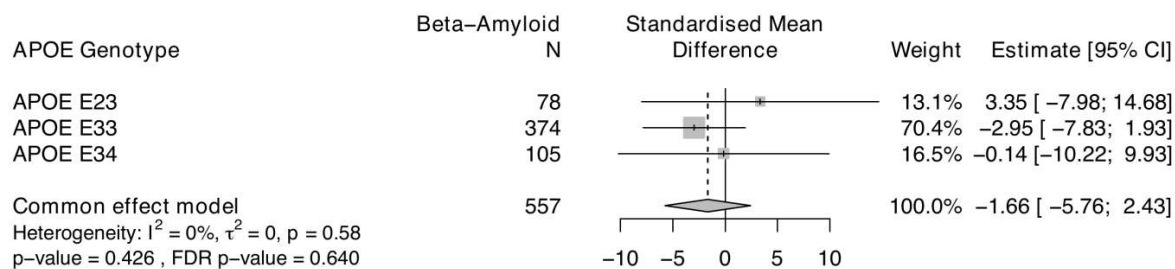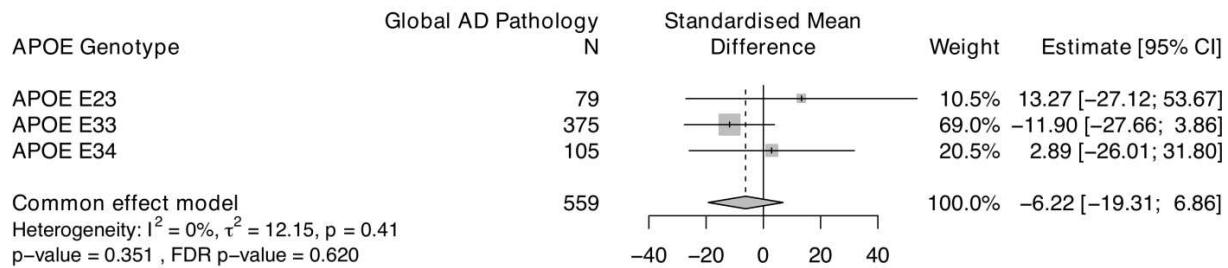
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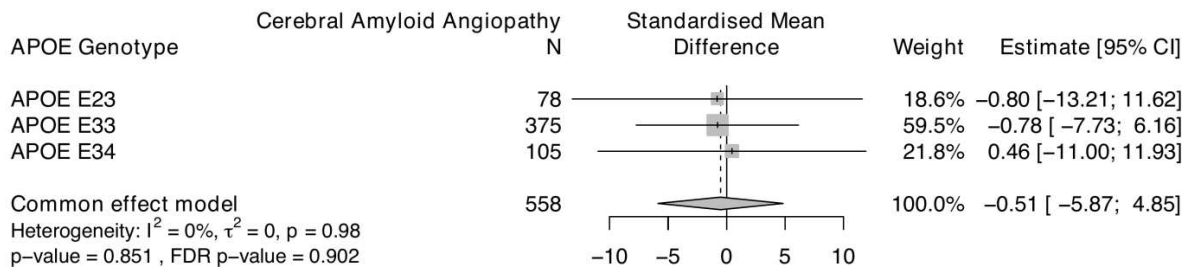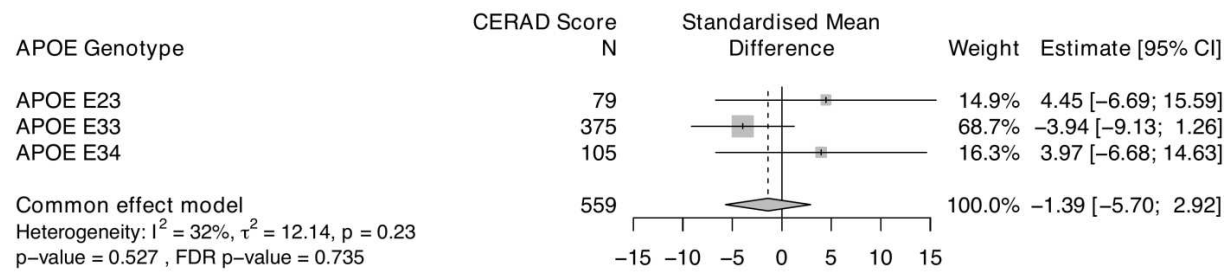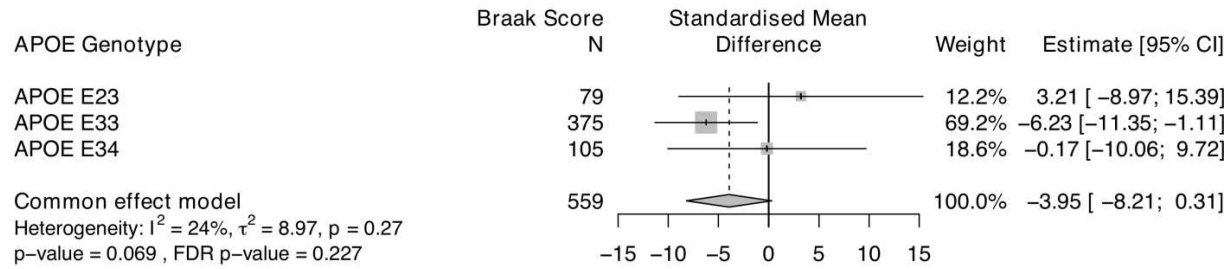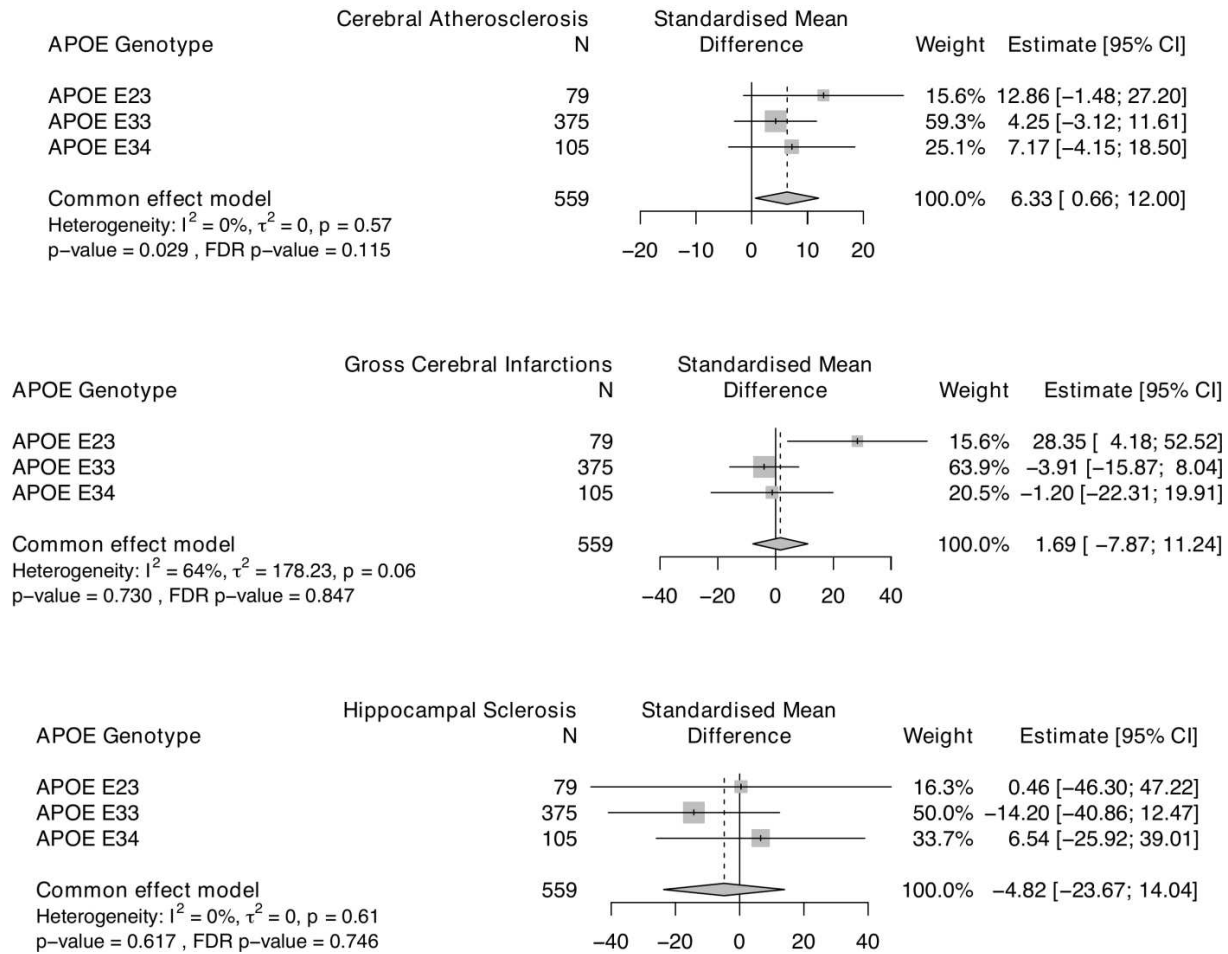
The Relationship between TG and Neuropathology

Supplementary Figure 4 – part 2 of 4

The Relationship between TG and Neuropathology

Supplementary Figure 4 – part 3 of 4

The Relationship between TG and Neuropathology

APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	77		12.0%	11.87 [−20.95; 44.69]
APOE E33	362		66.1%	4.64 [−9.35; 18.63]
APOE E34	101		21.8%	2.51 [−21.83; 26.85]
Common effect model	540		100.0%	5.04 [−6.33; 16.42]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.90$
p–value = 0.385 , FDR p–value = 0.620

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	79		16.3%	8.45 [−15.26; 32.15]
APOE E33	375		63.5%	7.15 [−4.87; 19.16]
APOE E34	105		20.2%	−14.15 [−35.47; 7.16]
Common effect model	559		100.0%	3.06 [−6.52; 12.64]

Heterogeneity: $I^2 = 36\%$, $\tau^2 = 49.30$, $p = 0.21$
p–value = 0.531 , FDR p–value = 0.735

APOE Genotype	TDP−43 N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	78		11.6%	−0.40 [−13.91; 13.11]
APOE E33	372		63.9%	−1.72 [−7.46; 4.03]
APOE E34	103		24.5%	−0.70 [−9.98; 8.58]
Common effect model	553		100.0%	−1.31 [−5.91; 3.28]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.97$
p–value = 0.575 , FDR p–value = 0.746

Supplementary Figure 4 – part 4 of 4

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Supplementary Figure 5. Results for non-significant association testing between longitudinally measured LDL-C and neuropathologies in individuals with NCI at baseline with censoring of LDL-C for a diagnosis of either MCI or dementia. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis and is shown in by forest plot following the same layout as described in Supplementary Figure 1.

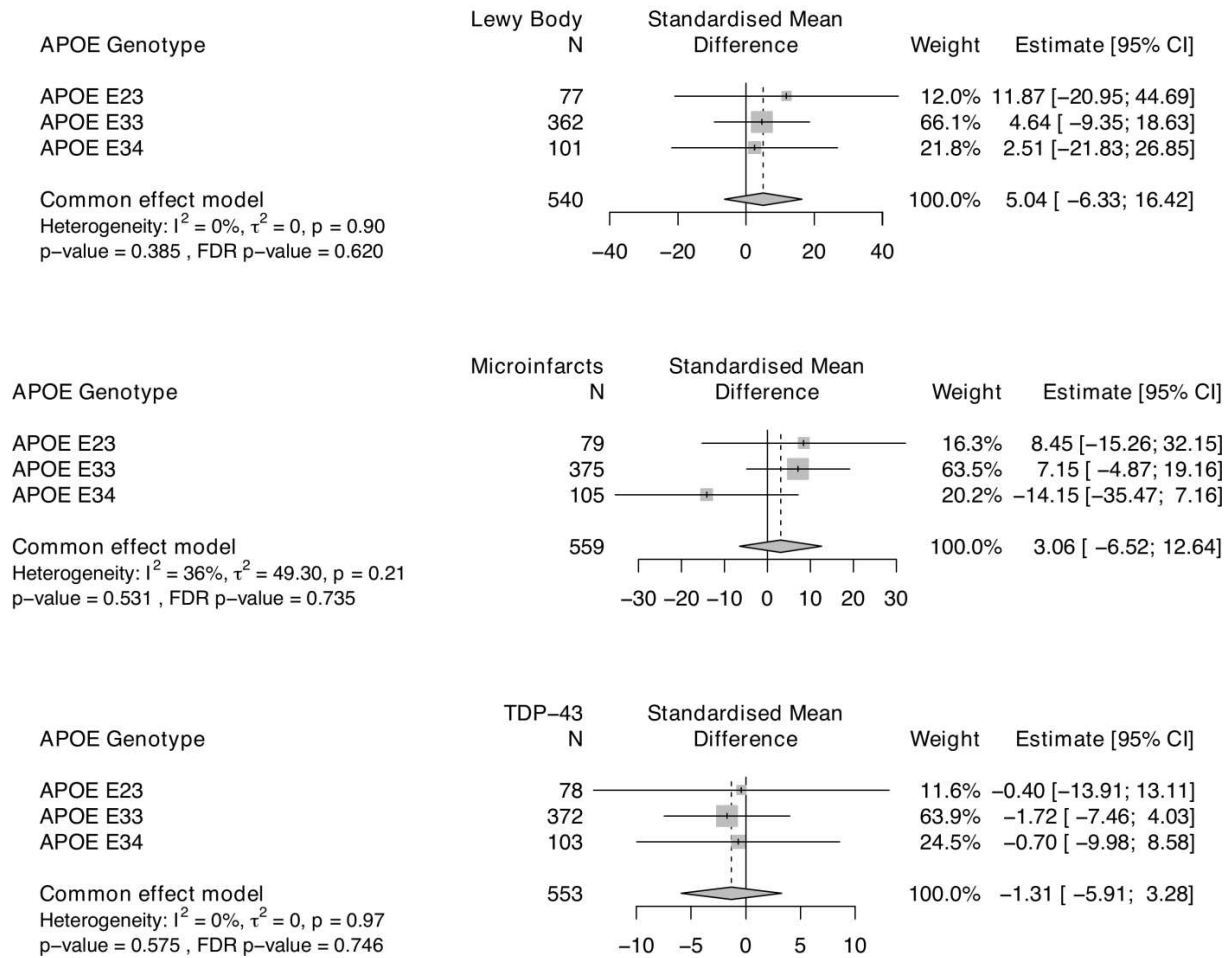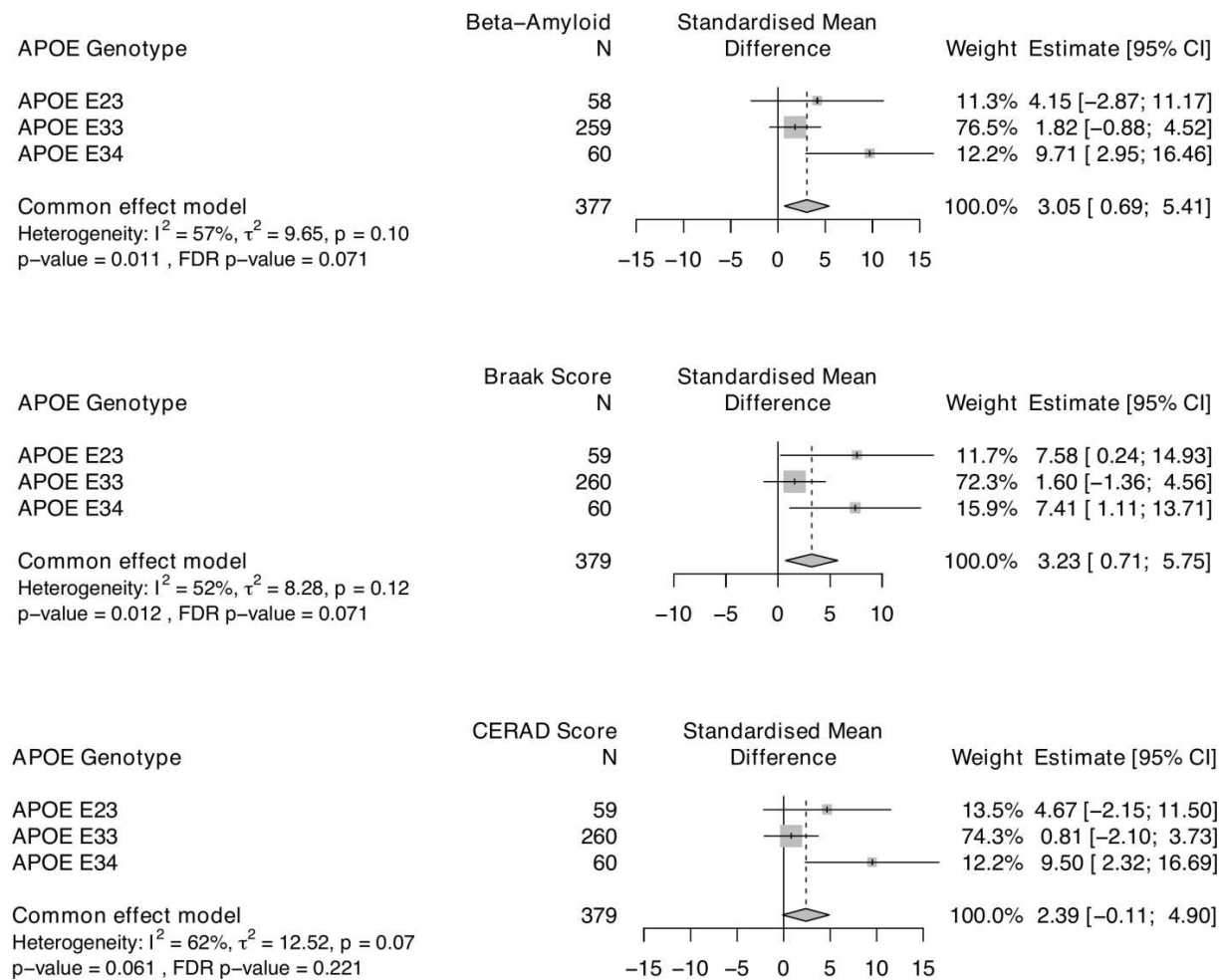The Relationship between LDL−C and Neuropathology

Supplementary Figure 5 – part 1 of 3

The Relationship between LDL−C and Neuropathology
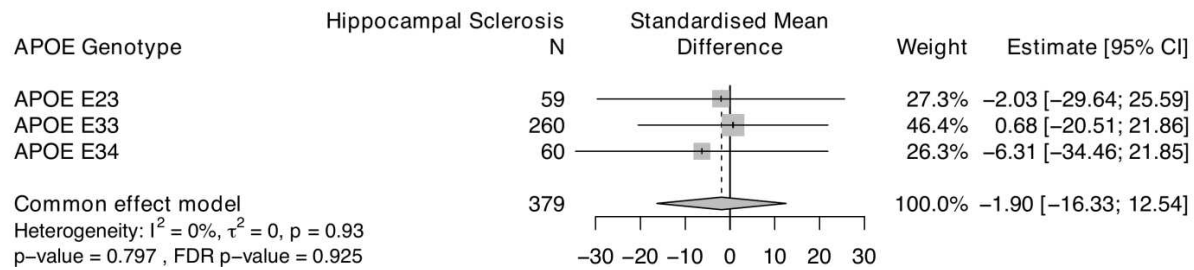

Supplementary Figure 5 – part 2 of 3

The Relationship between LDL−C and Neuropathology

APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	57		10.3%	0.13 [−21.30; 21.56]
APOE E33	251		75.8%	1.18 [−6.74; 9.10]
APOE E34	58		13.9%	10.85 [−7.65; 29.34]
Common effect model	366		100.0%	2.41 [−4.48; 9.30]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.63$
p−value = 0.493 , FDR p−value = 0.805

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	59		15.2%	8.70 [−5.91; 23.31]
APOE E33	260		70.9%	0.19 [−6.57; 6.95]
APOE E34	60		13.9%	11.63 [−3.61; 26.87]
Common effect model	379		100.0%	3.08 [−2.61; 8.77]

Heterogeneity: $I^2 = 19\%$, $\tau^2 = 15.05$, $p = 0.29$
p−value = 0.289 , FDR p−value = 0.612

APOE Genotype	TDP−43 N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	58		12.4%	8.06 [−0.40; 16.51]
APOE E33	257		71.7%	−2.42 [−5.94; 1.09]
APOE E34	59		15.9%	−2.60 [−10.07; 4.86]
Common effect model	374		100.0%	−1.15 [−4.13; 1.82]

Heterogeneity: $I^2 = 62\%$, $\tau^2 = 18.56$, $p = 0.07$
p−value = 0.448 , FDR p−value = 0.787

Supplementary Figure 5 – part 3 of 3

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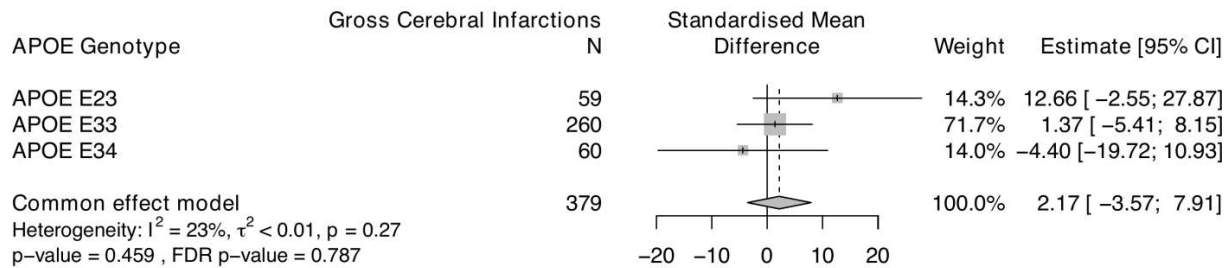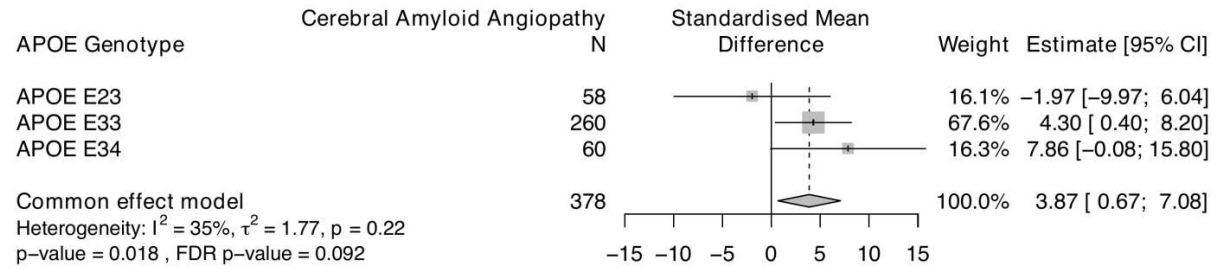
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Supplementary Figure 6. Results for significant association testing between longitudinally measured HDL-C and neuropathologies in individuals with NCI at baseline with censoring of HDL-C for a diagnosis of either MCI or dementia. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis and is shown in by forest plot following the same layout as described in Supplementary Figure 1.
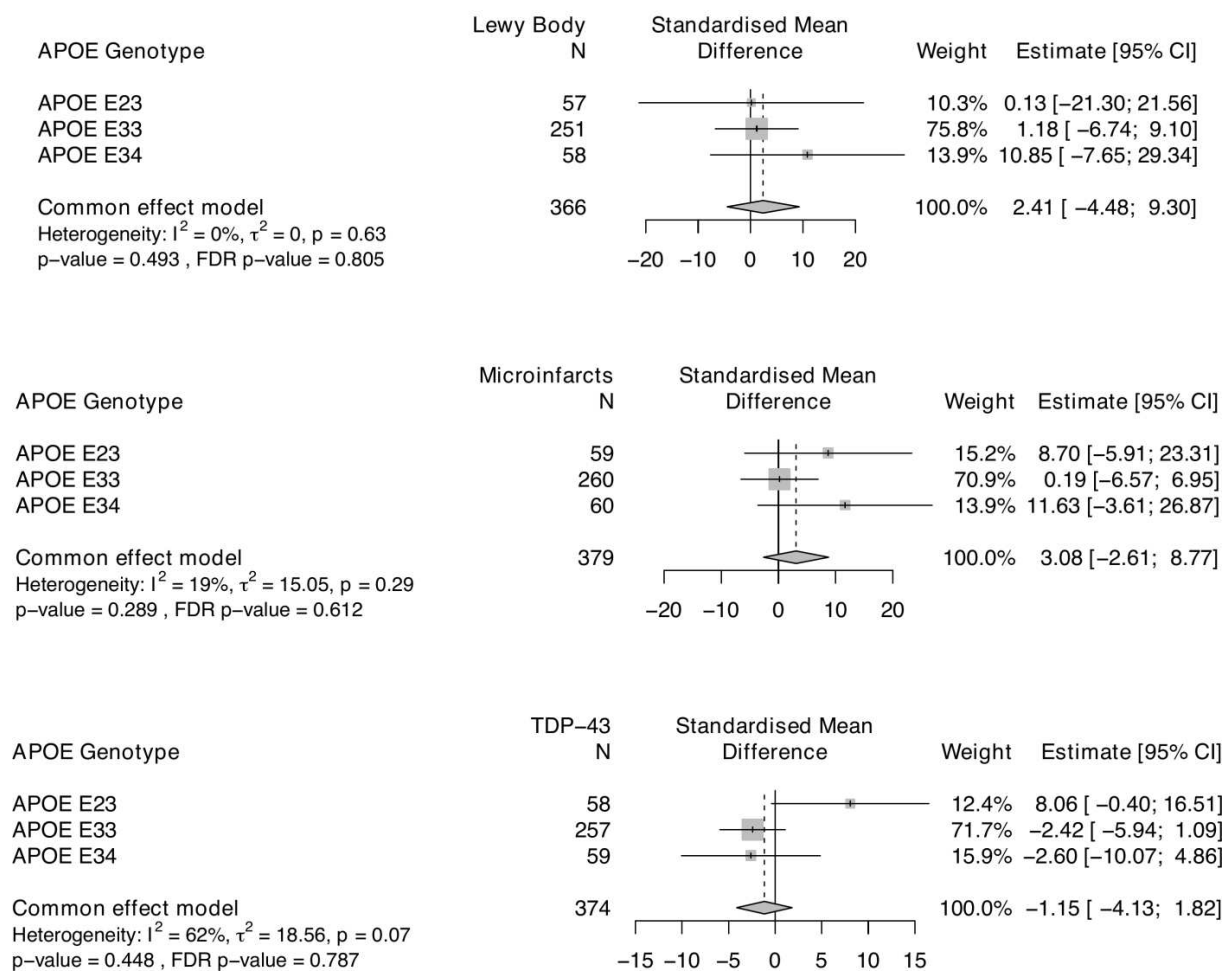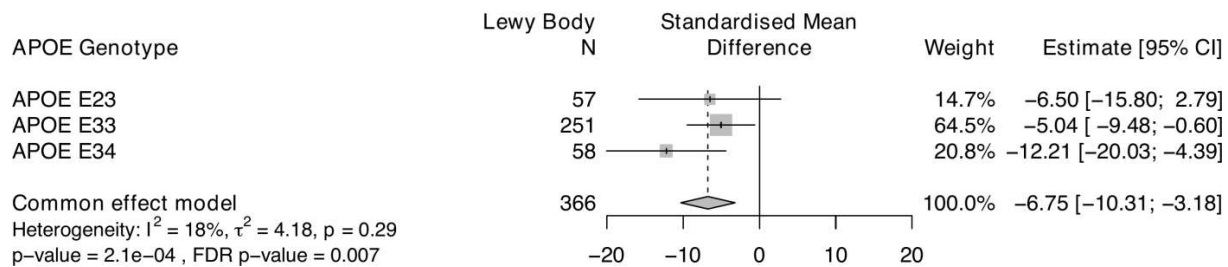

The Relationship between HDL−C and Neuropathology

APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	57		14.7%	−6.50 [−15.80; 2.79]
APOE E33	251		64.5%	−5.04 [−9.48; −0.60]
APOE E34	58		20.8%	−12.21 [−20.03; −4.39]
Common effect model	366		100.0%	−6.75 [−10.31; −3.18]

Heterogeneity: I^2 = 18%, τ^2 = 4.18, p = 0.29
p−value = 2.1e−04 , FDR p−value = 0.007

Supplementary Figure 6

Supplementary Figure 7. Results for non-significant association testing between longitudinally measured HDL-C and neuropathologies in individuals with NCI at baseline with censoring of HDL-C for a diagnosis of either MCI or dementia. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis and is shown in by forest plot following the same layout as described in Supplementary Figure 1.
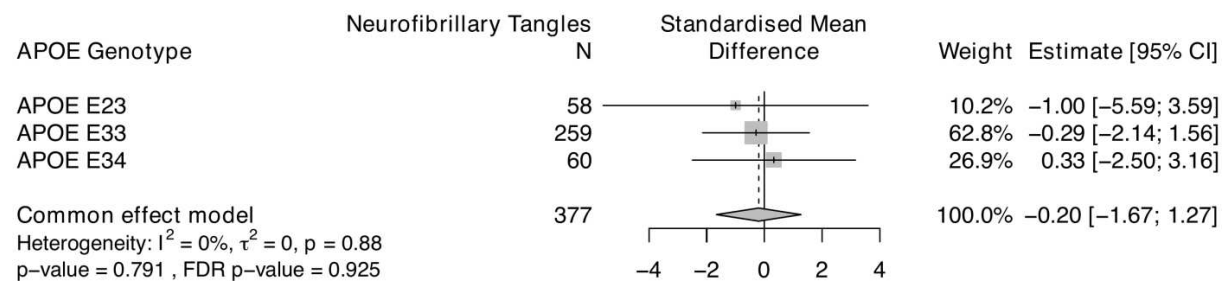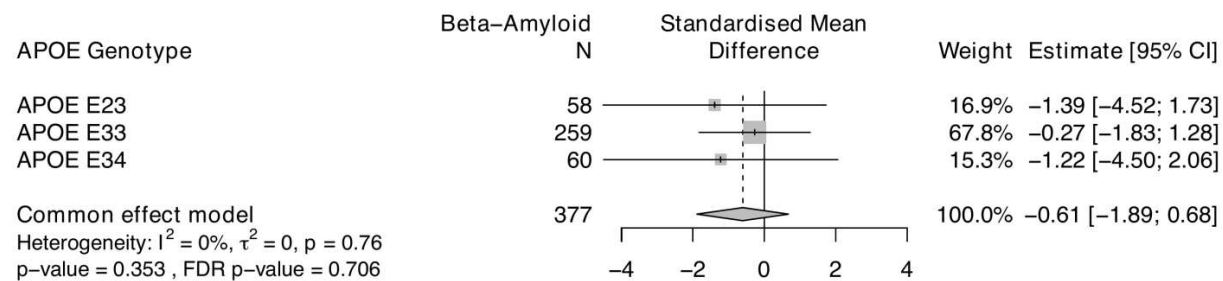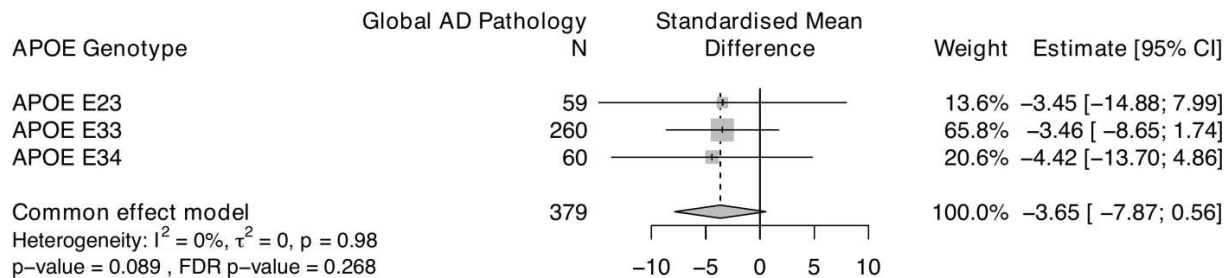
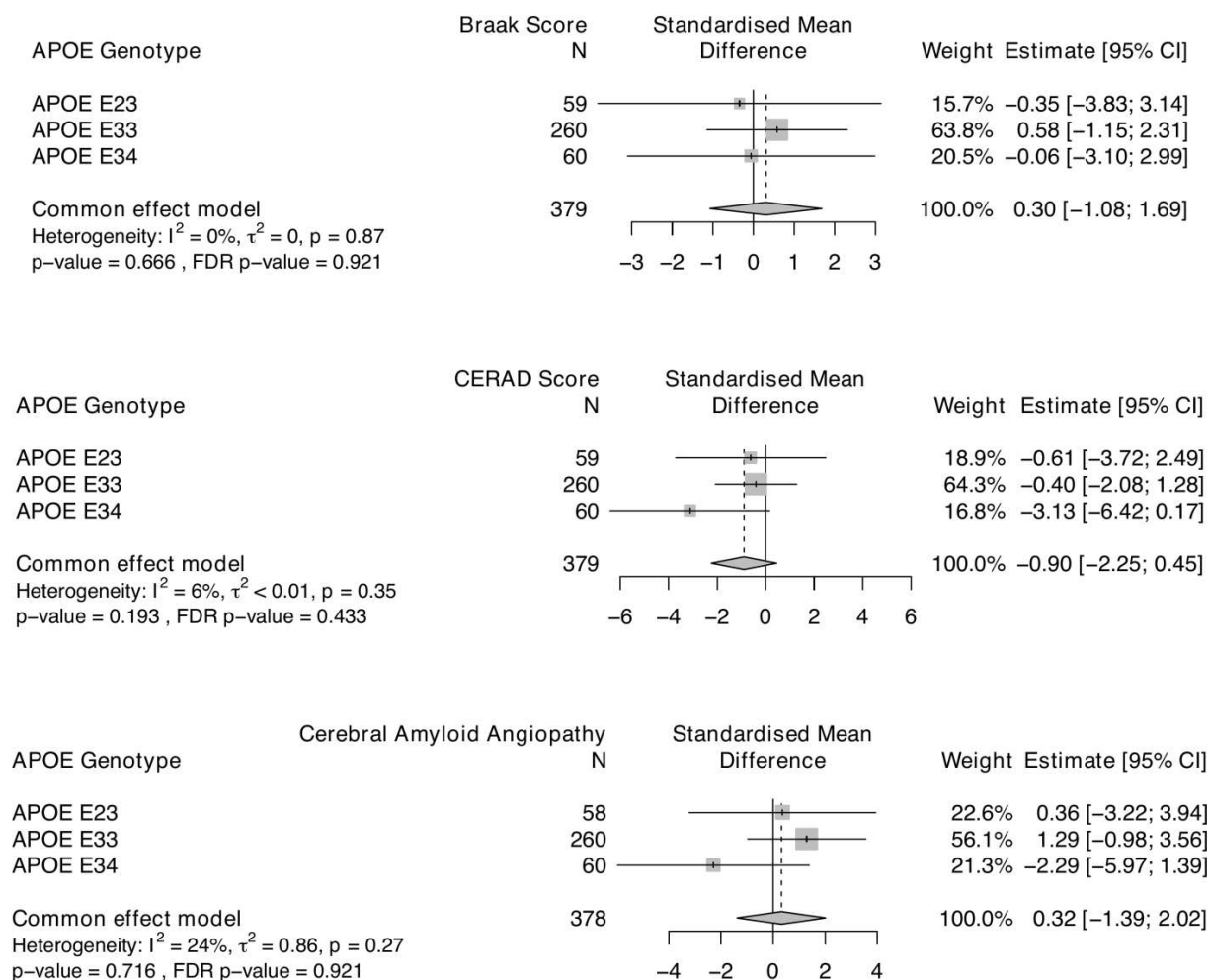### The Relationship between HDL–C and Neuropathology

Supplementary Figure 7 – part 1 of 4

The Relationship between HDL–C and Neuropathology

APOE Genotype	Braak Score N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	59		15.7%	−0.35 [−3.83; 3.14]
APOE E33	260		63.8%	0.58 [−1.15; 2.31]
APOE E34	60		20.5%	−0.06 [−3.10; 2.99]
Common effect model	379		100.0%	0.30 [−1.08; 1.69]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.87
p–value = 0.666 , FDR p–value = 0.921

APOE Genotype	CERAD Score N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	59		18.9%	−0.61 [−3.72; 2.49]
APOE E33	260		64.3%	−0.40 [−2.08; 1.28]
APOE E34	60		16.8%	−3.13 [−6.42; 0.17]
Common effect model	379		100.0%	−0.90 [−2.25; 0.45]

Heterogeneity: $I^2 = 6\%$, $\tau^2 < 0.01$, p = 0.35
p–value = 0.193 , FDR p–value = 0.433

APOE Genotype	Cerebral Amyloid Angiopathy N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	58		22.6%	0.36 [−3.22; 3.94]
APOE E33	260		56.1%	1.29 [−0.98; 3.56]
APOE E34	60		21.3%	−2.29 [−5.97; 1.39]
Common effect model	378		100.0%	0.32 [−1.39; 2.02]

Heterogeneity: $I^2 = 24\%$, $\tau^2 = 0.86$, p = 0.27
p–value = 0.716 , FDR p–value = 0.921

Supplementary Figure 7 – part 2 of 4

The Relationship between HDL−C and Neuropathology

APOE Genotype	Cerebral Atherosclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	59		22.2%	1.90 [−1.99; 5.78]
APOE E33	260		60.3%	−0.44 [−2.79; 1.92]
APOE E34	60		17.5%	1.53 [−2.84; 5.90]
Common effect model	379		100.0%	0.43 [−1.40; 2.25]

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.52
p−value = 0.648 , FDR p−value = 0.921

APOE Genotype	Gross Cerebral Infarctions N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	59		20.0%	−4.64 [−11.47; 2.19]
APOE E33	260		61.0%	−0.95 [−4.86; 2.96]
APOE E34	60		19.1%	−4.56 [−11.55; 2.43]
Common effect model	379		100.0%	−2.37 [−5.43; 0.68]

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.52
p−value = 0.127 , FDR p−value = 0.353

APOE Genotype	Hippocampal Sclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	59		35.4%	−0.08 [−12.00; 11.83]
APOE E33	260		33.9%	16.86 [4.69; 29.02]
APOE E34	60		30.7%	2.46 [−10.34; 15.25]
Common effect model	379		100.0%	6.45 [−0.64; 13.53]

Heterogeneity: I^2 = 54%, τ^2 = 45.84, p = 0.11
p−value = 0.075 , FDR p−value = 0.244

Supplementary Figure 7 – part 3 of 4

The Relationship between HDL–C and Neuropathology

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	59		20.8%	0.66 [−5.98; 7.30]
APOE E33	260		60.4%	−1.14 [−5.03; 2.76]
APOE E34	60		18.8%	3.11 [−3.88; 10.09]
Common effect model	379		100.0%	0.04 [−2.99; 3.06]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.57
p–value = 0.982 , FDR p–value = 0.982

APOE Genotype	TDP–43 N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	58		16.8%	−1.44 [−5.34; 2.46]
APOE E33	257		60.5%	−1.05 [−3.11; 1.00]
APOE E34	59		22.7%	2.90 [−0.45; 6.26]
Common effect model	374		100.0%	−0.22 [−1.82; 1.38]

Heterogeneity: $I^2 = 54\%$, $\tau^2 = 2.81$, p = 0.11
p–value = 0.788 , FDR p–value = 0.925

Supplementary Figure 7 – part 4 of 4

Supplementary Figure 8. Results for association testing between longitudinally measured TG and neuropathologies in individuals with NCI at baseline with censoring of TG levels for a diagnosis of either MCI or dementia. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis and is shown in by forest plot following the same layout as described in Supplementary Figure 1.
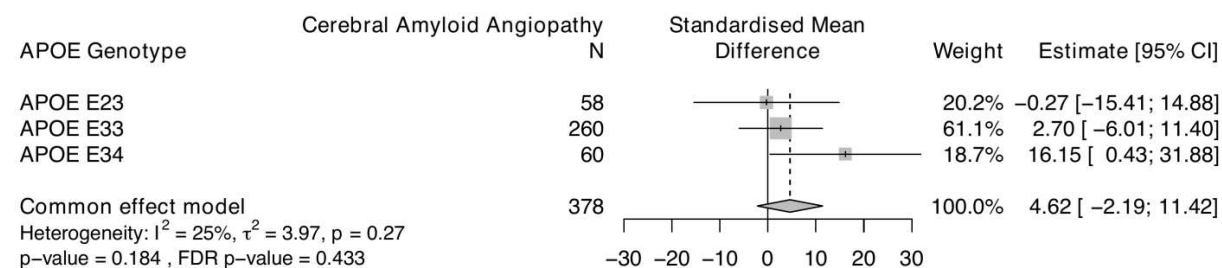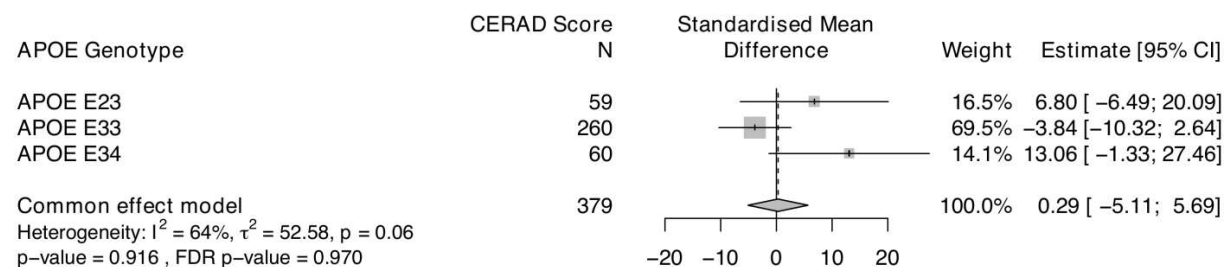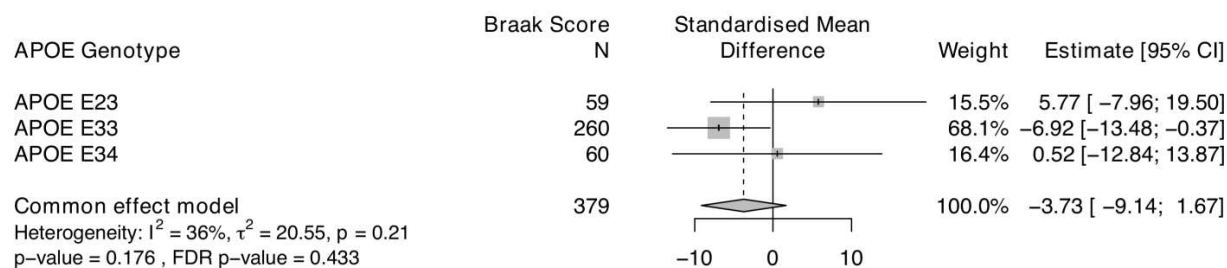
The Relationship between TG and Neuropathology

APOE Genotype	Global AD Pathology N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	59		12.3%	20.38 [−27.89; 68.65]
APOE E33	260		70.4%	−7.07 [−27.22; 13.08]
APOE E34	60		17.3%	12.89 [−27.81; 53.58]
Common effect model	379		100.0%	−0.25 [−17.17; 16.66]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 2.82$, $p = 0.46$
p−value = 0.977 , FDR p−value = 0.982

−60 −40 −20 0 20 40 60

APOE Genotype	Beta−Amyloid N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	58		14.1%	5.19 [−8.51; 18.90]
APOE E33	259		72.6%	−2.08 [−8.13; 3.97]
APOE E34	60		13.3%	9.06 [−5.07; 23.20]
Common effect model	377		100.0%	0.43 [−4.72; 5.58]

Heterogeneity: $I^2 = 22\%$, $\tau^2 = 13.74$, $p = 0.28$
p−value = 0.870 , FDR p−value = 0.950

−20 −10 0 10 20

APOE Genotype	Neurofibrillary Tangles N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	58		10.4%	10.53 [−7.75; 28.82]
APOE E33	259		67.9%	−3.18 [−10.34; 3.99]
APOE E34	60		21.6%	−0.53 [−13.22; 12.16]
Common effect model	377		100.0%	−1.18 [−7.08; 4.73]

Heterogeneity: $I^2 = 0\%$, $\tau^2 < 0.01$, $p = 0.39$
p−value = 0.697 , FDR p−value = 0.921
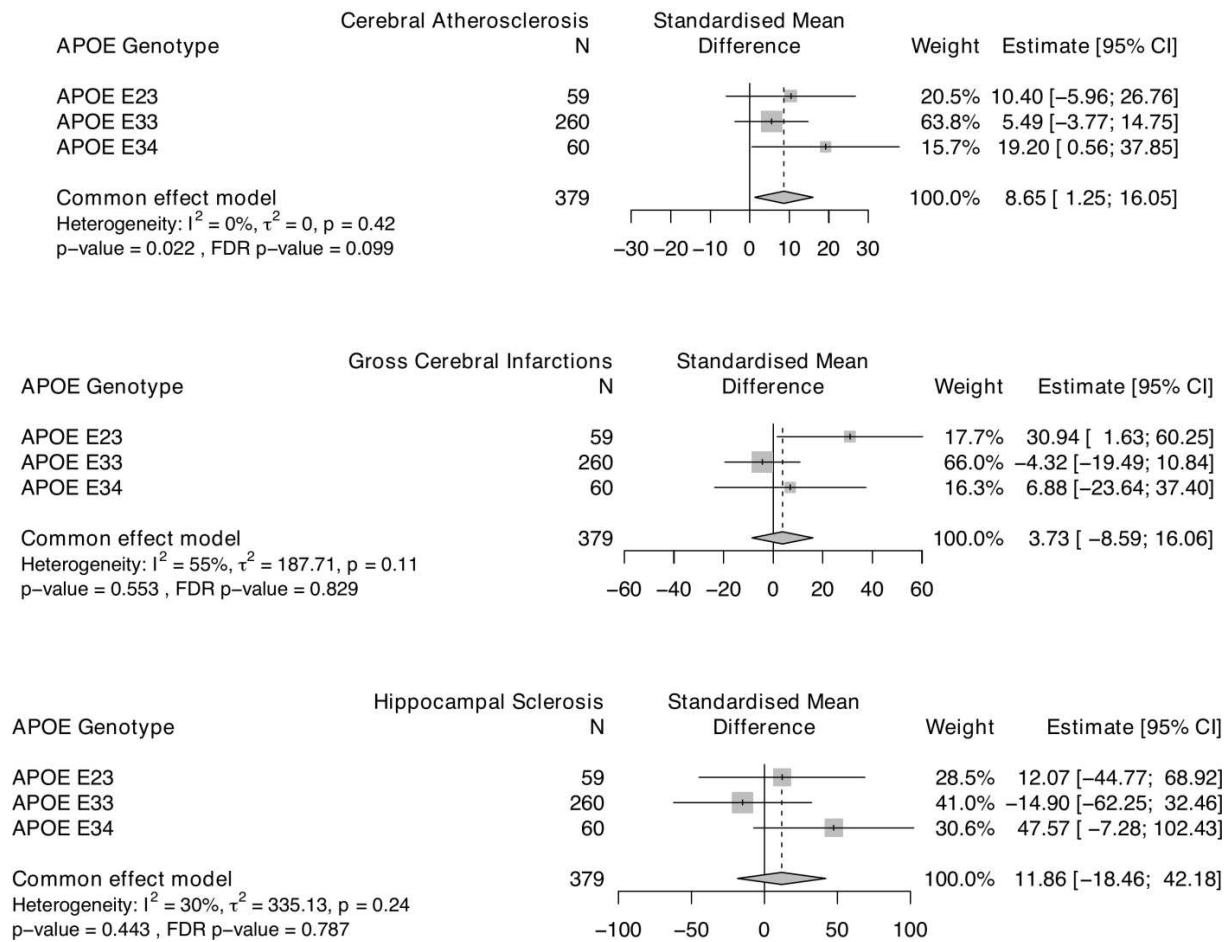
−20 −10 0 10 20

Supplementary Figure 8 – part 1 of 4
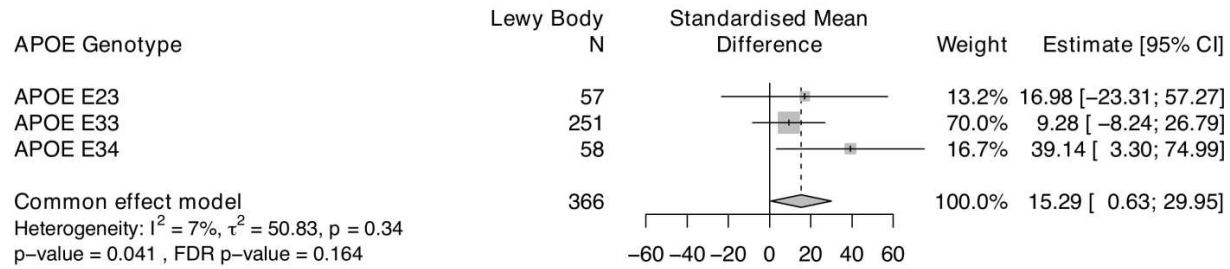
The Relationship between TG and Neuropathology

APOE Genotype	Braak Score N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	59		15.5%	5.77 [−7.96; 19.50]
APOE E33	260		68.1%	−6.92 [−13.48; −0.37]
APOE E34	60		16.4%	0.52 [−12.84; 13.87]
Common effect model	379		100.0%	−3.73 [−9.14; 1.67]

Heterogeneity: $I^2 = 36\%$, $\tau^2 = 20.55$, $p = 0.21$
p−value = 0.176 , FDR p−value = 0.433

−10   0   10

APOE Genotype	CERAD Score N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	59		16.5%	6.80 [−6.49; 20.09]
APOE E33	260		69.5%	−3.84 [−10.32; 2.64]
APOE E34	60		14.1%	13.06 [−1.33; 27.46]
Common effect model	379		100.0%	0.29 [−5.11; 5.69]

Heterogeneity: $I^2 = 64\%$, $\tau^2 = 52.58$, $p = 0.06$
p−value = 0.916 , FDR p−value = 0.970

−20 −10 0 10 20

APOE Genotype	Cerebral Amyloid Angiopathy N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	58		20.2%	−0.27 [−15.41; 14.88]
APOE E33	260		61.1%	2.70 [−6.01; 11.40]
APOE E34	60		18.7%	16.15 [0.43; 31.88]
Common effect model	378		100.0%	4.62 [−2.19; 11.42]

Heterogeneity: $I^2 = 25\%$, $\tau^2 = 3.97$, $p = 0.27$
p−value = 0.184 , FDR p−value = 0.433

−30 −20 −10 0 10 20 30

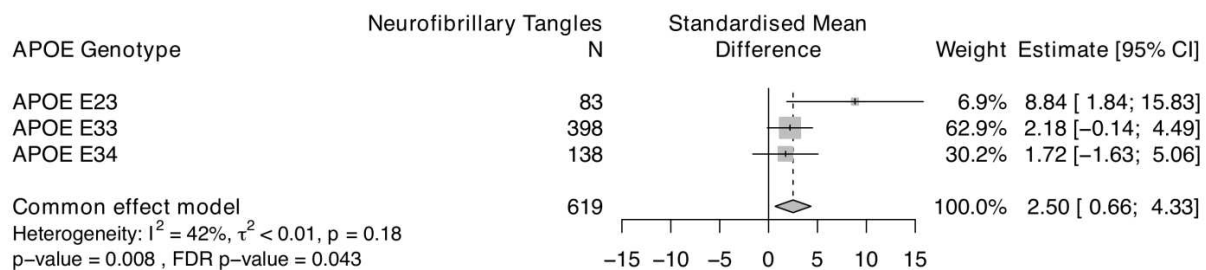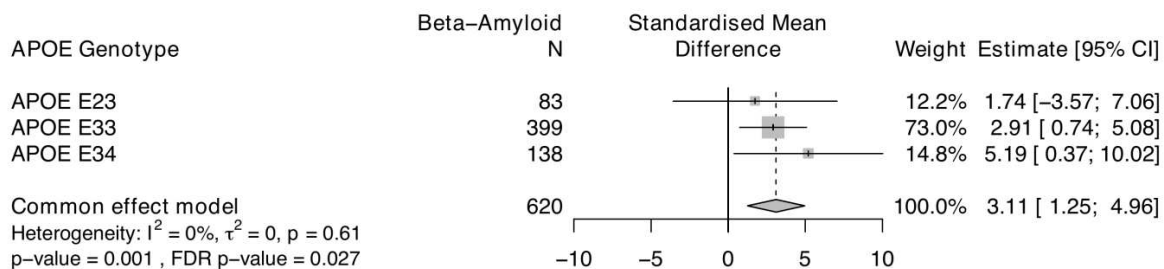*Supplementary Figure 8 – part 2 of 4*

The Relationship between TG and Neuropathology

Supplementary Figure 8 – part 3 of 4

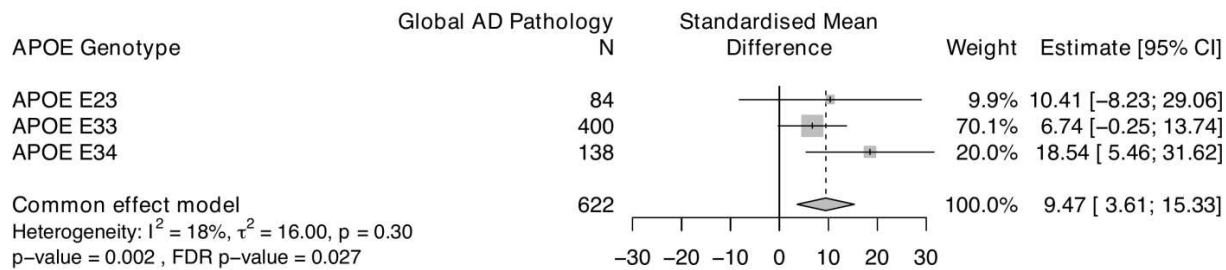## The Relationship between TG and Neuropathology

APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	57		13.2%	16.98 [−23.31; 57.27]
APOE E33	251		70.0%	9.28 [−8.24; 26.79]
APOE E34	58		16.7%	39.14 [3.30; 74.99]
Common effect model	366		100.0%	15.29 [0.63; 29.95]

Heterogeneity: $I^2 = 7\%$, $\tau^2 = 50.83$, $p = 0.34$
p−value = 0.041 , FDR p−value = 0.164

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	59		18.6%	0.16 [−27.98; 28.29]
APOE E33	260		65.2%	−0.67 [−15.68; 14.34]
APOE E34	60		16.2%	−22.30 [−52.37; 7.77]
Common effect model	379		100.0%	−4.03 [−16.15; 8.09]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.43$
p−value = 0.514 , FDR p−value = 0.805

APOE Genotype	TDP−43 N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	58		14.4%	0.36 [−16.46; 17.18]
APOE E33	257		66.5%	−3.08 [−10.92; 4.76]
APOE E34	59		19.1%	7.52 [−7.09; 22.13]
Common effect model	374		100.0%	−0.56 [−6.95; 5.83]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.45$
p−value = 0.864 , FDR p−value = 0.950

Supplementary Figure 8 – part 4 of 4

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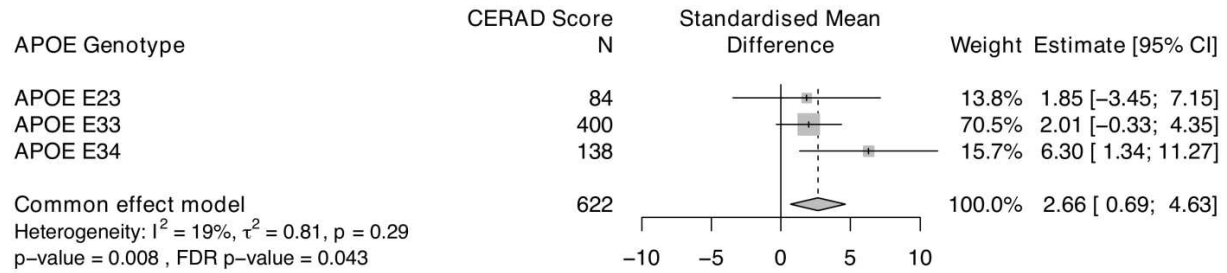
J Neurol Neurosurg Psychiatry

Supplementary Figure 9. Results for significant association testing between longitudinally measured LDL-C and neuropathologies in all individuals with antemortem blood lipids and neuropathology data without censoring of lipid values based on diagnosis. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis and is shown in by forest plot following the same layout as described in Supplementary Figure 1.
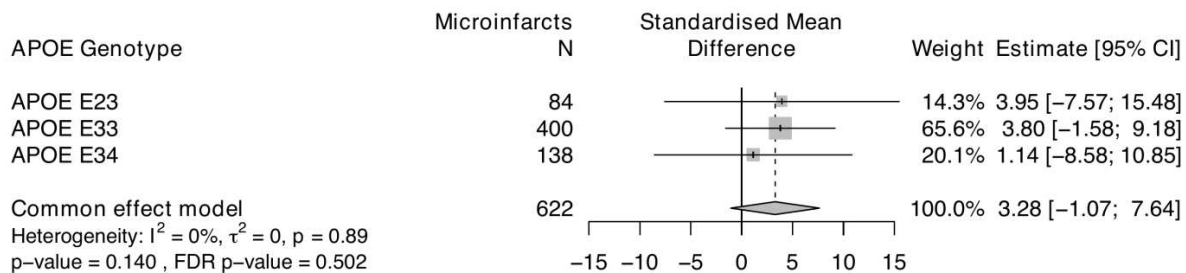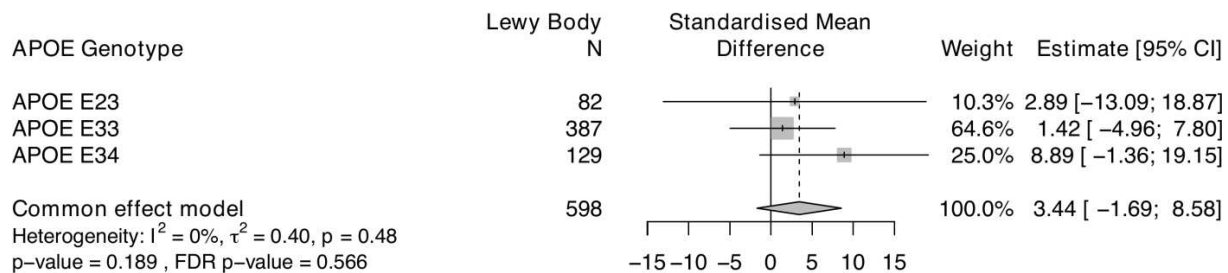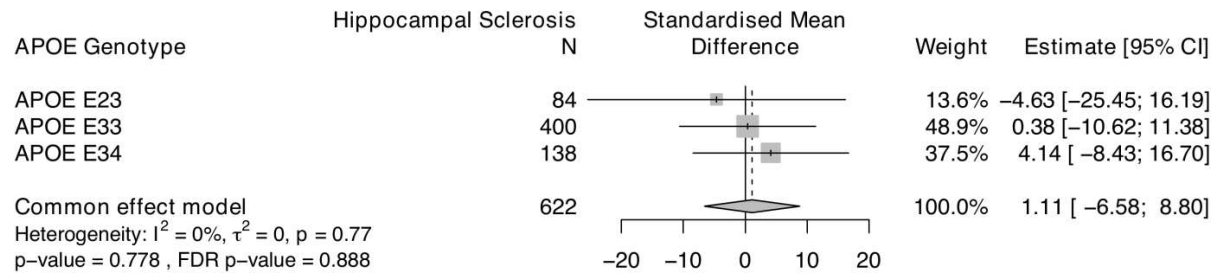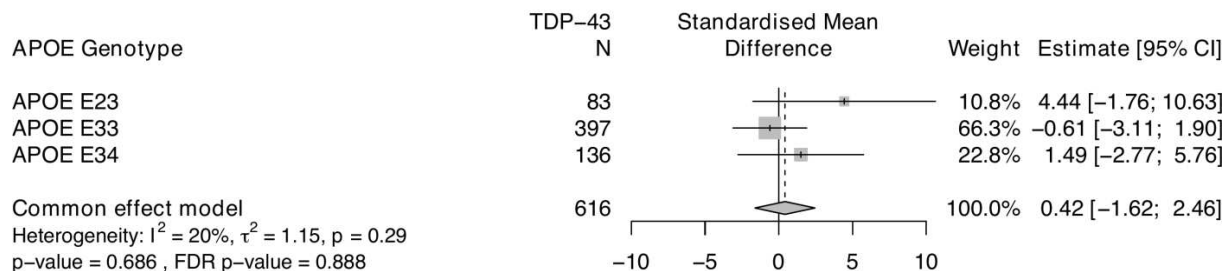
The Relationship between LDL–C and Neuropathology

Supplementary Figure 9 – part 1 of 2

The Relationship between LDL−C and Neuropathology

APOE Genotype	CERAD Score N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	84		13.8%	1.85 [−3.45; 7.15]
APOE E33	400		70.5%	2.01 [−0.33; 4.35]
APOE E34	138		15.7%	6.30 [1.34; 11.27]
Common effect model	622		100.0%	2.66 [0.69; 4.63]

Heterogeneity: $I^2 = 19\%$, $\tau^2 = 0.81$, p = 0.29
p−value = 0.008 , FDR p−value = 0.043

APOE Genotype	Cerebral Atherosclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	84		13.6%	8.21 [1.23; 15.19]
APOE E33	400		61.7%	4.33 [1.05; 7.60]
APOE E34	138		24.7%	−0.07 [−5.24; 5.10]
Common effect model	622		100.0%	3.77 [1.20; 6.34]

Heterogeneity: $I^2 = 47\%$, $\tau^2 = 5.20$, p = 0.15
p−value = 0.004 , FDR p−value = 0.037

Supplementary Figure 9 – part 2 of 2

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Supplementary Figure 10. Results for non-significant association testing between longitudinally measured LDL-C and neuropathologies in all individuals with antemortem blood lipids and neuropathology data without censoring of lipid values based on diagnosis. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis and is shown in by forest plot following the same layout as described in Supplementary Figure 1.

The Relationship between LDL–C and Neuropathology
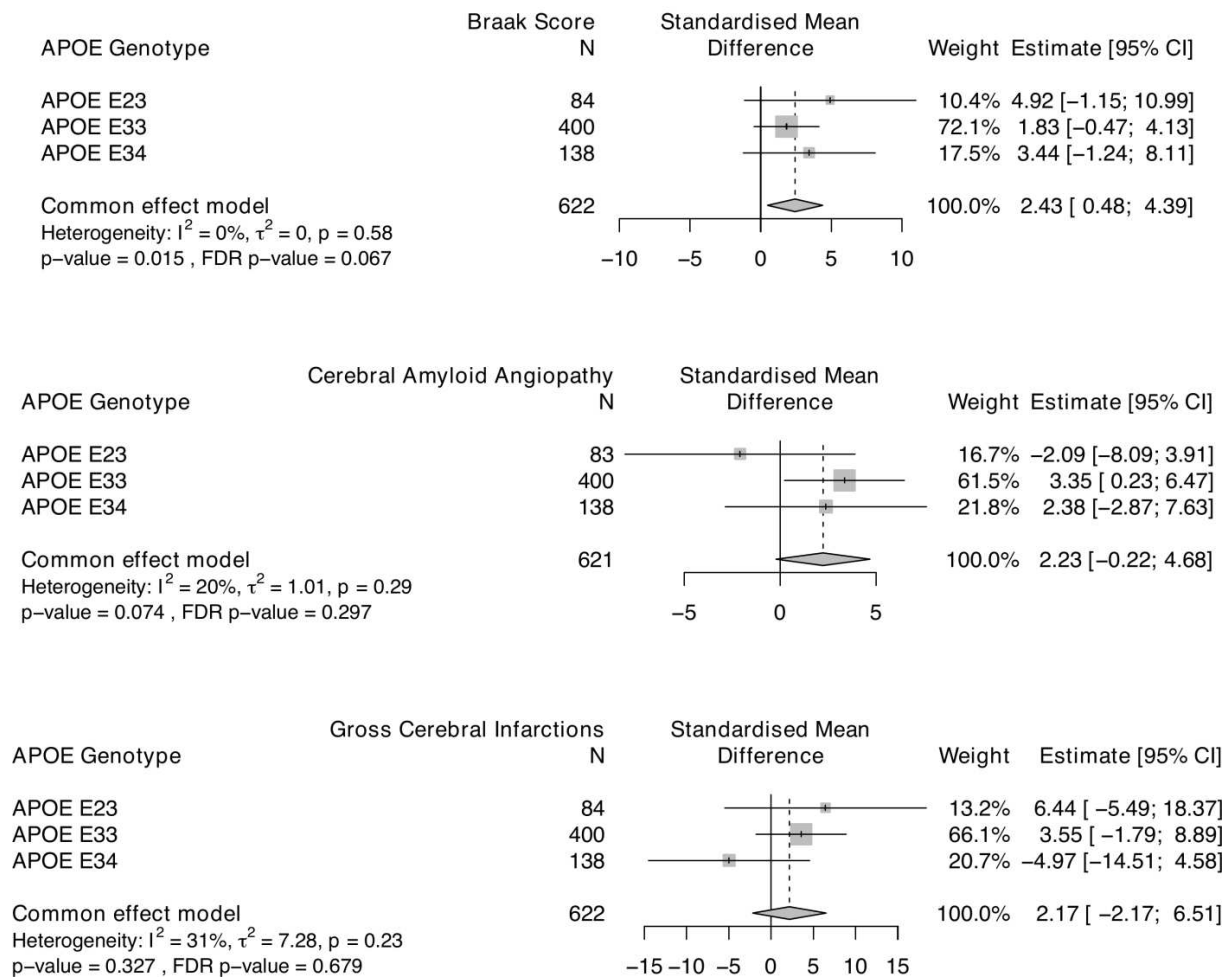
Supplementary Figure 10 – part 1 of 3

The Relationship between LDL−C and Neuropathology
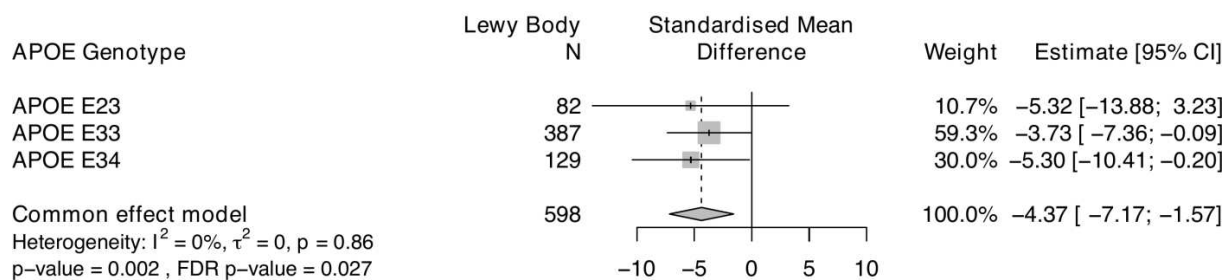

Supplementary Figure 10 – part 2 of 3

The Relationship between LDL−C and Neuropathology

Supplementary Figure 10 – part 3 of 3

Supplementary Figure 11. Results for significant association testing between longitudinally measured HDL-C and neuropathologies in all individuals with antemortem blood lipids and neuropathology data without censoring of lipid values based on diagnosis. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis and is shown in by forest plot following the same layout as described in Supplementary Figure 1.
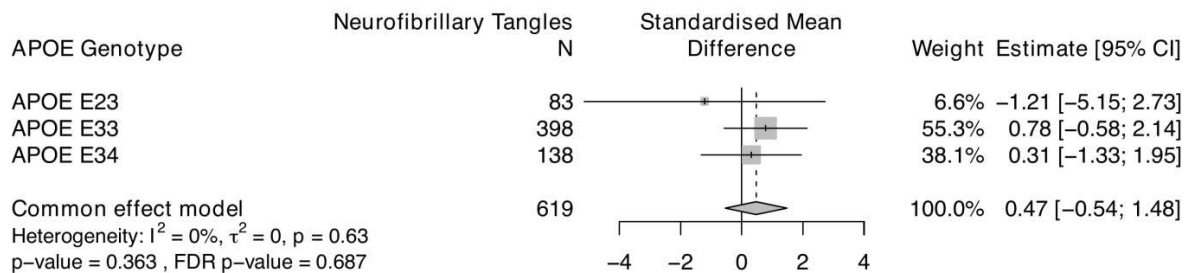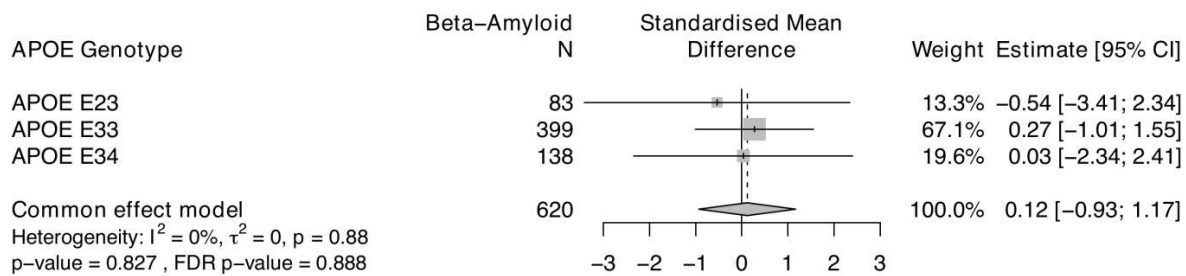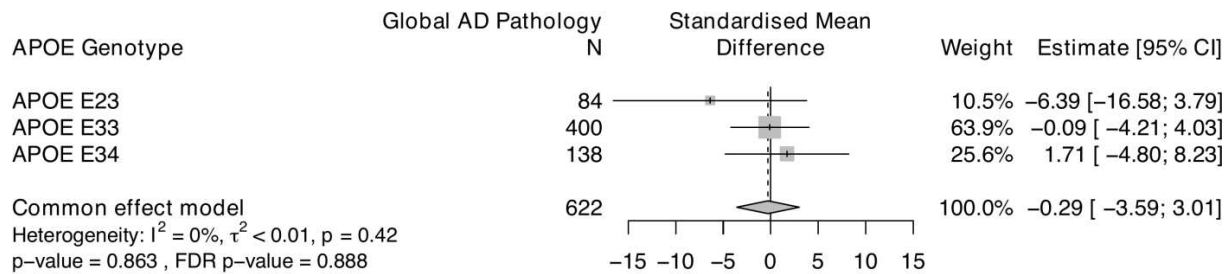
The Relationship between HDL–C and Neuropathology

APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	82		10.7%	−5.32 [−13.88; 3.23]
APOE E33	387		59.3%	−3.73 [−7.36; −0.09]
APOE E34	129		30.0%	−5.30 [−10.41; −0.20]
Common effect model	598		100.0%	−4.37 [−7.17; −1.57]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.86
p–value = 0.002 , FDR p–value = 0.027

Supplementary Figure 11

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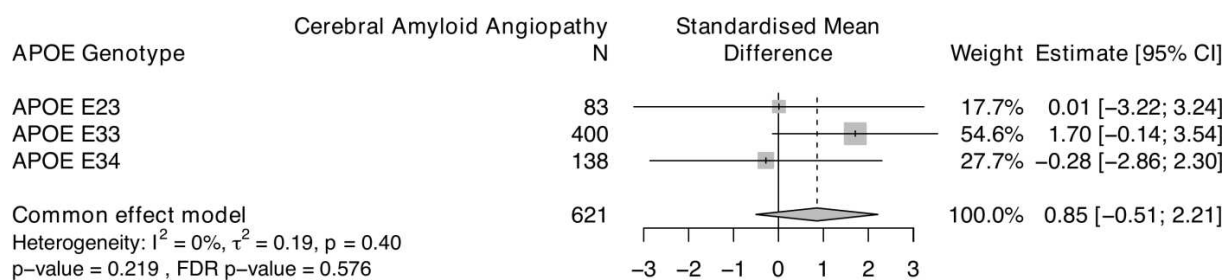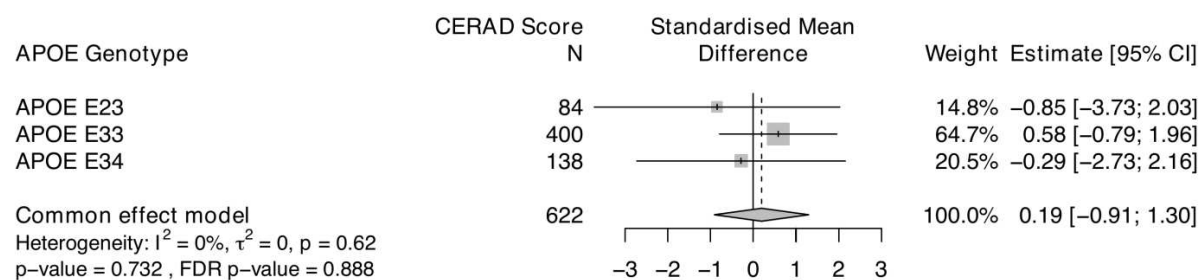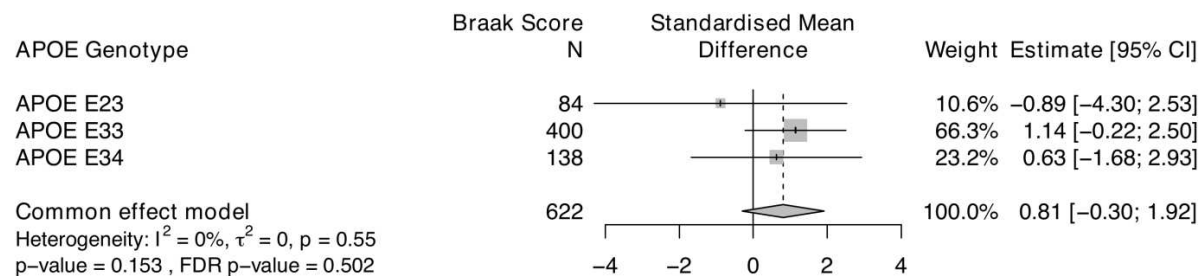
J Neurol Neurosurg Psychiatry

Supplementary Figure 12. Results for non-significant association testing between longitudinally measured HDL-C and neuropathologies in all individuals with antemortem blood lipids and neuropathology data without censoring of lipid values based on diagnosis. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis and is shown in by forest plot following the same layout as described in Supplementary Figure 1.

Supplementary Figure 12 – part 1 of 4

The Relationship between HDL–C and Neuropathology

APOE Genotype	Braak Score N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	84		10.6%	−0.89 [−4.30; 2.53]
APOE E33	400		66.3%	1.14 [−0.22; 2.50]
APOE E34	138		23.2%	0.63 [−1.68; 2.93]
Common effect model	622		100.0%	0.81 [−0.30; 1.92]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.55
p–value = 0.153 , FDR p–value = 0.502

APOE Genotype	CERAD Score N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	84		14.8%	−0.85 [−3.73; 2.03]
APOE E33	400		64.7%	0.58 [−0.79; 1.96]
APOE E34	138		20.5%	−0.29 [−2.73; 2.16]
Common effect model	622		100.0%	0.19 [−0.91; 1.30]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.62
p–value = 0.732 , FDR p–value = 0.888

APOE Genotype	Cerebral Amyloid Angiopathy N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	83		17.7%	0.01 [−3.22; 3.24]
APOE E33	400		54.6%	1.70 [−0.14; 3.54]
APOE E34	138		27.7%	−0.28 [−2.86; 2.30]
Common effect model	621		100.0%	0.85 [−0.51; 2.21]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.19$, p = 0.40
p–value = 0.219 , FDR p–value = 0.576

Supplementary Figure 12 – part 2 of 4

The Relationship between HDL–C and Neuropathology

APOE Genotype	Cerebral Atherosclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	84		13.2%	0.49 [−3.42; 4.40]
APOE E33	400		54.5%	−0.09 [−2.01; 1.83]
APOE E34	138		32.3%	1.56 [−0.94; 4.05]
Common effect model	622		100.0%	0.52 [−0.90; 1.94]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.59
p–value = 0.475 , FDR p–value = 0.815

APOE Genotype	Gross Cerebral Infarctions N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	84		13.7%	−0.76 [−7.30; 5.78]
APOE E33	400		59.0%	−1.09 [−4.23; 2.06]
APOE E34	138		27.3%	−2.76 [−7.39; 1.86]
Common effect model	622		100.0%	−1.50 [−3.92; 0.92]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.82
p–value = 0.224 , FDR p–value = 0.576

APOE Genotype	Hippocampal Sclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	84		13.8%	6.99 [−4.11; 18.10]
APOE E33	400		40.1%	7.23 [0.70; 13.76]
APOE E34	138		46.1%	−5.44 [−11.53; 0.65]
Common effect model	622		100.0%	1.36 [−2.77; 5.49]

Heterogeneity: $I^2 = 77\%$, $\tau^2 = 43.67$, p = 0.01
p–value = 0.519 , FDR p–value = 0.815

Supplementary Figure 12 – part 3 of 4

The Relationship between HDL–C and Neuropathology

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	84		15.2%	−3.01 [−9.25; 3.22]
APOE E33	400		58.4%	−0.60 [−3.78; 2.58]
APOE E34	138		26.4%	2.40 [−2.33; 7.12]
Common effect model	622		100.0%	−0.17 [−2.60; 2.25]

Heterogeneity: $I^2 = 0\%$, $\tau^2 < 0.01$, $p = 0.37$
p–value = 0.888 , FDR p–value = 0.888

APOE Genotype	TDP–43 N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	83		11.2%	0.30 [−3.10; 3.70]
APOE E33	397		58.7%	0.15 [−1.33; 1.64]
APOE E34	136		30.1%	1.74 [−0.33; 3.81]
Common effect model	616		100.0%	0.65 [−0.49; 1.79]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.04$, $p = 0.46$
p–value = 0.263 , FDR p–value = 0.613

Supplementary Figure 12 – part 4 of 4

Supplementary Figure 13. Results for significant association testing between longitudinally measured TG and neuropathologies in all individuals with antemortem blood lipids and neuropathology data without censoring of lipid values based on diagnosis. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis and is shown in by forest plot following the same layout as described in Supplementary Figure 1.
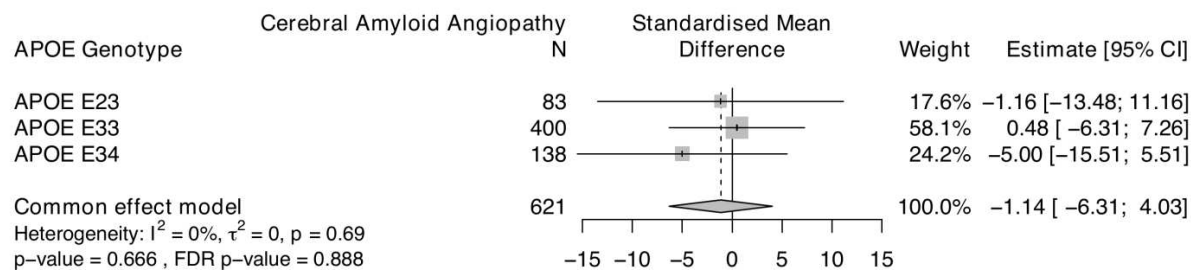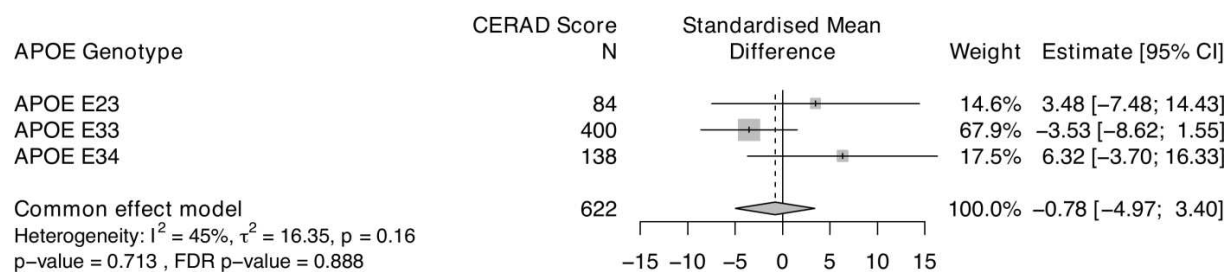
The Relationship between TG and Neuropathology

APOE Genotype	Cerebral Atherosclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	84		14.4%	14.84 [0.57; 29.10]
APOE E33	400		57.2%	6.02 [−1.15; 13.19]
APOE E34	138		28.4%	6.05 [−4.13; 16.23]
Common effect model	622		100.0%	7.30 [1.88; 12.72]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.53
p−value = 0.008 , FDR p−value = 0.043

Axis: −20 −10 0 10 20
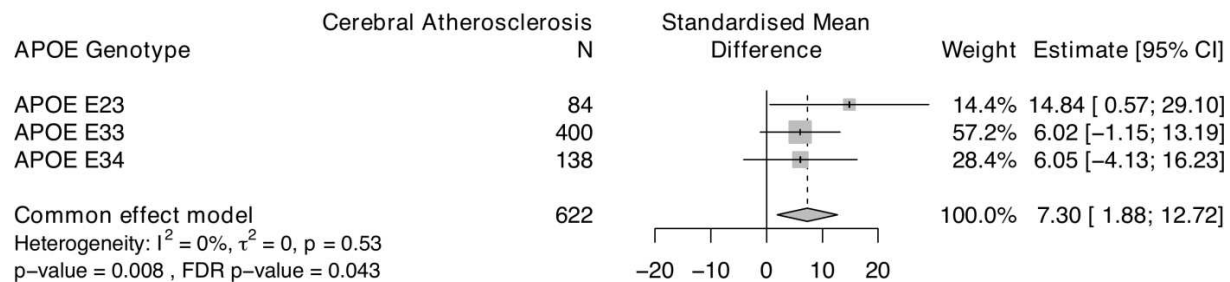
Supplementary Figure 13

Supplemental material

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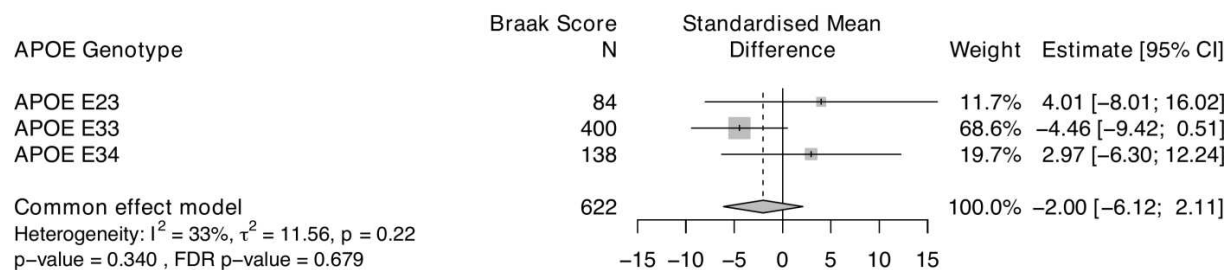*J Neurol Neurosurg Psychiatry*

Supplementary Figure 14. Results for non-significant association testing between longitudinally measured TG and neuropathologies in all individuals with antemortem blood lipids and neuropathology data without censoring of lipid values based on diagnosis. Each neuropathology was considered in a separate linear mixed model stratified by *APOE* genotype and adjusted for relevant covariates. Final significance was determined by meta-analysis and is shown in by forest plot following the same layout as described in Supplementary Figure 1.
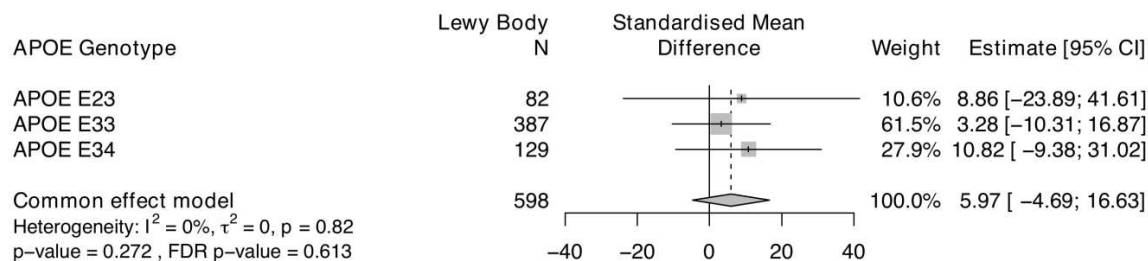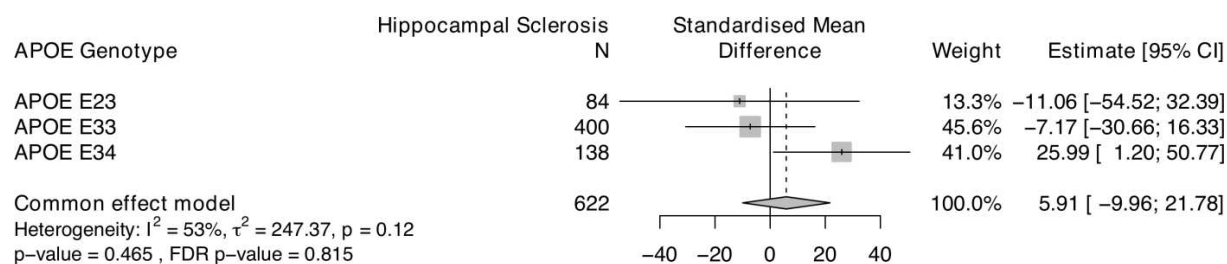

The Relationship between TG and Neuropathology

Supplementary Figure 14 – part 1 of 4

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The Relationship between TG and Neuropathology

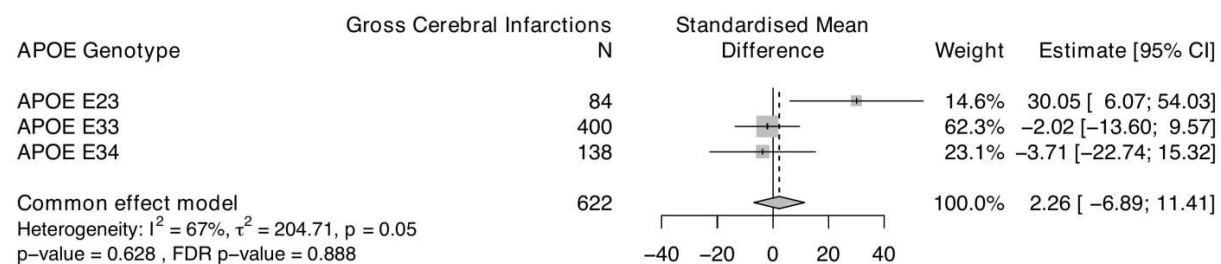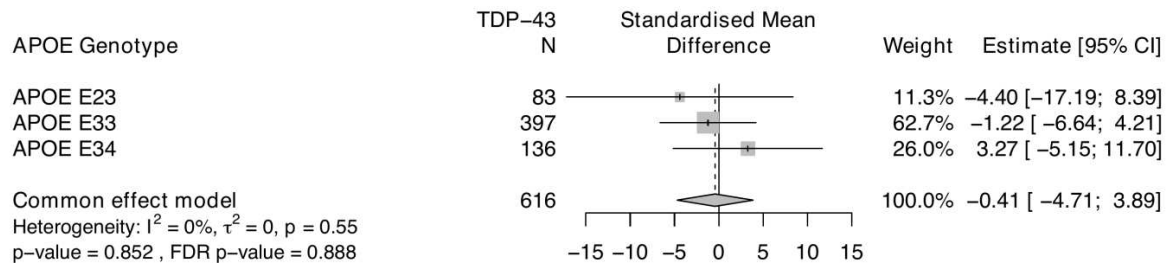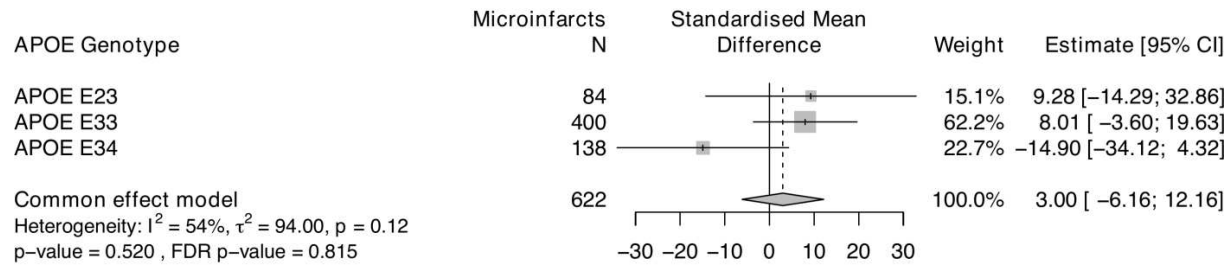*Supplementary Figure 14 – part 2 of 4*

The Relationship between TG and Neuropathology

Supplementary Figure 14 – part 3 of 4

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The Relationship between TG and Neuropathology

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	84		15.1%	9.28 [−14.29; 32.86]
APOE E33	400		62.2%	8.01 [−3.60; 19.63]
APOE E34	138		22.7%	−14.90 [−34.12; 4.32]
Common effect model	622		100.0%	3.00 [−6.16; 12.16]

Heterogeneity: $I^2 = 54\%$, $\tau^2 = 94.00$, p = 0.12
p−value = 0.520 , FDR p−value = 0.815

APOE Genotype	TDP−43 N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23	83		11.3%	−4.40 [−17.19; 8.39]
APOE E33	397		62.7%	−1.22 [−6.64; 4.21]
APOE E34	136		26.0%	3.27 [−5.15; 11.70]
Common effect model	616		100.0%	−0.41 [−4.71; 3.89]

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.55
p−value = 0.852 , FDR p−value = 0.888

Supplementary Figure 14 – part 4 of 4