<div align="center">**Supplementary Online Content**</div>

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Concentration of apoE and apoE subspecies[1] at screening visit by *APOE* genotype in the random subcohort of the Ginkgo Evaluation of Memory study (N=995)

	APOE ε2/2 (N=8)	*APOE ε2/3* (N=89)	*APOE ε2/4* (N=19)	*APOE ε3/3* (N=518)	*APOE ε3/4* (N=152)	*APOE ε4/4* (N=9)	*APOE genotype missing* (N=200)
Whole plasma apoE, mg/dl	26.0 (12.8, 34.8)	14.8 (9.2, 23.6)	13.6 (8.0, 25.4)	10.6 (6.5, 17.7)	9.1 (5.7, 14.9)	8.2 (4.8, 14.4)	10.7 (6.3, 20.3)
Non-HDL apoE, mg/dl	8.3 (0.7, 19.4)	5.5 (0.9, 11.3)	5.6 (1.2, 9.6)	4.4 (0.8, 8.8)	3.7 (0.4, 7.9)	5.1 (3.6, 6.6)	4.5 (0.8, 9.1)
HDL apoE, mg/dl	15.6 (8.6, 25.6)	9.2 (5.1, 15.6)	8.2 (3.2, 21.4)	5.9 (2.8, 12.1)	4.8 (2.2, 9.4)	3.3 (1.2, 9.9)	5.8 (2.4, 12.5)
% whole plasma apoE in HDL	61 (35, 95)	62 (40, 92)	55 (39, 89)	55 (35, 92)	56 (31, 94)	39 (22, 69)	54 (33, 93)
ApoE in HDL that contains apoC3, mg/dl	8.1 (5.2, 17.9)	4.8 (2.5, 8.2)	4.1 (2.0, 13.4)	3.1 (1.2, 6.5)	2.6 (0.9, 5.2)	2.0 (0.6, 5.5)	3.2 (1.3, 7.6)
ApoE in HDL that lacks apoC3, mg/dl	6.0 (0.004, 13.8)	4.4 (0.7, 10.3)	3.9 (0.3, 11.6)	2.7 (0.1, 7.2)	2.3 (0.004, 5.7)	0.7 (0.004, 4.5)	2.6 (0.04, 7.5)
ApoE in HDL that contains apoJ, mg/dl	0.6 (0.2, 0.9)	0.3 (0.2, 0.6)	0.3 (0.2, 0.6)	0.3 (0.2, 0.6)	0.3 (0.1, 0.4)	0.3 (0.1, 0.4)	0.3 (0.2, 0.6)
ApoE in HDL that lacks apoJ, mg/dl	14.8 (0.8, 24.9)	8.9 (4.8, 15.2)	7.8 (2.9, 20.8)	5.6 (2.6, 11.8)	4.6 (2.0, 9.1)	3.1 (1.0, 9.5)	5.4 (2.2, 12.1)

Abbreviations: Apo, Apolipoprotein. *APOE*, Apolipoprotein E gene. HDL, High-density lipoprotein.

[1]Values are median (Q5; Q95).

eTable 2. Hazard ratios (HRs)[1] for risk of dementia or difference in cognitive scores at baseline and 95% confidence intervals (95% CI) per SD higher plasma concentrations of apoE and apoE subspecies at screening visit in the Ginkgo Evaluation of Memory case-cohort, N=1351.

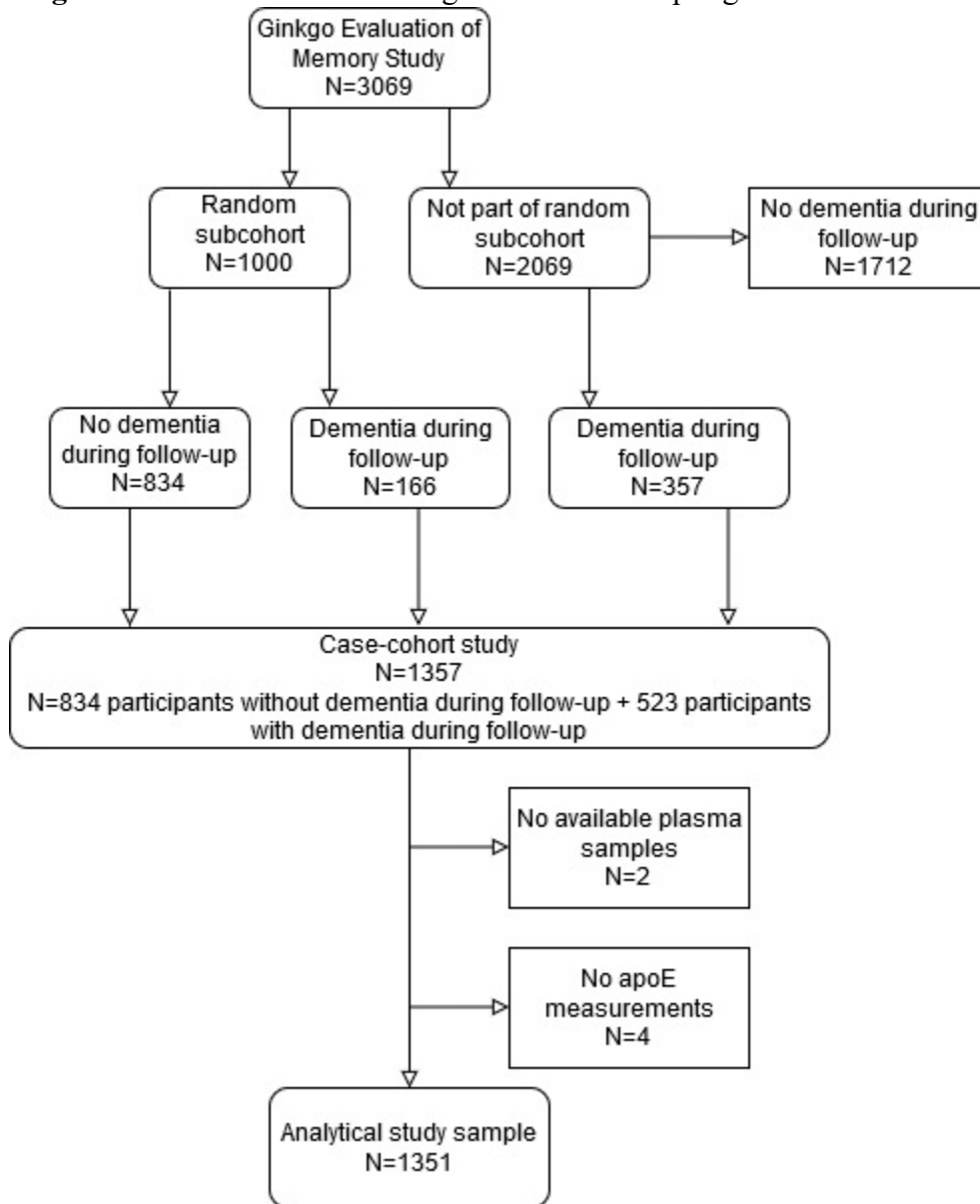|	HR for dementia (95% CI) per SD	HR (95% CI) for AD per SD	Difference in ADAS-cog (95% CI) per SD	Difference in 3MSE (95% CI) per SD
Whole plasma apoE				
Basic	**0.84 (0.75, 0.94)**	**0.79 (0.69, 0.91)**	**-0.21 (-0.30, -0.12)**	**0.20 (0.04, 0.36)**
Multivariable	**0.87 (0.78, 0.98)**	**0.82 (0.71, 0.94)**	**-0.18 (-0.26, -0.09)**	0.14 (-0.01, 0.29)
Multivariable + APOE[2]	0.92 (0.82, 1.03)	0.88 (0.77, 1.00)	**-0.15 (-0.24, -0.06)**	0.12 (-0.03, 0.28)
Multivariable excluding APOE ε4 carriers[3]	0.91 (0.80, 1.03)	0.86 (0.73, 1.00)	**-0.14 (-0.23, -0.05)**	0.08 (-0.09, 0.24)
Non-HDL apoE				
Basic	**0.85 (0.74, 0.98)**	**0.85 (0.73, 0.99)**	**-0.12 (-0.23, -0.01)**	**0.24 (0.04, 0.44)**
Multivariable	0.88 (0.76, 1.02)	0.87 (0.74, 1.02)	-0.07 (-0.18, 0.04)	0.15 (-0.04, 0.34)
Multivariable + APOE[2]	0.89 (0.77, 1.03)	0.88 (0.75, 1.03)	-0.06 (-0.17, 0.05)	0.14 (-0.05, 0.33)
Multivariable excluding APOE ε4 carriers[2]	0.89 (0.75, 1.05)	0.87 (0.73, 1.05)	-0.07 (-0.19, 0.04)	**0.23 (0.03, 0.43)**
HDL apoE				
Basic	**0.85 (0.74, 0.96)**	**0.77 (0.65, 0.90)**	**-0.25 (-0.35, -0.15)**	0.16 (-0.02, 0.34)
Multivariable	**0.87 (0.77, 0.99)**	**0.80 (0.68, 0.93)**	**-0.23 (-0.33, -0.13)**	0.12 (-0.05, 0.29)
Multivariable + APOE[2]	0.94 (0.83, 1.07)	0.88 (0.75, 1.02)	**-0.20 (-0.30, -0.10)**	0.10 (-0.07, 0.27)
Multivariable excluding APOE ε4 carriers[2]	0.92 (0.79, 1.07)	0.85 (0.70, 1.02)	**-0.18 (-0.28, -0.07)**	-0.03 (-0.21, 0.16)
ApoE in HDL that contains apoC3				
Basic	1.02 (0.91, 1.14)	0.92 (0.80, 1.06)	-0.09 (-0.18, 0.003)	-0.10 (-0.26, 0.07)
Multivariable	1.03 (0.92, 1.15)	0.94 (0.82, 1.08)	**-0.10 (-0.19, -0.01)**	-0.11 (-0.26, 0.05)
Multivariable + APOE[2]	1.07 (0.95, 1.19)	1.00 (0.87, 1.14)	-0.08 (-0.17, 0.01)	-0.12 (-0.28, 0.04)
Multivariable excluding APOE ε4 carriers[2]	1.05 (0.92, 1.20)	0.95 (0.80, 1.13)	-0.04 (-0.14, 0.05)	-0.15 (-0.32, 0.02)
ApoE in HDL that lacks apoC3				
Basic	**0.79 (0.69, 0.91)**	**0.78 (0.66, 0.92)**	**-0.23 (-0.33, -0.13)**	**0.31 (0.12, 0.49)**
Multivariable	**0.82 (0.72, 0.94)**	**0.80 (0.68, 0.94)**	**-0.19 (-0.29, -0.10)**	**0.26 (0.09, 0.44)**
Multivariable + APOE[2]	**0.86 (0.76, 0.99)**	0.86 (0.73, 1.00)	**-0.17 (-0.27, -0.07)**	**0.25 (0.07, 0.42)**
Multivariable excluding APOE ε4 carriers[2]	0.86 (0.74, 1.00)	0.86 (0.72, 1.03)	**-0.18 (-0.29, -0.07)**	0.12 (-0.07, 0.31)
ApoE in HDL that contains apoJ				
Basic	0.96 (0.84, 1.11)	0.86 (0.73, 1.01)	0.08 (-0.03, 0.19)	**-0.23 (-0.42, -0.03)**
Multivariable	1.00 (0.86, 1.15)	0.90 (0.76, 1.07)	0.05 (-0.06, 0.16)	**-0.22 (-0.41, -0.02)**
Multivariable + APOE[2]	1.02 (0.88, 1.17)	0.93 (0.78, 1.10)	0.05 (-0.06, 0.16)	**-0.22 (-0.41, -0.02)**
Multivariable excluding APOE ε4 carriers[2]	0.99 (0.84, 1.16)	0.85 (0.69, 1.05)	0.04 (-0.07, 0.16)	**-0.23 (-0.43, -0.02)**

eTable 2 continued on next page

eTable 2 *continued.* Hazard ratios (HRs)[1] for risk of dementia or difference in cognitive scores at baseline and 95% confidence intervals (95% CI) per SD higher plasma concentrations of apoE and apoE subspecies at screening visit in the Ginkgo Evaluation of Memory case-cohort, N=1351.

	HR for dementia (95% CI) per SD	HR (95% CI) for AD per SD	Difference in ADAS-cog (95% CI) per SD	Difference in 3MSE (95% CI) per SD
ApoE in HDL that lacks apoJ				
Basic	0.86 (0.74, 1.00)	0.83 (0.70, 1.00)	**-0.31 (-0.43, -0.19)**	**0.31 (0.09, 0.52)**
Multivariable	0.87 (0.75, 1.01)	0.84 (0.70, 1.01)	**-0.26 (-0.38, -0.15)**	**0.26 (0.05, 0.47)**
Multivariable + *APOE*[2]	0.93 (0.80, 1.08)	0.92 (0.77, 1.09)	**-0.24 (-0.36, -0.12)**	**0.24 (0.03, 0.44)**
Multivariable excluding *APOE* ε4 carriers[2]	0.93 (0.78, 1.10)	0.92 (0.75, 1.13)	**-0.23 (-0.36, -0.12)**	0.12 (-0.11, 0.34)

Abbreviations: ADAS-cog, Cognitive subscale of the Alzheimer Disease Assessment Scale. Apo, Apolipoprotein. *APOE*, Apolipoprotein E gene. HDL, High-density lipoprotein. 3MSE, Modified Mini-Mental State Examination score.
[1]Hazard Ratios (HRs) were obtained from weighted Cox proportional hazard regression models adjusted for age, sex, race/ethnicity, clinic site, fasting status. Each lipoprotein was modeled separately, except for complementary subspecies (e.g., apoE in HDL containing or lacking apoC3) which were included simultaneously in models. Multivariable analyses were adjusted for age, sex, race/ethnicity, clinic site, fasting status, education, weekly number of alcoholic drinks, smoking status, body mass index, lipid-lowering medication use, history of cardiovascular disease, history of diabetes, CES-D, and treatment assignment. [2]Multivariable analyses were additionally adjusted for *APOE* ε4 carrier status (*APOE ε4* carrier, *APOE ε4* non-carrier, missing). [3]N=1070.

eFigure 1. Flowchart summarizing case-cohort sampling.

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                    ┌─────────────────────┐
                    │ Ginkgo Evaluation of│
                    │   Memory Study      │
                    │     N=3069          │
                    └─────────────────────┘
                      │                │
          ┌───────────┘                └───────────┐
          ▼                                        ▼
  ┌──────────────┐                   ┌──────────────────┐      ┌──────────────────┐
  │  Random      │                   │ Not part of random│─────▶│ No dementia during│
  │  subcohort   │                   │   subcohort       │      │   follow-up       │
  │  N=1000      │                   │   N=2069          │      │   N=1712          │
  └──────────────┘                   └──────────────────┘      └──────────────────┘
     │        │                              │
     ▼        ▼                              ▼
┌─────────┐ ┌───────────┐           ┌───────────────┐
│No dementia│ │Dementia during│     │Dementia during│
│during    │ │follow-up      │     │follow-up      │
│follow-up │ │N=166          │     │N=357          │
│N=834     │ └───────────┘         └───────────────┘
└─────────┘
     │         │                            │
     ▼         ▼                            ▼
  ┌─────────────────────────────────────────────────────────┐
  │              Case-cohort study                          │
  │                 N=1357                                  │
  │ N=834 participants without dementia during follow-up +  │
  │ 523 participants with dementia during follow-up         │
  └─────────────────────────────────────────────────────────┘
                 │
                 │────▶ ┌──────────────────┐
                 │      │No available plasma│
                 │      │   samples         │
                 │      │   N=2             │
                 │      └──────────────────┘
                 │
                 │────▶ ┌──────────────────┐
                 │      │  No apoE          │
                 │      │  measurements     │
                 │      │  N=4              │
                 │      └──────────────────┘
                 ▼
          ┌──────────────────┐
          │Analytical study  │
          │ sample           │
          │ N=1351           │
          └──────────────────┘
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eFigure 2. Measurement of plasma concentration of apoE in different lipoprotein subspecies by ELISA.
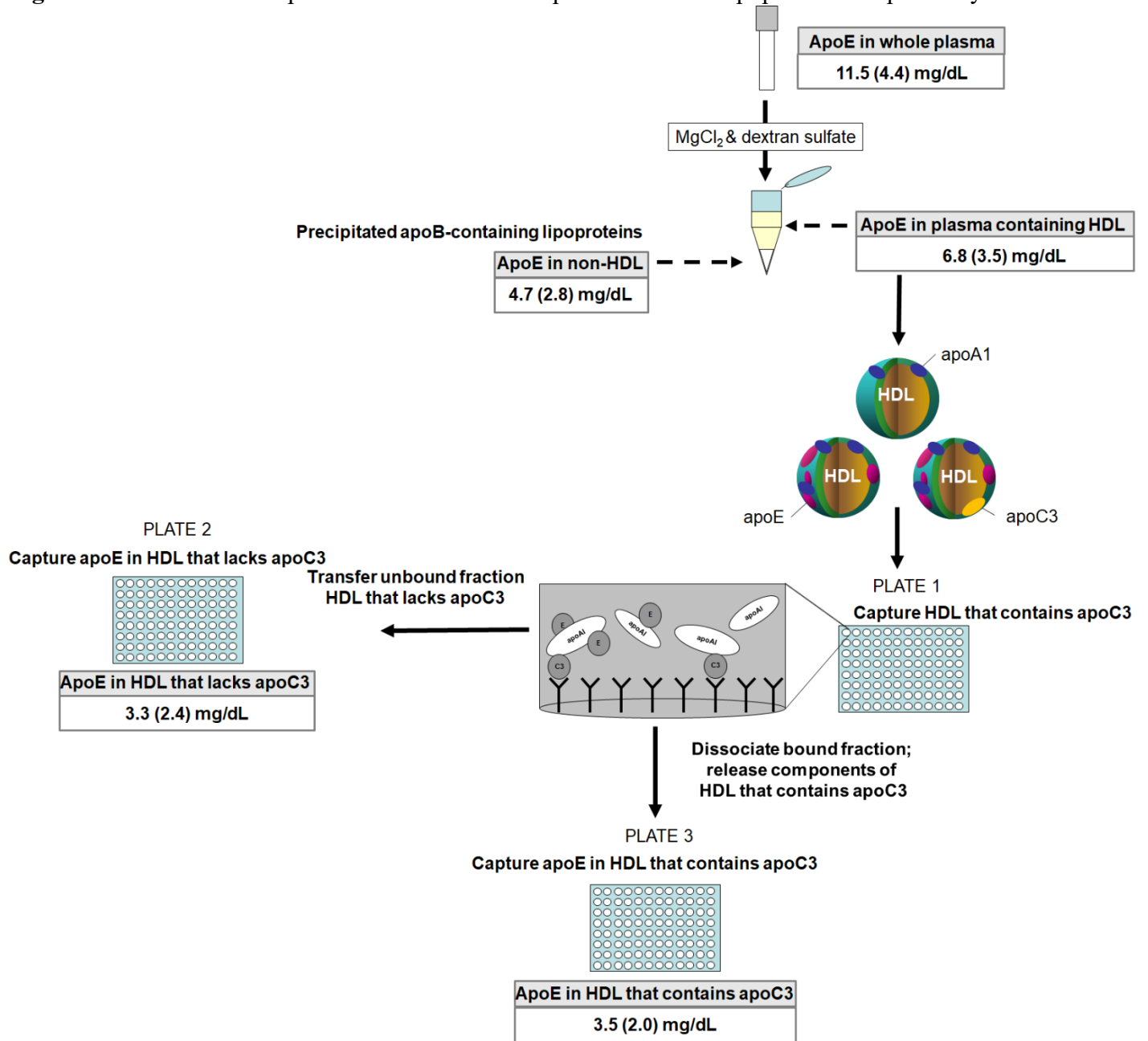
Concentrations (mean [SD]) of apoE in whole plasma, in the fraction of plasma without HDL (non-HDL), in HDL, and in HDL that contains or lacks apoC3 refer to the random subcohort of the Ginkgo Evaluation of Memory study (N=995).

Abbreviations: Apo, Apolipoprotein. ELISA, Enzyme-linked immunosorbent assay. HDL, High-density lipoprotein.

eFigure 3. Average trajectories of ADAS-cog scores by tertiles of whole plasma apoE (A) and apoE in HDL (B) at screening visit in the Ginkgo Evaluation of Memory case-cohort.
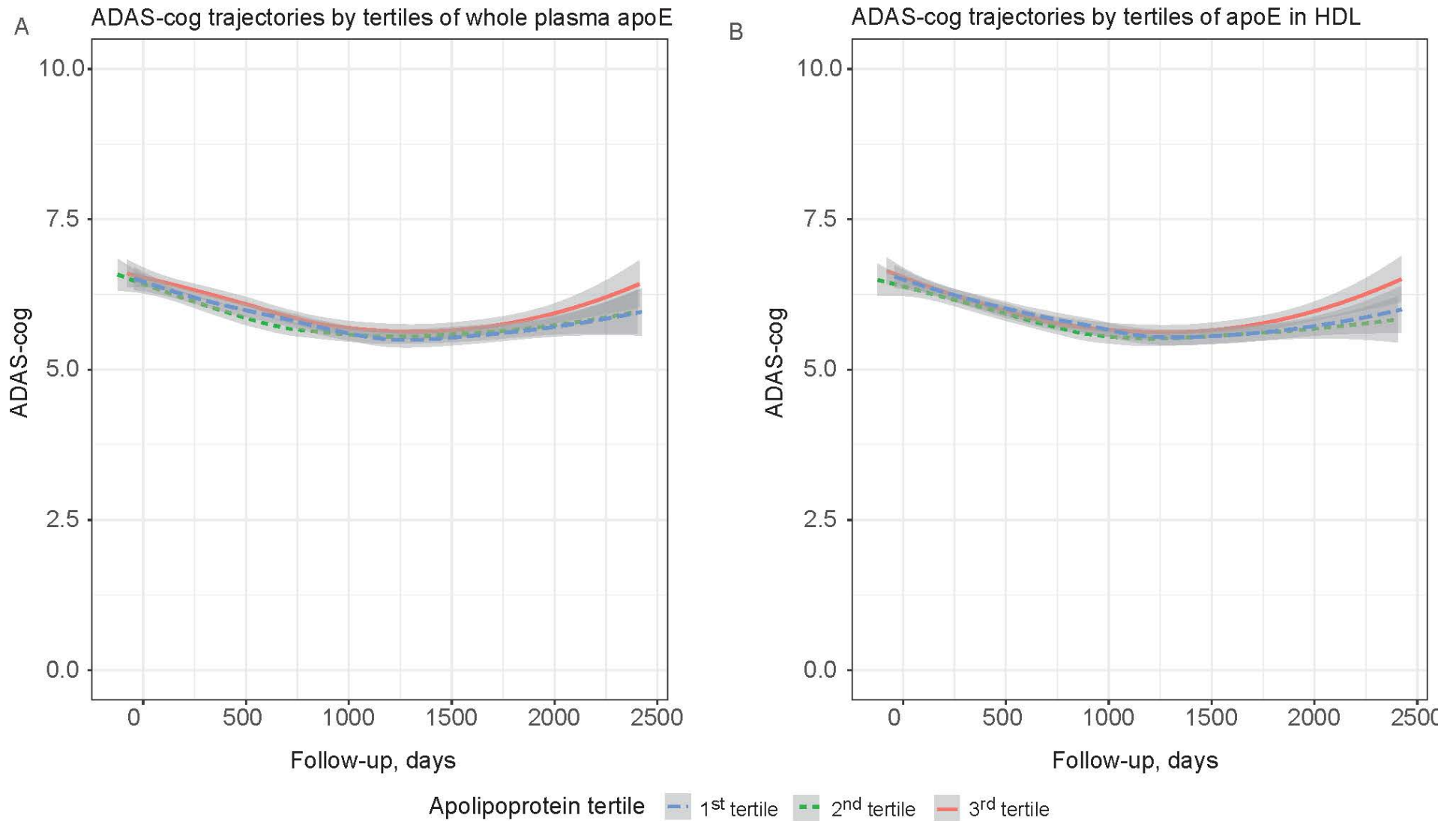
Abbreviations: ADAS-cog, Cognitive subscale of the Alzheimer Disease Assessment Scale. Apo, Apolipoprotein. HDL, High-density lipoprotein.

eFigure 4. HDL and its apolipoprotein-defined subspecies and other apolipoproteins at study entry (2000 to 2002) and follow-up
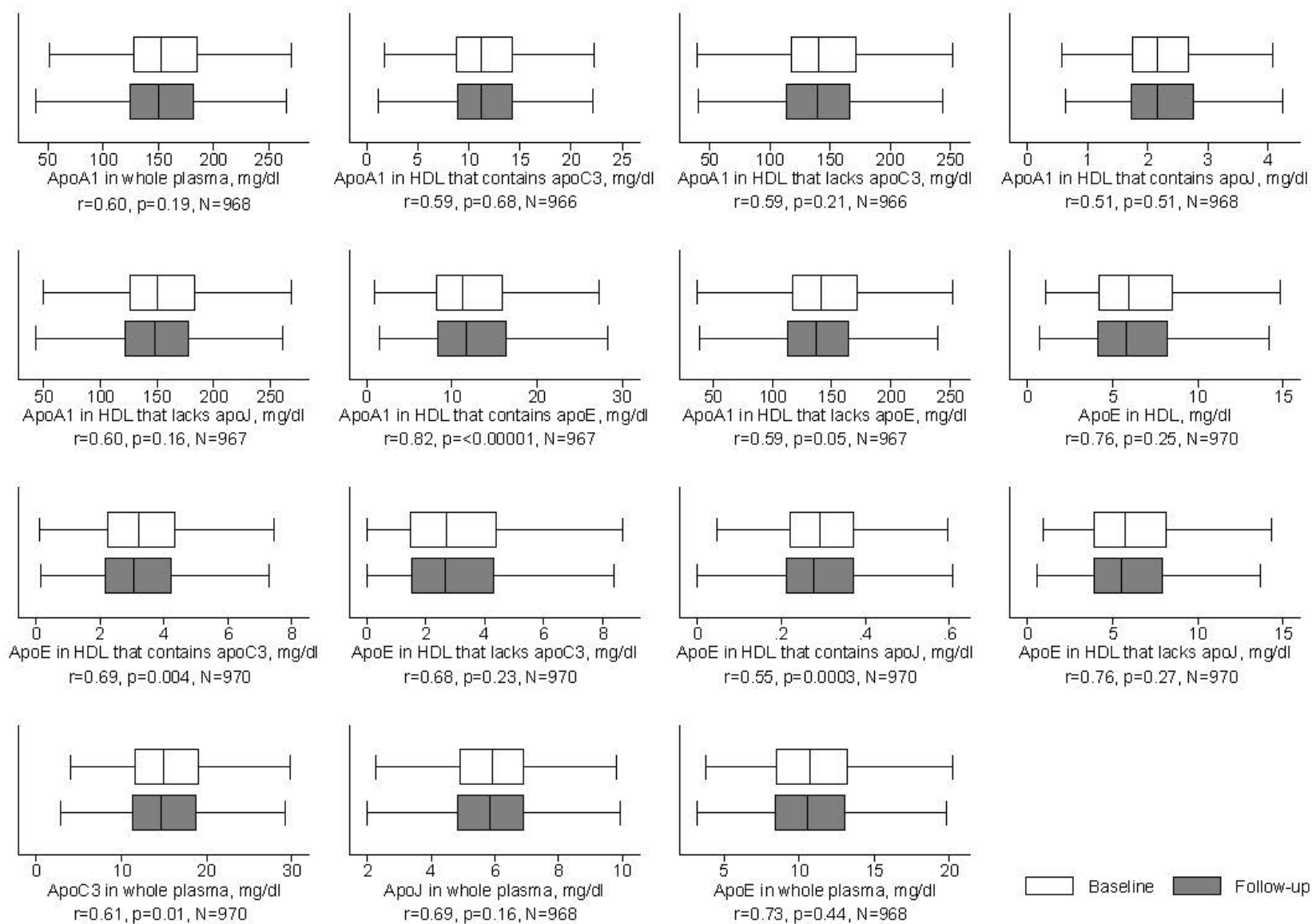
. Partial correlation coefficients (r) are shown of biomarkers assessed at study entry (2000 to 2002) and 3-year follow-up (4-year or 9-year follow-up for subset of participants) controlling for age at randomization and sex. P values for test of equality (p) are shown of biomarkers assessed at study entry and follow-up by using the Wilcoxon signed-ranks test.