Supplementary Figures

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

Authors

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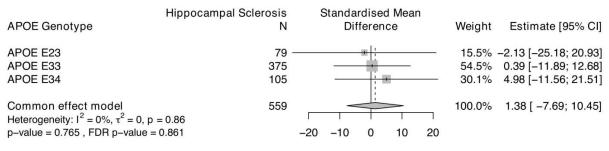
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Supplementary Figure 1. Results for non-significant association testing between longitudinally measured LDL-C and neuropathologies in individuals with NCI or MCI at baseline with censoring of LDL-C for a diagnosis of either dementia. Each neuropathology 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, I², and the residual heterogenity, tau², 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

Cereb	ral Atherosclerosis	Standardised Mean	Weight Estimate [95% CI]
APOE Genotype	N	Difference	
APOE E23	79		- 13.5% 7.70 [0.34; 15.07]
APOE E33	375		65.1% 3.03 [-0.32; 6.38]
APOE E34	105		21.4% -0.37 [-6.21; 5.46]
Common effect model Heterogeneity: $I^2 = 30\%$, $\tau^2 < 0.01$, p = 0.24 p-value = 0.034 , FDR p-value = 0.121	559 -15 -	-10 -5 0 5 10	100.0% 2.93 [0.23; 5.63] 15

Gro APOE Genotype	oss Cerebral Infarctions N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 375 105		- 12.8% 69.3% 17.9%	5.24 [-7.46; 17.93] 2.57 [-2.89; 8.04] -2.62 [-13.38; 8.14]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = p-value = 0.392 , FDR p-value = 0		-15 -10 -5 0 5 10 15	100.0%	1.99 [–2.56; 6.54]



Supplementary Figure 1 – part 1 of 2

APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	77 362 101		- 10.6% 3.98 [-12.86; 20.83] 70.9% 2.47 [-4.04; 8.97] - 18.6% 8.21 [-4.49; 20.92]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.73 p–value = 0.186 , FDR p–value = 0.446	540 -20	-10 0 10 2	100.0% 3.69 [–1.78; 9.17] 0

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 375 105		- 13.9% 5.20 [-7.06; 17.45] 68.6% 2.15 [-3.37; 7.67] - 17.5% 7.18 [-3.75; 18.10]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.69 p-value = 0.139 , FDR p-value = 0.384	559 -	15 -10 -5 0 5 10 15	100.0% 3.45 [-1.12; 8.02]

APOE Genotype	TDP–43 N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	78 372 103		- 10.2% 5.64 [-1.19; 12.47] 69.2% -0.73 [-3.34; 1.89] 20.7% 2.40 [-2.39; 7.19]
Common effect model Heterogeneity: $I^2 = 45\%$, $\tau^2 = 4.35$, p = 0.16 p-value = 0.611 , FDR p-value = 0.746	553 		100.0% 0.57 [-1.61; 2.74]

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

Hipp APOE Genotype	ocampal Sclerosis N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 375 105		 18.2% 7.68 [-3.87; 19.23] 44.8% 10.54 [3.18; 17.89] 37.0% 1.40 [-6.69; 9.49]
Common effect model Heterogeneity: $I^2 = 27\%$, $\tau^2 = 9.68$, p = 0.26 p-value = 0.008, FDR p-value = 0.043	559	-15-10-5 0 5 10 15	100.0% 6.63 [1.71; 11.55]
APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	77 — 362 101		12.5% –7.23 [–15.71; 1.25] 63.2% –3.97 [–7.74; –0.20] 24.3% –6.40 [–12.48; –0.32]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.69 p-value = 0.001 , FDR p-value = 0.020	540 -15	-10 -5 0 5 10 15	100.0% –4.97 [–7.96; –1.97]

Supplementary Figure 2

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

Glo APOE Genotype	bal AD Pathology N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 375 105		11.0% -7.20 [-17.78; 3.38] 65.6% -0.38 [-4.71; 3.95] 23.5% 0.67 [-6.56; 7.91]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 < 0.01$, p = 0.45 p-value = 0.622 , FDR p-value = 0.746	559	-15 -10 -5 0 5 10 15	100.0% –0.88 [–4.39; 2.62]
	Beta–Amyloid	Standardised Mean	
APOE Genotype	N	Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34 Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.62 p-value = 0.903, FDR p-value = 0.903	78 - 374 105 557		14.0% -1.36 [-4.30; 1.57] 66.8% 0.23 [-1.11; 1.57] 19.3% -0.16 [-2.66; 2.34] 100.0% -0.07 [-1.16; 1.03]

APOE Genotype	ofibrillary Tangles N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	78 — 373 105		7.7%-0.91[-4.96; 3.13]59.5%0.80[-0.65; 2.25]32.8%0.39[-1.57; 2.34]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.73 p–value = 0.352 , FDR p–value = 0.620	556	-4 -2 0 2 4	100.0% 0.53 [-0.59; 1.65]

Supplementary Figure 3 – part 1 of 4

APOE Genotype	Braak Score N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 375 105	-	11.4% -1.05 [-4.50; 2.40] 66.3% 1.22 [-0.21; 2.65] 22.3% 0.70 [-1.77; 3.17]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.49$ p-value = 0.156 , FDR p-value = 0.400	559 -4	-2 0 2 4	100.0% 0.84 [-0.32; 2.01] 4
APOE Genotype	CERAD Score N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33	79 — 375		15.7% –1.14 [–4.06; 1.78] 65.5% 0.61 [–0.82; 2.04]

105

559

Common effect model Heterogeneity: $1^2 = 0\%$, $\tau^2 = 0$, p = 0.47p-value = 0.877, FDR p-value = 0.902

APOE E34

		ardised fferenc			Weight	Estimate [95% CI]
	*				65.5%	-1.14 [-4.06; 1.78] 0.61 [-0.82; 2.04] -0.69 [-3.35; 1.98]
r	-	\Rightarrow	-		100.0%	0.09 [–1.06; 1.25]
-4	-2	0	2	4		

Cerebral Amylo APOE Genotype	oid Angiopathy N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	78 375 105	* *	19.3% -0.44 [-3.71; 2.82] - 56.1% 1.60 [-0.31; 3.52] 24.6% -0.02 [-2.91; 2.88]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.46 p-value = 0.267 , FDR p-value = 0.582	558 _3	-2 -1 0 1 2 3	100.0% 0.81 [-0.62; 2.24]

Supplementary Figure 3 – part 2 of 4

APOE Genotype	Cerebral Atherosclerosis N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 375 105		14.9% 1.00 [-2.88; 4.88] 56.2% 0.07 [-1.93; 2.07] 28.9% 2.23 [-0.56; 5.02]
Common effect model Heterogeneity: $1^2 = 0\%$, $\tau^2 = 0.03$, p p–value = 0.275 , FDR p–value = 0.		-4 -2 0 2	100.0% 0.84 [-0.66; 2.33] 4

APOE Genotype	Gross Cerebral Infarctions N		ised Mean rence	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 375 105 —		<u> </u>	60.9%	-0.43 [-6.99; 6.13] -0.69 [-3.97; 2.59] -2.70 [-7.94; 2.54]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p p-value = 0.386 , FDR p-value		-5	0 5	100.0%	–1.13 [–3.69; 1.43]

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 — 375 105	*	16.9% -3.06 [-9.33; 3.21] 60.2% -0.74 [-4.07; 2.58] 22.9% 3.22 [-2.16; 8.61]
Common effect model Heterogeneity: $I^2 = 18\%$, $\tau^2 < 0.01$, p = 0.29 p–value = 0.864 , FDR p–value = 0.902	559	-5 0 5	100.0% -0.23 [-2.80; 2.35]

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 APOE E33 APOE E34	78 372 103		11.8% -0.17 [-3.72; 3.39] 59.9% 0.30 [-1.27; 1.88] - 28.4% 2.87 [0.58; 5.16]
Common effect model Heterogeneity: $I^2 = 46\%$, $\tau^2 = 1.25$, p = 0.16 p-value = 0.117, FDR p-value = 0.352	553	-4 -2 0 2 4	100.0% 0.97 [-0.24; 2.19]

Supplementary Figure 3 - part 4 of 4

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.

The Relationship between TG and Neuropathology

APOE Genotype	Global AD Pathology N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 375 105		 10.5% 13.27 [-27.12; 53.67] 69.0% -11.90 [-27.66; 3.86] 20.5% 2.89 [-26.01; 31.80]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 12.15$, p = 0 p-value = 0.351 , FDR p-value = 0.620	.41	-40 -20 0 20 40	100.0% –6.22 [–19.31; 6.86]
APOE Genotype	Beta–Amyloid N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	78 374 105		- 13.1% 3.35 [-7.98; 14.68] 70.4% -2.95 [-7.83; 1.93] 16.5% -0.14 [-10.22; 9.93]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.5 p-value = 0.426 , FDR p-value = 0.64		-10 -5 0 5 10	100.0% –1.66 [–5.76; 2.43]
N	eurofibrillary Tangles	Standardised Mean	
APOE Genotype	N	Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	78 373 105		- 7.9% 2.84 [-12.17; 17.85] 63.6% -3.10 [-8.38; 2.17] 28.5% -0.24 [-8.12; 7.64]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.6 p-value = 0.396 , FDR p-value = 0.62		-15 -10 -5 0 5 10 15	100.0% -1.82 [-6.03; 2.39]

Supplementary Figure 4 – part 1 of 4

APOE Genotype	Braak Score N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 375 105			3.21 [-8.97; 15.39] -6.23 [-11.35; -1.11] -0.17 [-10.06; 9.72]
Common effect model Heterogeneity: $I^2 = 24\%$, $\tau^2 = 8.97$, p = 0.27 p-value = 0.069 , FDR p-value = 0.227	559	-10 -5 0 5 10	100.0% 15	–3.95 [–8.21; 0.31]

APOE Genotype	CERAD Score N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 375 105		- 14.9% 4.45 [-6.69; 15.59] 68.7% -3.94 [-9.13; 1.26] 16.3% 3.97 [-6.68; 14.63]
Common effect model Heterogeneity: I^2 = 32%, τ^2 = 12.14, p = 0.23 p–value = 0.527 , FDR p–value = 0.735	559	-10 -5 0 5 10 1	100.0% –1.39 [–5.70; 2.92] 5

Cerebral Amy APOE Genotype	vloid Angiopathy N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	78 — 375 105 —			-0.80 [-13.21; 11.62] -0.78 [-7.73; 6.16] 0.46 [-11.00; 11.93]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.98 p-value = 0.851 , FDR p-value = 0.902	558	10 -5 0 5 10	100.0%	-0.51 [-5.87; 4.85]

Supplementary Figure 4 – part 2 of 4

Cerebral APOE Genotype	Atherosclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 375 105		59.3%	12.86 [–1.48; 27.20] 4.25 [–3.12; 11.61] 7.17 [–4.15; 18.50]
Common effect model Heterogeneity: $1^2 = 0\%$, $\tau^2 = 0$, p = 0.57 p-value = 0.029 , FDR p-value = 0.115	559 -	-20 -10 0 10 20	100.0%	6.33 [0.66; 12.00]

APOE Genotype	Gross Cerebral Infarctions N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 375 105		 15.6% 28.35 [4.18; 52.52] 63.9% -3.91 [-15.87; 8.04] 20.5% -1.20 [-22.31; 19.91]
Common effect model Heterogeneity: $I^2 = 64\%$, $\tau^2 = 178.23$, p-value = 0.730 , FDR p-value = 0.84		-40 -20 0 20 40	100.0% 1.69 [-7.87; 11.24]

Hippocampa APOE Genotype	al Sclerosis N		rdised Mear ference	n Weigł	nt Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 — 375 - 105				% –14.20 [–40.86; 12.47]
Common effect model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, p = 0.61 p-value = 0.617 , FDR p-value = 0.746	559 「 —4	-20	0 20	100.04 40	% -4.82 [-23.67; 14.04]

Supplementary Figure 4 – part 3 of 4

APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	77 362 101		- 12.0% 66.1% 21.8%	
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.90 p-value = 0.385 , FDR p-value = 0.620	540 ⊤ –40	0 -20 0 20 4	100.0% 0	5.04 [-6.33; 16.42]

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	79 375 105 -		16.3% 63.5% 20.2%	8.45 [–15.26; 32.15] 7.15 [–4.87; 19.16] –14.15 [–35.47; 7.16]
Common effect model Heterogeneity: $I^2 = 36\%$, $\tau^2 = 49.30$, p = 0.21 p–value = 0.531 , FDR p–value = 0.735	559	-30 -20 -10 0 10 20 30	100.0%	3.06 [-6.52; 12.64]

APOE Genotype	TDP-43 N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	78 - 372 103		11.6% -0.40 [-13.91; 13.11] 63.9% -1.72 [-7.46; 4.03] 24.5% -0.70 [-9.98; 8.58]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.97 p-value = 0.575, FDR p-value = 0.746	553	-10 -5 0 5 10	100.0% –1.31 [–5.91; 3.28]

Supplementary Figure 4 – part 4 of 4

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

APOE Genotype	Beta–Amyloid N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	58 259 60		11.3% 4.15 [-2.87; 11.17] 76.5% 1.82 [-0.88; 4.52] 12.2% 9.71 [2.95; 16.46]
Common effect model Heterogeneity: $l^2 = 57\%$, $\tau^2 = 9.65$, p = 0.10 p-value = 0.011 , FDR p-value = 0.071	377 –	15 -10 -5 0 5 10 15	100.0% 3.05 [0.69; 5.41]
APOE Genotype	Braak Score N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60		- 11.7% 7.58 [0.24; 14.93] 72.3% 1.60 [-1.36; 4.56] 15.9% 7.41 [1.11; 13.71]
Common effect model Heterogeneity: $I^2 = 52\%$, $\tau^2 = 8.28$, p = 0.12 p-value = 0.012 , FDR p-value = 0.071	379	-10 -5 0 5 10	100.0% 3.23 [0.71; 5.75]
	CERAD Score	Standardised Mean	
APOE Genotype	N	Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60	*	13.5% 4.67 [-2.15; 11.50] 74.3% 0.81 [-2.10; 3.73] - 12.2% 9.50 [2.32; 16.69]
Common effect model Heterogeneity: $I^2 = 62\%$, $\tau^2 = 12.52$, p = 0.07 p-value = 0.061 , FDR p-value = 0.221	379	-15 -10 -5 0 5 10 15	100.0% 2.39 [-0.11; 4.90]

Supplementary Figure 5 – part 1 of 3

APOE Genotype	Cerebral Amyloid Angiopathy N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	58 260 60		67.6%	-1.97 [-9.97; 6.04] 4.30 [0.40; 8.20] 7.86 [-0.08; 15.80]
Common effect model Heterogeneity: $1^2 = 35\%$, $\tau^2 = 1.7$ p–value = 0.018 , FDR p–value =		-10 -5 0 5 10	100.0% 15	3.87 [0.67; 7.08]

APOE Genotype	Gross Cerebral Infarctions N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60		 14.3% 12.66 [-2.55; 27.87] 71.7% 1.37 [-5.41; 8.15] 14.0% -4.40 [-19.72; 10.93]
Common effect model Heterogeneity: $I^2 = 23\%$, $\tau^2 < 0.01$, p p-value = 0.459 , FDR p-value = 0.7		-20 -10 0 10 20	100.0% 2.17 [-3.57; 7.91]

Hippocampa APOE Genotype	l Sclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 - 260 60 —		46.4%	-2.03 [-29.64; 25.59] 0.68 [-20.51; 21.86] -6.31 [-34.46; 21.85]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.93 p-value = 0.797 , FDR p-value = 0.925	379 「 —3	0 -20 -10 0 10 20 3	100.0% 1 30	–1.90 [–16.33; 12.54]

Supplementary Figure 5 – part 2 of 3

APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	57 251 58		10.3% 0.13 [-21.30; 21.56] 75.8% 1.18 [-6.74; 9.10] - 13.9% 10.85 [-7.65; 29.34]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.63 p-value = 0.493 , FDR p-value = 0.805	366	-20 -10 0 10 20	100.0% 2.41 [-4.48; 9.30]

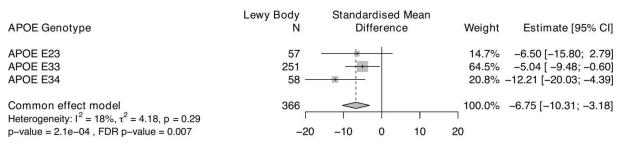
APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60		15.2% 8.70 [-5.91; 23.31] 70.9% 0.19 [-6.57; 6.95] - 13.9% 11.63 [-3.61; 26.87]
Common effect model Heterogeneity: $I^2 = 19\%$, $\tau^2 = 15.05$, p = 0.29 p-value = 0.289 , FDR p-value = 0.612	379	-20 -10 0 10 20	100.0% 3.08 [-2.61; 8.77]

APOE Genotype	TDP–43 N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	58 257 59		71.7% -	8.06 [–0.40; 16.51] -2.42 [–5.94; 1.09] 2.60 [–10.07; 4.86]
Common effect model Heterogeneity: $I^2 = 62\%$, $\tau^2 = 18.56$, p = 0.07 p-value = 0.448 , FDR p-value = 0.787	374 15	5 -10 -5 0 5 10	100.0% - 1 15	-1.15 [–4.13; 1.82]

Supplementary Figure 5 – part 3 of 3

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



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

Globa	al AD Pathology	Standardised Mean	
APOE Genotype	N	Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 — 260 60 -		13.6% –3.45 [–14.88; 7.99] 65.8% –3.46 [–8.65; 1.74] 20.6% –4.42 [–13.70; 4.86]
Common effect model	379		100.0% -3.65 [-7.87; 0.56]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.98 p-value = 0.089 , FDR p-value = 0.268		-10 -5 0 5 10	
APOE Genotype	Beta–Amyloid N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	58 259 60		16.9% –1.39 [–4.52; 1.73] 67.8% –0.27 [–1.83; 1.28] 15.3% –1.22 [–4.50; 2.06]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.76 p-value = 0.353 , FDR p-value = 0.706	377	-4 -2 0 2 4	100.0% -0.61 [-1.89; 0.68]

Neurofibril APOE Genotype	lary Tangles N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	58 — 259 60		10.2%-1.00 [-5.59; 3.59]62.8%-0.29 [-2.14; 1.56]26.9%0.33 [-2.50; 3.16]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.88 p–value = 0.791 , FDR p–value = 0.925	377	-4 -2 0 2 4	100.0% –0.20 [–1.67; 1.27]

Supplementary Figure 7 – part 1 of 4

APOE Genotype	Braak Score N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 — 260 60		15.7% -0.35 [-3.83; 3.14] 63.8% 0.58 [-1.15; 2.31] 20.5% -0.06 [-3.10; 2.99]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.87 p-value = 0.666 , FDR p-value = 0.921	379	-3 -2 -1 0 1 2 3	100.0% 0.30 [-1.08; 1.69]

APOE Genotype	CERAD Score N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60 —		18.9% -0.61 [-3.72; 2.49] 64.3% -0.40 [-2.08; 1.28] 16.8% -3.13 [-6.42; 0.17]
Common effect model Heterogeneity: $I^2 = 6\%$, $\tau^2 < 0.01$, p = 0.35 p-value = 0.193 , FDR p-value = 0.433	379 -6		100.0% -0.90 [-2.25; 0.45]

APOE Genotype	Cerebral Amyloid Angiopathy N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	58 260 60		22.6% 0.36 [-3.22; 3.94] 56.1% 1.29 [-0.98; 3.56] 21.3% -2.29 [-5.97; 1.39]
Common effect model Heterogeneity: $I^2 = 24\%$, $\tau^2 = 0$ p-value = 0.716 , FDR p-value		-4 -2 0 2 4	100.0% 0.32 [-1.39; 2.02]

Supplementary Figure 7 – part 2 of 4

Ce APOE Genotype	erebral Atherosclerosis N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60		 22.2% 1.90 [-1.99; 5.78] 60.3% -0.44 [-2.79; 1.92] 17.5% 1.53 [-2.84; 5.90]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0$ p-value = 0.648 , FDR p-value = 0.		-4 -2 0 2 4	100.0% 0.43 [-1.40; 2.25]

APOE Genotype	Gross Cerebral Infarctions N		ardised N ifference		Weight	Estimate [95% CI]
APOE E23 APOE E33	59 — 260					-4.64 [-11.47; 2.19] -0.95 [-4.86; 2.96]
APOE E34	60 —		<u> </u>			-4.56 [-11.55; 2.43]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.52		'≯	1	100.0%	-2.37 [-5.43; 0.68]
p-value = 0.127 , FDR p-valu		-10 –5	0	5 1	0	

APOE Genotype	lippocampal Sclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60	-	- 33.9%	-0.08 [-12.00; 11.83] 16.86 [4.69; 29.02] 2.46 [-10.34; 15.25]
Common effect model Heterogeneity: $I^2 = 54\%$, $\tau^2 = 45.84$, p = 0 p-value = 0.075 , FDR p-value = 0.244	.11	-20 -10 0 10 20	100.0%	6.45 [–0.64; 13.53]

Supplementary Figure 7 – part 3 of 4

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60		20.8% 0.66 [-5.98; 7.30] 60.4% -1.14 [-5.03; 2.76]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.57 p-value = 0.982 , FDR p-value = 0.982	379 	-5 0 5	100.0% 0.04 [-2.99; 3.06] 10

APOE Genotype	TDP–43 N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	58 257 59		16.8% -1.44 [-5.34; 2.46] 60.5% -1.05 [-3.11; 1.00] - 22.7% 2.90 [-0.45; 6.26]
Common effect model Heterogeneity: $I^2 = 54\%$, $\tau^2 = 2.81$, p = 0.11 p–value = 0.788 , FDR p–value = 0.925	374 -6	-4 -2 0 2 4	100.0% -0.22 [-1.82; 1.38] 6

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 APOE E33 APOE E34	59 260 60	*	 12.3% 20.38 [-27.89; 68.65] 70.4% -7.07 [-27.22; 13.08] 17.3% 12.89 [-27.81; 53.58]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 2.82$, p = 0 p–value = 0.977 , FDR p–value = 0.982		60 -40 -20 0 20 40 6	100.0% –0.25 [–17.17; 16.66] 0
	Beta-Amyloid	Standardised Mean	
APOE Genotype	N		Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	58 259 60		- 14.1% 5.19 [-8.51; 18.90] 72.6% -2.08 [-8.13; 3.97] 13.3% 9.06 [-5.07; 23.20]
Common effect model Heterogeneity: $I^2 = 22\%$, $\tau^2 = 13.74$, p p-value = 0.870 , FDR p-value = 0.950		-20 -10 0 10	100.0% 0.43 [-4.72; 5.58] 20
		Oten developed Macon	
APOE Genotype	Neurofibrillary Tangles N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	58 259 60		 10.4% 10.53 [-7.75; 28.82] 67.9% -3.18 [-10.34; 3.99] 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

1 -20 -10 0 10 20

Supplementary Figure 8 – part 1 of 4

APOE Genotype	Braak Score N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60		- 15.5% 5.77 [-7.96; 19.50] 68.1% -6.92 [-13.48; -0.37] 16.4% 0.52 [-12.84; 13.87]
Common effect model Heterogeneity: $I^2 = 36\%$, $\tau^2 = 20.55$, p = 0.21 p-value = 0.176 , FDR p-value = 0.433	379	-10 0 10	100.0% –3.73 [–9.14; 1.67]

APOE Genotype	CERAD Score N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60		16.5% 6.80 [-6.49; 20.09] 69.5% -3.84 [-10.32; 2.64] - 14.1% 13.06 [-1.33; 27.46]
Common effect model Heterogeneity: $I^2 = 64\%$, $\tau^2 = 52.58$, p = 0.06 p-value = 0.916 , FDR p-value = 0.970	379	-20 -10 0 10 20	100.0% 0.29 [-5.11; 5.69]

Ce APOE Genotype	erebral Amyloid Angiopathy N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	58 260 60		20.2% 61.1% — 18.7%	-0.27 [-15.41; 14.88] 2.70 [-6.01; 11.40] 16.15 [0.43; 31.88]
Common effect model Heterogeneity: $I^2 = 25\%$, $\tau^2 = 3.97$ p-value = 0.184 , FDR p-value = 0	•	0 -20 -10 0 10 20	100.0% 	4.62 [–2.19; 11.42]

Supplementary Figure 8 - part 2 of 4

Cerebral Ath APOE Genotype	erosclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60		63.8%	10.40 [–5.96; 26.76] 5.49 [–3.77; 14.75] 19.20 [0.56; 37.85]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.42 p-value = 0.022 , FDR p-value = 0.099	379 _30	-20-10 0 10 20 30	100.0%	8.65 [1.25; 16.05]

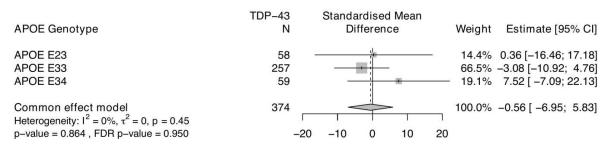
Gross Cerebral APOE Genotype	Infarctions N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60			30.94 [1.63; 60.25] -4.32 [-19.49; 10.84] 6.88 [-23.64; 37.40]
Common effect model Heterogeneity: $1^2 = 55\%$, $\tau^2 = 187.71$, p = 0.11 p-value = 0.553 , FDR p-value = 0.829	379 -60 -4	0 -20 0 20 40	100.0% 	3.73 [–8.59; 16.06]

Hi APOE Genotype	ppocampal Sclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60			12.07 [-44.77; 68.92] -14.90 [-62.25; 32.46] 47.57 [-7.28; 102.43]
Common effect model Heterogeneity: $I^2 = 30\%$, $\tau^2 = 335.13$, p = 0.2 p-value = 0.443 , FDR p-value = 0.787	24 379	-50 0 50	100.0% 100	11.86 [–18.46; 42.18]

Supplementary Figure 8 - part 3 of 4

APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	57 251 58		13.2% 70.0% - 16.7%	
Common effect model Heterogeneity: $I^2 = 7\%$, $\tau^2 = 50.83$, p = 0.34 p-value = 0.041 , FDR p-value = 0.164	366	-60 -40 -20 0 20 40 60	100.0%	15.29 [0.63; 29.95]

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	59 260 60 —		18.6% 0.16 [-27.98; 28.29] 65.2% -0.67 [-15.68; 14.34] 16.2% -22.30 [-52.37; 7.77]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.43 p-value = 0.514 , FDR p-value = 0.805	379	-40 -20 0 20 40	100.0% -4.03 [-16.15; 8.09]



Supplementary Figure 8 – part 4 of 4

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

APOE Genotype	Global AD Pathology N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 400 138		9.9% 10.41 [-8.23; 29.06] 70.1% 6.74 [-0.25; 13.74] 20.0% 18.54 [5.46; 31.62]
Common effect model Heterogeneity: $I^2 = 18\%$, $\tau^2 = 16.00$, p = 0. p-value = 0.002 , FDR p-value = 0.027		-20 -10 0 10 20	100.0% 9.47 [3.61; 15.33] 30
APOE Genotype	Beta–Amyloid N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34 Common effect model	83 399 138 620		12.2% 1.74 [-3.57; 7.06] 73.0% 2.91 [0.74; 5.08] — 14.8% 5.19 [0.37; 10.02] 100.0% 3.11 [1.25; 4.96]
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.61 p-value = 0.001 , FDR p-value = 0.027		-5 0 5	10
APOE Genotype	eurofibrillary Tangles N	Standardised Mean Difference	Weight Estimate [95% CI]

APOE E33 398 €2.99 APOE E34 138 €2.99 Common effect model 619 €0.09	APOE Genotype N	Difference	Weight Estimate [95% CI]
Common effect model 619 100.09	APOE E33 398		 6.9% 8.84 [1.84; 15.83] 62.9% 2.18 [-0.14; 4.49] 30.2% 1.72 [-1.63; 5.06]
Heterogeneity: $T = 42\%$, $T < 0.01$, $p = 0.18$ p-value = 0.008, FDR p-value = 0.043 -15 -10 -5 0 5 10 15	Common effect model 619 Heterogeneity: $I^2 = 42\%$, $\tau^2 < 0.01$, p = 0.18		100.0% 2.50 [0.66; 4.33]

Supplementary Figure 9 – part 1 of 2

APOE Genotype	CERAD Score N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 400 138		13.8%1.85 [-3.45; 7.15]70.5%2.01 [-0.33; 4.35]-15.7%6.30 [1.34; 11.27]
Common effect model Heterogeneity: $I^2 = 19\%$, $\tau^2 = 0.81$, p = 0.29 p-value = 0.008 , FDR p-value = 0.043	622 -10		100.0% 2.66 [0.69; 4.63]

Cerebra Cerebra	al Atherosclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 400 138		- 13.6% 61.7% 24.7%	8.21 [1.23; 15.19] 4.33 [1.05; 7.60] -0.07 [-5.24; 5.10]
Common effect model Heterogeneity: $I^2 = 47\%$, $\tau^2 = 5.20$, p = 0.15 p-value = 0.004 , FDR p-value = 0.037	622		100.0% 1 15	3.77 [1.20; 6.34]

Supplementary Figure 9 – part 2 of 2

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

APOE Genotype	Braak Score N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 400 138		10.4% 4.92 [-1.15; 10.99] 72.1% 1.83 [-0.47; 4.13] 17.5% 3.44 [-1.24; 8.11]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.58 p-value = 0.015 , FDR p-value = 0.067	622 -10	-5 0 5 10	100.0% 2.43 [0.48; 4.39]
Cerebral / APOE Genotype	Amyloid Angiopathy N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	83 — 400 138		16.7% –2.09 [–8.09; 3.91] 61.5% 3.35 [0.23; 6.47] – 21.8% 2.38 [–2.87; 7.63]
Common effect model Heterogeneity: $I^2 = 20\%$, $\tau^2 = 1.01$, p = 0.29 p-value = 0.074 , FDR p-value = 0.297	621	-5 0 5	100.0% 2.23 [-0.22; 4.68]
Gross (Cerebral Infarctions	Standardised Mean Difference	Weight Estimate [95% CI]
		2	

APOE E23	84		- 13.2% 6.44 [-5.49; 18.37]
APOE E33	400		66.1% 3.55 [-1.79; 8.89]
APOE E34	138		20.7% -4.97 [-14.51; 4.58]
Common effect model	622		100.0% 2.17 [-2.17; 6.51]
Heterogeneity: $I^2 = 31\%$, $\tau^2 = 7.28$, p = 0.23			
p-value = 0.327 , FDR p-value = 0.679		-15-10-5051015	

Supplementary Figure 10 - part 1 of 3

APOE Genotype	Hippocampal Sclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 - 400 138		13.6% 48.9% 37.5%	-4.63 [-25.45; 16.19] 0.38 [-10.62; 11.38] 4.14 [-8.43; 16.70]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = p$ -value = 0.778 , FDR p-value = 0		-20 -10 0 10 20	100.0%	1.11 [–6.58; 8.80]

APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	82 387 129		64.6%	2.89 [-13.09; 18.87] 1.42 [-4.96; 7.80] 8.89 [-1.36; 19.15]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.40$, p = 0.48 p-value = 0.189, FDR p-value = 0.566	598	-15-10-5 0 5 10 15	100.0%	3.44 [-1.69; 8.58]

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 400 138		 14.3% 3.95 [-7.57; 15.48] 65.6% 3.80 [-1.58; 9.18] 20.1% 1.14 [-8.58; 10.85]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.89 p-value = 0.140 , FDR p-value = 0.502	622 -15	-10 -5 0 5 10	100.0% 3.28 [-1.07; 7.64] 15

Supplementary Figure 10 - part 2 of 3

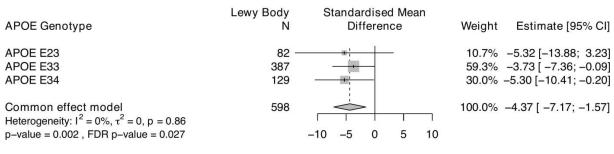
The Relationship between LDL-C and Neuropathology

APOE Genotype	TDP-43 N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	83 397 136		 10.8% 4.44 [-1.76; 10.63] 66.3% -0.61 [-3.11; 1.90] 22.8% 1.49 [-2.77; 5.76]
Common effect model Heterogeneity: $I^2 = 20\%$, $\tau^2 = 1.15$, p = 0.29 p-value = 0.686 , FDR p-value = 0.888	616 10	-5 0 5	100.0% 0.42 [-1.62; 2.46] 10

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



Supplementary Figure 11

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.

The Relationship between HDL-C and Neuropathology

Glob	al AD Pathology	Standardised Mean	
APOE Genotype	N	Difference	Weight Estimate [95% CI]
APOE E23	84 —		10.5% -6.39 [-16.58; 3.79]
APOE E33	400		63.9% -0.09 [-4.21; 4.03]
APOE E34	138		25.6% 1.71 [-4.80; 8.23]
Common effect model	622		100.0% -0.29 [-3.59; 3.01]
Heterogeneity: $I^2 = 0\%$, $\tau^2 < 0.01$, p = 0.42	622		100.0% -0.29 [-3.59, 3.01]
p-value = 0.863, FDR $p-value = 0.888$	-1	15 –10 –5 0 5 10	15
	Beta-Amyloid	Standardised Mean	
APOE Genotype	Ν	Difference	Weight Estimate [95% CI]
APOE E23	83 —		13.3% -0.54 [-3.41; 2.34]
APOE E33	399	· · · · · · · · · · · · · · · · · · ·	67.1% 0.27 [-1.01; 1.55]
APOE E34	138		19.6% 0.03 [-2.34; 2.41]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.88 p-value = 0.827 , FDR p-value = 0.888	620 「 —3	3 -2 -1 0 1 2	100.0% 0.12 [-0.93; 1.17] 3

Neurofibrill	ary Tangles	Standardised Mean	Weight Estimate [95% CI]
APOE Genotype	N	Difference	
APOE E23	83 —		6.6% -1.21 [-5.15; 2.73]
APOE E33	398		55.3% 0.78 [-0.58; 2.14]
APOE E34	138		38.1% 0.31 [-1.33; 1.95]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.63 p–value = 0.363 , FDR p–value = 0.687	619	-4 -2 0 2 4	100.0% 0.47 [-0.54; 1.48]

Supplementary Figure 12 – part 1 of 4

APOE Genotype	Braak Score N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 400 138		10.6% -0.89 [-4.30; 2.53] 66.3% 1.14 [-0.22; 2.50] 23.2% 0.63 [-1.68; 2.93]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.55 p-value = 0.153 , FDR p-value = 0.502	622 	-2 0 2	100.0% 0.81 [-0.30; 1.92] 4

APOE Genotype	CERAD Score N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 - 400 138		14.8% -0.85 [-3.73; 2.03] 64.7% 0.58 [-0.79; 1.96] 20.5% -0.29 [-2.73; 2.16]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.62 p-value = 0.732 , FDR p-value = 0.888	622	-3 -2 -1 0 1 2 3	100.0% 0.19 [-0.91; 1.30]

APOE Genotype	Cerebral Amyloid Angiopathy N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	83 400 138		17.7% 0.01 [-3.22; 3.24] - 54.6% 1.70 [-0.14; 3.54] 27.7% -0.28 [-2.86; 2.30]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$ p-value = 0.219 , FDR p-valu		-3 -2 -1 0 1 2 3	100.0% 0.85 [-0.51; 2.21]

Supplementary Figure 12 – part 2 of 4

Cerebral Ath APOE Genotype	erosclerosis Star N	ndardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84	*	 13.2% 0.49 [-3.42; 4.40] 54.5% -0.09 [-2.01; 1.83] 32.3% 1.56 [-0.94; 4.05]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.59 p-value = 0.475, FDR p-value = 0.815	622 -4 -2	2 0 2	100.0% 0.52 [-0.90; 1.94] 7 4

APOE Genotype	Gross Cerebral Infarctions N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 - 400 138 -		13.7% -0.76 [-7.30; 5.78] 59.0% -1.09 [-4.23; 2.06] 27.3% -2.76 [-7.39; 1.86]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p p-value = 0.224, FDR p-value =		-6 -4 -2 0 2 4 6	100.0% -1.50 [-3.92; 0.92]

APOE Genotype	Hippocampal Sclerosis N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 400 138		- 13.8% 40.1% 46.1%	6.99 [-4.11; 18.10] 7.23 [0.70; 13.76] -5.44 [-11.53; 0.65]
Common effect model Heterogeneity: $I^2 = 77\%$, $\tau^2 = 43.67$, p = p-value = 0.519 , FDR p-value = 0.815		-15 -10 -5 0 5 10 15	100.0%	1.36 [–2.77; 5.49]

Supplementary Figure 12 - part 3 of 4

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 400 138	* 	15.2% –3.01 [–9.25; 3.22] 58.4% –0.60 [–3.78; 2.58] 26.4% 2.40 [–2.33; 7.12]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 < 0.01$, p = 0.37 p-value = 0.888 , FDR p-value = 0.888	622	-5 0 5	100.0% -0.17 [-2.60; 2.25]

APOE Genotype	TDP–43 N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	83 397 136		- 11.2% 0.30 [-3.10; 3.70] 58.7% 0.15 [-1.33; 1.64] - 30.1% 1.74 [-0.33; 3.81]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.04$, p = 0.46 p-value = 0.263 , FDR p-value = 0.613	616	-3 -2 -1 0 1 2 3	100.0% 0.65 [-0.49; 1.79]

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

Ce APOE Genotype	rebral Atherosclerosis N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 400 138		 14.4% 14.84 [0.57; 29.10] 57.2% 6.02 [-1.15; 13.19] 28.4% 6.05 [-4.13; 16.23]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0 p-value = 0.008 , FDR p-value = 0.0		-20 -10 0 10 20	100.0% 7.30 [1.88; 12.72]

Supplementary Figure 13

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

APOE Genotype	Global AD Pathology N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 400 138		 10.5% 14.02 [-24.58; 52.61] 67.4% -7.55 [-22.76; 7.66] 22.1% 9.87 [-16.69; 36.44]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 31.71$, p = 0 p-value = 0.821 , FDR p-value = 0.888	.38	-40 -20 0 20 40	100.0% –1.44 [–13.93; 11.04]
APOE Genotype	Beta–Amyloid N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	83 399 138		12.9% 0.52 [-10.53; 11.57] 70.2% -1.93 [-6.67; 2.82] - 16.9% 3.00 [-6.67; 12.68]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.6 p-value = 0.701, FDR p-value = 0.88		-10 -5 0 5 10	100.0% -0.78 [-4.75; 3.19]
	_		
APOE Genotype	eurofibrillary Tangles N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34	83 398 138		- 7.0% 4.15 [–10.42; 18.73] 59.3% –0.66 [–5.66; 4.34] 33.7% 1.75 [–4.87; 8.38]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.7 p-value = 0.803 , FDR p-value = 0.88		-15-10-5 0 5 10 15	100.0% 0.49 [-3.36; 4.34]

Supplementary Figure 14 – part 1 of 4

APOE Genotype	Braak Score N	Standardised Mean Difference	Weight Estimate [95% CI]
APOE E23 APOE E33 APOE E34 Common effect model	84 400 138 622		 11.7% 4.01 [-8.01; 16.02] 68.6% -4.46 [-9.42; 0.51] 19.7% 2.97 [-6.30; 12.24] 100.0% -2.00 [-6.12; 2.11]
Heterogeneity: $I^2 = 33\%$, $\tau^2 = 11.56$, p = 0.22 p-value = 0.340 , FDR p-value = 0.679	-15	5 –10 –5 0 5 10 1	15

APOE Genotype	CERAD Score N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 400 138		67.9%	3.48 [-7.48; 14.43] -3.53 [-8.62; 1.55] 6.32 [-3.70; 16.33]
Common effect model Heterogeneity: $I^2 = 45\%$, $\tau^2 = 16.35$, p = 0.16 p–value = 0.713 , FDR p–value = 0.888	622 -15	5 -10 -5 0 5 10 1		-0.78 [-4.97; 3.40]

Cerebral Amyloid / APOE Genotype	Angiopathy N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	83 — 400 138 —	*	58.1%	-1.16 [-13.48; 11.16] 0.48 [-6.31; 7.26] -5.00 [-15.51; 5.51]
Common effect model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, p = 0.69 p-value = 0.666 , FDR p-value = 0.888	621 _15 _	10 -5 0 5 10		-1.14 [-6.31; 4.03]

Supplementary Figure 14 - part 2 of 4

Gros	s Cerebral Infarctions	Standardised Mean	Weight Estimate [95% CI]
APOE Genotype	N	Difference	
APOE E23	84		- 14.6% 30.05 [6.07; 54.03]
APOE E33	400		62.3% -2.02 [-13.60; 9.57]
APOE E34	138		23.1% -3.71 [-22.74; 15.32]
Common effect model Heterogeneity: $I^2 = 67\%$, $\tau^2 = 204.71$, p = 0. p-value = 0.628 , FDR p-value = 0.888	622 05	-40 -20 0 20 40	100.0% 2.26 [-6.89; 11.41]

APOE Genotype	Hippocampal Sclerosis N	Standardised Mea Difference	an Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 - 400 138		- 13.3% 45.6% - 41.0%	
Common effect model Heterogeneity: $I^2 = 53\%$, $\tau^2 = 247.37$, p = p-value = 0.465 , FDR p-value = 0.815	622	-40 -20 0 20	100.0% 40	5.91 [–9.96; 21.78]

APOE Genotype	Lewy Body N	Standardised Mean Difference	Weight	Estimate [95% CI]
APOE E23 APOE E33 APOE E34	82 387 129		61.5%	8.86 [–23.89; 41.61] 3.28 [–10.31; 16.87] 10.82 [–9.38; 31.02]
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, p = 0.82 p-value = 0.272 , FDR p-value = 0.613	598 	-20 0 20	100.0% 40	5.97 [-4.69; 16.63]

Supplementary Figure 14 – part 3 of 4

APOE Genotype	Microinfarcts N	Standardised Mean Difference	Weigh	t Estimate [95% CI]
APOE E23 APOE E33 APOE E34	84 400 138	*	— 15.1% 62.2% 22.7%	
Common effect model Heterogeneity: $I^2 = 54\%$, $\tau^2 = 94.00$, $p = 0.12$ p-value = 0.520 , FDR p-value = 0.815	622 –	30 -20 -10 0 10 20	100.0% 30	3.00 [-6.16; 12.16]
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: l^2 = 0%, τ^2 = 0, p = 0.55 p-value = 0.852 , FDR p-value = 0.888 –15 –10 –5 0 5 10 15

Supplementary Figure 14 – part 4 of 4