

Blood-based biomarkers of Alzheimer's disease and incident dementia in the community

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Supplementary files.

Supplementary Table 1. Hazard ratios (HR) for **all-cause dementia** with 95% confidence intervals (CIs) by baseline biomarkers in the dementia-free analytical sample, by age, sex and APOEε4

	Age		Sex		APOE4 genotype**	
	Age <78 years (N=1412)	Age 78 + years (N=878)	Male (N=880)	Female (N=1410)	No ε4 alleles (N=1568)	At least one ε4 allele (N=653)
Biomarkers						
Aβ42/Aβ40						
Q4 (Ref*)	1.00	1.00	1.00	1.00	1.00	1.00
Q3	0.97 (0.52-1.84)	0.99 (0.64-1.52)	0.88 (0.48-1.62)	0.98 (0.63-1.51)	0.91 (0.59-1.40)	1.24 (0.67-2.31)
Q2	2.00 (1.13-3.53)	1.15 (0.78-1.71)	1.26 (0.73-2.19)	1.32 (0.88-1.99)	1.12 (0.74-1.69)	1.76 (1.02-3.01)
Q1	0.78 (0.40-1.55)	1.12 (0.76-1.66)	0.80 (0.45-1.42)	1.22 (0.80-1.84)	0.98 (0.64-1.51)	1.29 (0.74-2.26)
P-tau181						
Q1 (Ref.)	1.00	1.00	1.00	1.00	1.00	1.00
Q2	1.04 (0.56-1.96)	1.73 (0.95-3.15)	1.24 (0.59-2.63)	1.48 (0.88-2.52)	1.58 (0.89-2.80)	1.21 (0.62-2.37)
Q3	1.36 (0.73-2.53)	1.47 (0.83-2.59)	1.51 (0.76-3.02)	1.47 (0.88-2.45)	1.87 (1.08-3.25)	1.19 (0.64-2.23)
Q4	3.13 (1.62-6.05)	2.44 (1.41-4.21)	1.71 (0.85-3.45) #	3.05 (1.85-5.01) #	2.69 (1.56-4.64)	2.68 (1.45-4.98)
P-tau217						
Q1 (Ref.)	1.00	1.00	1.00	1.00	1.00	1.00
Q2	1.79 (0.90-3.54)	1.66 (0.89-3.10)	0.77 (0.34-1.70) #	2.32 (1.32-4.07) #	2.25 (1.26-4.02)	1.11 (0.51-2.40)
Q3	2.17 (1.10-4.28)	1.60 (0.90-2.85)	1.09 (0.53-2.23) #	2.53 (1.47-4.36) #	2.30 (1.31-4.04)	1.50 (0.75-3.00)
Q4	5.48 (2.72-11.02) #	1.96 (1.11-3.46) #	2.01 (0.98-4.14)	3.29 (1.90-5.71)	2.58 (1.45-4.60)	3.41 (1.72-6.76)
T-tau						
Q1 (Ref)	1.00	1.00	1.00	1.00	1.00	1.00
Q2	1.03 (0.55-1.92)	0.74 (0.49-1.11)	0.99 (0.56-1.74)	0.71 (0.46-1.09)	0.74 (0.47-1.17)	0.90 (0.53-1.53)
Q3	1.73 (0.95-3.15)	1.09 (0.76-1.56)	1.03 (0.60-1.78)	1.22 (0.84-1.78)	1.30 (0.88-1.93)	1.07 (0.65-1.75)

Q4	2.08 (1.13-3.83)	0.92 (0.64-1.31)	0.95 (0.51-1.78)	1.18 (0.82-1.70)	1.02 (0.68-1.52)	1.46 (0.88-2.41)
NfL						
Q1 (Ref.)	1.00	1.00	1.00	1.00	1.00	1.00
Q2	1.13 (0.61-2.10)	0.83 (0.33-2.11)	1.20 (0.55-2.61)	1.17 (0.60-2.27)	1.17 (0.51-2.69)	1.13 (0.60-2.13)
Q3	2.53 (1.32-4.84)	1.32 (0.57-3.08)	2.08 (0.98-4.41)	2.50 (1.33-4.70)	2.68 (1.23-5.83)	1.97 (1.04-3.76)
Q4	3.53 (1.59-7.86)	2.00 (0.86-4.68)	3.20 (1.39-7.41)	3.75 (1.92-7.32)	4.73 (2.10-10.63) #	2.25 (1.10-4.58) #
GFAP						
Q1 (Ref.)	1.00	1.00	1.00	1.00	1.00	1.00
Q2	2.09 (1.02-4.28)	1.03 (0.50-2.14)	2.40 (1.14-5.06)	1.09 (0.55-2.14)	1.17 (0.61-2.25)	2.20 (1.01-4.82)
Q3	4.00 (2.02-7.94)	1.27 (0.64-2.51)	4.14 (2.03-8.42)	1.83 (0.97-3.47)	1.93 (1.05-3.56)	3.19 (1.52-6.70)
Q4	7.36 (3.49-15.48) #	1.80 (0.92-3.51) #	5.44 (2.62-11.32)	2.50 (1.31-4.78)	2.60 (1.38-4.91)	4.85 (2.28-10.29)

HRs are derived from Cox regression survival models.

Models are adjusted for age, sex, education, ischemic heart disease, atrial fibrillation, heart failure, cerebrovascular diseases, chronic kidney diseases, obesity, anaemia, hypertension, APOE genotype.

*For the A β 42/A β 40 ratio the highest quartile (Q4) was chosen as reference

**69 missing values in APOE genotype

p for interaction <0.05

Supplementary Table 2. Hazard ratios (HR) for **AD dementia** with 95% confidence intervals (CIs) by baseline biomarkers in the dementia-free analytical sample, by age, sex and APOEε4

	Age		Sex		APOE4 genotype**	
	Age <78 years (N=1412)	Age 78+ years (N=878)	Male (N=880)	Female (N=1410)	No ε4 alleles (N=1568)	At least one ε4 allele (N=653)
Biomarkers						
Aβ42/Aβ40						
Q4 (Ref*)	1.00	1.00	1.00	1.00	1.00	1.00
Q3	1.08 (0.46-2.53)	0.95 (0.53-1.72)	0.97 (0.38-2.46)	0.93 (0.53-1.63)	0.88 (0.47-1.67)	1.34 (0.63-2.85)
Q2	2.35 (1.09-5.05)	1.43 (0.85-2.40)	2.12 (0.96-4.65)	1.45 (0.86-2.43)	1.43 (0.80-2.57)	1.96 (1.02-3.77)
Q1	0.76 (0.30-1.95)	1.22 (0.72-2.07)	1.19 (0.52-2.74)	1.12 (0.65-1.92)	1.22 (0.66-2.24)	1.15 (0.57-2.32)
P-tau181						
Q1 (Ref.)	1.00	1.00	1.00	1.00	1.00	1.00
Q2	1.49 (0.62-3.58)	3.05 (1.16-8.03)	2.67 (0.71-10.02)	1.95 (0.94-4.04)	1.15 (0.57-2.32)	1.58 (0.63-4.00)
Q3	1.90 (0.79-4.57)	2.70 (1.06-6.86)	4.02 (1.16-13.90)	1.71 (0.83-3.53)	3.22 (1.24-8.36)	2.02 (0.85-4.77)
Q4	5.00 (2.00-12.54)	4.08 (1.63-10.21)	3.78 (1.07-13.31)	3.78 (1.87-7.62)	4.45 (1.72-11.48)	4.55 (1.93-10.74)
P-tau217						
Q1 (Ref.)	1.00	1.00	1.00	1.00	1.00	1.00
Q2	1.89 (0.73-4.87)	1.57 (0.69-3.58)	0.77 (0.23-2.51)	2.32 (1.12-4.82)	3.52 (1.44-8.59) #	0.65 (0.24-1.77) #
Q3	2.65 (1.05-6.67)	1.38 (0.64-2.98)	1.33 (0.47-3.75)	2.25 (1.10-4.62)	2.77 (1.14-6.75) #	1.32 (0.58-3.04) #
Q4	7.57 (2.93-19.56) #	2.05 (0.97-4.32) #	2.61 (0.92-7.36)	3.57 (1.75-7.30)	3.45 (1.41-8.47)	3.63 (1.62-8.16)
T-tau						
Q1 (Ref)	1.00	1.00	1.00	1.00	1.00	1.00
Q2	0.99 (0.43-2.30)	0.73 (0.43-1.24)	1.00 (0.46-2.16)	0.71 (0.41-1.23)	1.03 (0.55-1.92)	0.66 (0.34-1.28)
Q3	2.04 (0.91-4.53)	1.08 (0.68-1.71)	1.09 (0.52-2.25)	1.23 (0.76-1.99)	1.73 (0.99-3.02) #	0.86 (0.47-1.56) #

Q4	2.45 (1.10-5.45)	0.89 (0.56-1.42)	1.13 (0.49-2.62)	1.17 (0.73-1.89)	1.18 (0.65-2.11)	1.37 (0.77-2.45)
NfL						
Q1 (Ref.)	1.00	1.00	1.00	1.00	1.00	1.00
Q2	1.00 (0.43-2.32)	1.15 (0.32-4.15)	0.51 (0.17-1.52) #	2.27 (0.84-6.13) #	2.10 (0.45-9.69)	0.97 (0.43-2.16)
Q3	2.91 (1.24-6.80)	1.40 (0.42-4.61)	1.13 (0.43-2.95) #	4.45 (1.68-11.77) #	3.82 (0.86-16.84)	2.48 (1.13-5.41)
Q4	7.13 (2.72-18.67)	2.97 (0.90-9.86)	3.39 (1.23-9.30) #	8.67 (3.17-23.71) #	11.83 (2.66-52.73) #	3.30 (1.39-7.79) #
GFAP						
Q1 (Ref.)	1.00	1.00	1.00	1.00	1.00	1.00
Q2	2.78 (0.94-8.20)	1.13 (0.41-3.13)	4.09 (1.10-15.25)	1.07 (0.44-2.60)	1.31 (0.46-3.73)	2.47 (0.87-6.99)
Q3	6.34 (2.31-17.36)	1.34 (0.51-3.49)	9.33 (2.68-32.54)	1.75 (0.76-4.03)	2.41 (0.90-6.47)	4.01 (1.50-10.69)
Q4	13.24 (4.50-38.93)	2.45 (0.97-6.22)	12.17 (3.44-43.15)	3.31 (1.44-7.63)	3.91 (1.43-10.68)	7.22 (2.69-19.38)

HRs are derived from Cox regression survival models.

Models are adjusted for age, sex, education, ischemic heart disease, atrial fibrillation, heart failure, cerebrovascular diseases, chronic kidney diseases, obesity, anaemia, hypertension, APOE genotype.

*For the A β 42/A β 40 ratio the highest quartile (Q4) was chosen as reference

**69 missing values in APOE genotype

p for interaction <0.05

Supplementary Table 3. Incidence rates (IR) per 100 person/year and hazard ratios (HR) for **all-cause (n = 286) and Alzheimer's dementia (AD) (n = 169)** with 95% confidence intervals (CIs) by baseline biomarkers in the dementia-free analytical sample considering only participants **with memory complaints at baseline**.

	All-cause dementia		AD dementia	
	IR (95%CI)	HR (95%CI)	IR (95%CI)	HR (95%CI)
Biomarkers				
Aβ42/Aβ40				
Q4 (Ref*)	1.14 (0.84-1.56)	1.00	0.63 (0.41-0.95)	1.00
Q3	1.54 (1.18-2.00)	0.93 (0.61-1.41)	0.88 (0.62-1.24)	0.99 (0.57-1.72)
Q2	3.16 (2.61-3.83)	1.38 (0.94-2.03)	2.04 (1.60-2.59)	1.74 (1.06-2.88)
Q1	2.79 (2.26-3.45)	1.04 (0.70-1.55)	1.56 (1.17-2.07)	1.11 (0.65-1.89)
P for trend		0.495		0.387
P-tau181				
Q1 (Ref.)	0.64 (0.43-0.97)	1.00	0.25 (0.13-0.48)	1.00
Q2	1.45 (1.11-1.90)	1.56 (0.94-2.58)	0.91 (0.64-1.27)	2.53 (1.19-5.35)
Q3	2.30 (1.86-2.86)	2.08 (1.29-3.33)	1.50 (1.15-1.96)	3.42 (1.67-7.00)
Q4	4.71 (3.96-5.61)	2.86 (1.78-4.60)	2.71 (2.15-3.41)	4.25 (2.07-8.74)
P for trend		<0.001		<0.001
P-tau217				
Q1 (Ref.)	0.58 (0.38-0.88)	1.00	0.29 (0.16-0.52)	1.00
Q2	1.27 (0.95-1.71)	2.04 (1.19-3.47)	0.81 (0.56-1.17)	2.31 (1.14-4.68)
Q3	2.59 (2.11-3.18)	2.86 (1.74-4.70)	1.46 (1.12-1.92)	2.99 (1.54-5.83)
Q4	4.74 (3.99-5.64)	3.53 (2.13-5.86)	2.89 (2.31-3.61)	4.06 (2.07-7.94)
P for trend		<0.001		<0.001
T-tau				
Q1 (Ref)	1.48 (1.13-1.93)	1.00	0.89 (0.63-1.26)	1.00
Q2	1.64 (1.26-2.12)	0.91 (0.62-1.34)	0.89 (0.63-1.27)	0.81 (0.49-1.34)
Q3	2.57 (2.08-3.18)	1.24 (0.87-1.77)	1.63 (1.25-2.13)	1.24 (0.79-1.95)
Q4	2.90 (2.36-3.57)	1.36 (0.95-1.95)	1.66 (1.26-2.18)	1.39 (0.88-2.20)
P for trend		0.045		0.069
NfL				
Q1 (Ref.)	0.45 (0.28-0.73)	1.00	0.25 (0.13-0.49)	1.00
Q2	1.10 (0.81-1.48)	1.58 (0.88-2.85)	0.63 (0.42-0.93)	1.66 (0.76-3.63)
Q3	2.68 (2.19-3.27)	3.05 (1.73-5.36)	1.49 (1.14-1.95)	3.27 (1.55-6.91)
Q4	5.26 (4.43-6.25)	4.63 (2.52-8.48)	3.29 (2.65-4.09)	6.57 (2.98-14.50)
P for trend		<0.001		<0.001
GFAP				

Q1 (Ref.)	0.58 (0.38-0.88)	1.00	0.18 (0.09-0.39)	1.00
Q2	1.16 (0.86-1.57)	1.73 (1.00-3.01)	0.61 (0.40-0.93)	2.65 (1.12-6.25)
Q3	2.61 (2.12-3.23)	2.64 (1.58-4.43)	1.59 (1.22-2.08)	4.60 (2.05-10.33)
Q4	4.86 (4.10-5.75)	3.94 (2.32-6.69)	3.13 (2.54-3.86)	8.00 (3.54-18.09)
P for trend		<0.001		<0.001

HRs are derived from Cox regression survival models, adjusted for age, sex, education, ischemic heart disease, atrial fibrillation, heart failure, cerebrovascular diseases, chronic kidney diseases, obesity, anaemia, hypertension, APOE genotype.

*For the A β 42/A β 40 ratio the highest quartile (Q4) was chosen as reference

Supplementary Table 4. Hazard ratios (HR) for **all-cause and Alzheimer´s dementia** with 95% confidence intervals (CIs) by baseline biomarkers in the dementia-free analytical sample **excluding those with a MMSE<27 (n=228)**

	All-cause dementia		AD dementia	
	IR (95%CI)	HR (95%CI)	IR (95%CI)	HR (95%CI)
Biomarkers				
Aβ42/Aβ40				
Q4 (Ref*)	0.90 (0.68-1.20)	1.00	0.50 (0.34-0.73)	1.00
Q3	1.14 (0.88-1.47)	0.90 (0.60-1.33)	0.60 (0.42-0.86)	0.85 (0.50-1.46)
Q2	2.00 (1.63-2.46)	1.27 (0.88-1.83)	1.30 (1.01-1.68)	1.59 (0.99-2.55)
Q1	1.73 (1.38-2.19)	1.03 (0.70-1.50)	1.04 (0.77-1.40)	1.09 (0.66-1.81)
P for trend		0.475		0.261
P-tau181				
Q1 (Ref.)	0.52 (0.36-0.75)	1.00	0.22 (0.13-0.39)	1.00
Q2	1.10 (0.85-1.42)	1.56 (0.98-2.48)	0.68 (0.49-0.94)	2.19 (1.13-4.27)
Q3	1.46 (1.16-1.84)	1.58 (1.01-2.47)	0.83 (0.61-1.13)	2.01 (1.04-3.87)
Q4	3.27 (2.71-3.95)	2.78 (1.79-4.32)	2.07 (1.64-2.62)	3.90 (2.05-7.41)
P for trend		<0.001		<0.001
P-tau217				
Q1 (Ref.)	0.48 (0.33-0.70)	1.00	0.25 (0.15-0.42)	1.00
Q2	1.00 (0.76-1.32)	1.72 (1.06-2.77)	0.60 (0.42-0.86)	1.83 (0.96-3.49)
Q3	1.68 (1.36-2.08)	2.05 (1.30-3.23)	0.89 (0.67-1.19)	1.98 (1.07-3.66)
Q4	3.26 (2.69-3.95)	2.87 (1.81-4.56)	2.14 (1.69-2.71)	3.42 (1.85-6.31)
P for trend		<0.001		0.001
T-tau				
Q1 (Ref)	1.10 (0.85-1.43)	1.00	0.61 (0.43-0.87)	1.00
Q2	0.97 (0.73-1.28)	0.80 (0.54-1.18)	0.61 (0.43-0.87)	0.91 (0.55-1.50)
Q3	1.70 (1.36-2.13)	1.12 (0.78-1.59)	1.11 (0.85-1.46)	1.19 (0.75-1.89)
Q4	2.01 (1.62-2.48)	1.38 (0.97-1.96)	1.07 (0.80-1.44)	1.40 (0.88-2.23)
P for trend		0.055		0.164
NfL				
Q1 (Ref.)	0.38 (0.24-0.58)	1.00	0.20 (0.11-0.36)	1.00
Q2	0.77 (0.57-1.04)	1.24 (0.73-2.11)	0.40 (0.27-0.61)	1.20 (0.58-2.52)
Q3	2.09 (1.71-2.55)	2.70 (1.62-4.50)	1.12 (0.85-1.47)	2.97 (1.48-5.97)
Q4	3.53 (2.91-4.27)	3.88 (2.23-6.74)	2.42 (1.92-3.05)	6.56 (3.16-13.62)
P for trend		<0.001		<0.001
GFAP				
Q1 (Ref.)	0.45 (0.30-0.66)	1.00	0.18 (0.10-0.33)	1.00
Q2	0.84 (0.63-1.12)	1.48 (0.89-2.48)	0.43 (0.28-0.64)	1.76 (0.83-3.74)
Q3	1.77 (1.43-2.20)	2.41 (1.49-3.90)	1.01 (0.75-1.34)	3.00 (1.48-6.07)

Q4	3.41 (2.85-4.10)	3.60 (2.19-5.93)	2.33 (1.87-2.90)	6.04 (2.97-12.29)
P for trend		<0.001		<0.001

HRs are derived from Cox regression survival models, adjusted for age, sex, education, ischemic heart disease, atrial fibrillation, heart failure, cerebrovascular diseases, chronic kidney diseases, obesity, anaemia, hypertension, APOE genotype.

*For the A β 42/A β 40 ratio the highest quartile (Q4) was chosen as reference

Supplementary Table 5. Incidence rates (IR) per 100 person/year and hazard ratios (HR) for all-cause (n = 161) and Alzheimer´s dementia (AD) (n = 89) with 95% confidence intervals (CIs) by baseline biomarkers in the dementia-free analytical sample **considering only the first six years of follow-up.**

	All-cause dementia		AD dementia	
	IR (95%CI)	HR (95%CI)	IR (95%CI)	HR (95%CI)
Biomarkers				
Aβ42/Aβ40				
Q4 (Ref*)	0.51 (0.31-	1.00	0.20 (0.09-	1.00
Q3	0.93 (0.64-	1.38 (0.73-2.62)	0.51 (0.31-	2.03 (0.78-5.29)
Q2	2.09 (1.63-	1.88 (1.05-3.39)	1.24 (0.89-	3.20 (1.32-7.75)
Q1	2.16 (1.67-	1.79 (1.00-3.21)	1.19 (0.84-	2.77 (1.14-6.75)
P for trend		0.044		0.029
P-tau 181				
Q1 (Ref.)	0.24 (0.11-	1.00	0.07 (0.02-	1.00
Q2	0.69 (0.45-	2.12 (0.89-5.05)	0.46 (0.27-	5.14 (1.15-22.99)
Q3	1.30 (0.94-	2.41 (1.05-5.49)	0.78 (0.52-	5.59 (1.30-24.12)
Q4	3.75 (3.07-	4.50 (2.02-9.99)	1.98 (1.50-	9.81 (2.32-41.42)
P for trend		<0.001		0.001
P-tau 217				
Q1 (Ref.)	0.16 (0.07-	1.00	0.10 (0.03-	1.00
Q2	0.62 (0.39-	3.13 (1.15-8.48)	0.45 (0.26-	3.93 (1.11-13.92)
Q3	1.38 (1.01-	3.76 (1.46-9.66)	0.71 (0.46-	3.40 (0.99-11.63)
Q4	3.84 (3.14-	5.79 (2.28-	2.06 (1.57-	5.94 (1.78-19.75)
P for trend		<0.001		0.008
T-tau				
Q1 (Ref)	0.67 (0.43-	1.00	0.40 (0.23-	1.00
Q2	0.88 (0.60-	1.15 (0.63-2.10)	0.44 (0.26-	1.03 (0.47-2.29)
Q3	1.94 (1.49-	1.98 (1.17-3.36)	1.20 (0.86-	2.03 (1.03-4.03)
Q4	2.24 (1.74-	1.71 (1.01-2.87)	1.12 (0.78-	1.60 (0.81-3.18)
P for trend		0.029		0.111
NfL				
Q1 (Ref.)	0.10 (0.03-	1.00	0.03 (0.01-	1.00
Q2	0.23 (0.11-	1.59 (0.41-6.18)	0.13 (0.05-	2.99 (0.33-26.91)
Q3	1.55 (1.15-	5.70 (1.71-	0.76 (0.50-	10.55 (1.38-80.83)
Q4	4.22 (3.49-	8.09 (2.36-	2.50 (1.90-	21.31 (2.74-
P for trend		<0.001		<0.001
GFAP				
Q1 (Ref.)	0.20 (0.09-	1.00	0.07 (0.02-	1.00
Q2	0.44 (0.25-	1.61 (0.57-4.56)	0.20 (0.09-	2.05 (0.41-10.23)
Q3	1.60 (1.20-	3.13 (1.21-8.13)	0.84 (0.56-	4.74 (1.08-20.72)
Q4	3.67 (3.01-	4.13 (1.58-	2.18 (1.68-	8.07 (1.85-35.19)
P for trend		<0.001		<0.001

HRs are derived from Cox regression survival models, adjusted for age, sex, education, ischemic heart disease, atrial fibrillation, heart failure, cerebrovascular diseases, chronic kidney diseases, obesity, anaemia, hypertension, APOE genotype.

*For the A β 42/A β 40 ratio the highest quartile (Q4) was chosen as reference

Supplementary Table 6. Hazard ratios (HR) for all-cause and Alzheimer´s dementia (AD) with 95% confidence intervals (CIs) by baseline biomarkers in the dementia-free analytical sample with **inverse probability weighting**

	All-cause	AD dementia
	HR (95%CI)	HR (95%CI)
Biomarkers		
Aβ42/Aβ40		
Q4 (Ref*)	1.00	1.00
Q3	0.98 (0.69-1.39)	0.99 (0.62-1.59)
Q2	1.35 (0.98-1.85)	1.66 (1.11-2.47)
Q1	1.10 (0.79-1.53)	1.16 (0.75-1.78)
P for trend	0.319	0.212
P-tau 181		
Q1 (Ref.)	1.00	1.00
Q2	1.37 (0.90-2.09)	2.06 (1.12-3.81)
Q3	1.50 (1.00-2.25)	2.23 (1.24-4.01)
Q4	2.51 (1.67-3.77)	3.65 (2.03-6.56)
P for trend	<0.001	<0.001
P-tau217		
Q1 (Ref.)	1.00	1.00
Q2	1.73 (1.11-2.70)	1.80 (0.98-3.32)
Q3	1.98 (1.30-3.02)	1.97 (1.11-3.51)
Q4	2.85 (1.84-4.42)	3.29 (1.83-5.94)
P for trend	<0.001	<0.001
T-tau		
Q1 (Ref)	1.00	1.00
Q2	0.78 (0.56-1.10)	0.78 (0.50-1.20)
Q3	1.14 (0.83-1.56)	1.17 (0.78-1.76)
Q4	1.13 (0.83-1.54)	1.17 (0.78-1.75)
P for trend	0.128	0.163
NfL		
Q1 (Ref.)	1.00	1.00
Q2	1.12 (0.68-1.85)	1.14 (0.59-2.23)
Q3	2.19 (1.35-3.55)	2.32 (1.21-4.46)
Q4	3.36 (2.01-5.61)	5.10 (2.62-9.93)
P for trend	<0.001	<0.001
GFAP		
Q1 (Ref.)	1.00	1.00
Q2	1.55 (0.93-2.57)	1.86 (0.87-3.95)

Q3	2.51 (1.55-4.05)	3.26 (1.59-6.68)
Q4	3.55 (2.16-5.85)	5.68 (2.75-11.73)
P for trend	<0.001	<0.001

HRs are derived from Cox regression survival models adjusted for age, sex, education, ischemic heart disease, atrial fibrillation, heart failure, cerebrovascular diseases, chronic kidney disease, obesity, anaemia, hypertension, APOE genotype.

*For the A β 42/A β 40 ratio the highest quartile (Q4) was chosen as reference.

Supplementary Table 7. Predictive performance measures of blood biomarkers of AD for detecting 10-year all-cause and AD dementia in the **training set in the SNAC-K cohort**

		Training set					
		All-cause dementia					
		AUC (95%CI)	Correctly classified participants (accuracy) (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Biomarker	Cutoff						
Aβ42/40	0.057	58.1 (54.2;62.0)	53.3 (51.1;55.6)	68.9 (62.5;75.3)	51.3 (48.8;53.7)	15.6 (13.2; 17.9)	92.7 (90.8; 94.4)
P-tau 181, pg/mL	1.512	69.3 (65.6;73.0)	67.3 (65.0;69.4)	62.6 (55.9;69.1)	67.9 (65.6;70.1)	20.3 (17.1; 23.4)	93.3 (91.7; 94.7)
P-tau 217, pg/mL	0.134	72.6 (69.0;76.1)	67.9 (65.8-70.1)	69.5 (63.0;75.8)	67.7 (65.5;70.0)	21.9 (18.8;25.2)	94.4 (93.0;95.8)
T-tau, pg/mL	0.832	54.4 (50.4;58.4)	52.1 (49.8;54.3)	62.1 (55.4;68.9)	50.7 (48.3;53.1)	14.1 (11.9;16.6)	91.1 (89.1;93.0)
NfL, pg/mL	20.171	75.7 (72.7;78.8)	64.1 (61.9;66.3)	78.8 (72.9;84.4)	62.2 (59.8;64.6)	21.4 (18.5;24.4)	95.7 (94.5;96.9)
GFAP, pg/mL	142.515	74.1 (71.0;77.3)	66.9 (64.8;69.1)	73.4 (67.2;79.4)	66.1 (63.7;68.4)	22.1 (19.0;25.2)	95.0 (93.7;96.3)
		AD dementia					
Aβ42/40	0.056	58.9 (53.9;63.6)	52.3 (50.0;54.7)	69.6 (60.9;78.0)	51.1 (48.6;53.5)	9.3 (7.4;11.2)	95.9 (94.5;97.2)
P-tau 181, pg/mL	1.410	71.5 (66.9;76.0)	63.4 (61.2;65.8)	66.1 (57.4;74.5)	63.2 (60.9;65.6)	11.5 (9.1;13.9)	96.3 (95.1;97.4)
P-tau 217, pg/mL	0.143	74.7 (70.3;79.0)	68.9 (66.8;71.2)	73.2 (65.1;81.2)	68.6 (66.4;71.0)	14.4 (11.6;17.3)	97.3 (96.3;98.2)

T-tau, pg/mL	0.846	57.9 (52.6;63.1)	53.2 (50.8;55.7)	67.0 (57.9;75.2)	52.3 (49.8;54.8)	9.2 (7.3;11.1)	95.7 (94.2;97.0)
NfL, pg/mL	21.399	78.0 (74.5;81.3)	64.2 (61.9;66.5)	85.7 (79.0;91.8)	62.6 (60.2;65.1)	14.2 (11.6;16.8)	98.38 (97.6;99.1)
GFAP, pg/mL	148.737	77.0 (72.9;80.7)	66.1 (63.8;68.4)	75.9 (67.7;83.7)	65.4 (63.0;67.7)	13.6 (11.0;16.3)	97.4 (96.4;98.3)

Supplementary Table 8. Predictive performance measures of different combinations of blood biomarkers of AD for detecting 10-year all-cause and AD dementia

		AUC (95%CI)	Correctly classified participants (accuracy) (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
		All-cause dementia					
Number of altered biomarkers	1 biomarker	60.9 (45.8- 76.4)	66.8 (61.1- 72.1)	54.6 (25.0- 85.7)	67.3 (61.5- 72.9)	6.4 (2.1- 11.6)	97.3 (94.7- 99.5)
	2 biomarkers	71.2 (57.3- 83.9)	77.2 (71.5- 82.1)	64.3 (37.5- 88.9)	78.0 (72.5- 83.0)	15.0 (6.5- 24.5)	97.3 (94.7- 99.5)
	3 biomarkers	83.78 (78.5- 88.4)	79.7 (74.7- 84.2)	90.2 (81.3- 97.9)	77.4 (71.9- 82.7)	46.5 (36.4- 56.4)	97.3 (94.7- 99.5)
Combinations of biomarkers	P-tau 217 + NfL	79.0 (73.4- 84.3)	81.3 (77.7- 84.9)	75.8 (65.0- 85.9)	82.3 (78.5- 86.2)	43.1 (34.3- 52.4)	95.1 (92.6- 97.3)
	P-tau 217+ GFAP	76.9 (71.3- 82.8)	82.0 (78.6- 85.7)	69.7 (58.9- 80.7)	84.2 (80.5- 87.8)	43.8 (34.7- 53.7)	94.0 (91.3- 96.5)
	GFAP+ NfL	77.2 (71.7- 82.5)	77.2 (73.5- 81.1)	77.3 (67.1- 87.1)	77.2 (72.9- 81.4)	37.5 (29.6- 45.7)	95.1 (92.4- 97.4)
		AD dementia					
Number of altered biomarkers	1 biomarker	74.3 (59.2- 85.5)	69.1 (63.7- 74.8)	80.0 (50.0- 100.0)	68.7 (62.9- 74.4)	9.2 (3.5- 15.8)	98.9 (97.0- 100.0)
	2 biomarkers	76.9 (62.2- 88.3)	74.2 (68.9- 79.5)	80.0 (50.0- 100.0)	73.9 (68.4- 79.3)	11.6 (4.6- 19.7)	98.9 (97.1- 100.0)
	3 biomarkers	81.3 (73.7- 87.5)	73.6 (68.2- 78.9)	90.5 (76.2- 100.0)	72.1 (66.4- 77.7)	22.1 (13.9- 31.1)	98.9 (97.1- 100.0)

Combinations of biomarkers	P-tau 217 + NfL	65.3 (56.9-73.7)	74.6 (70.5-78.7)	54.1 (37.8-70.0)	76.6 (72.3-80.8)	18.4 (11.5-26.1)	94.5 (91.8-96.8)
	P-tau 217+ GFAP	71.2 (63.3-79.5)	78.7 (74.8-82.5)	62.2 (46.7-78.3)	80.3 (76.2-84.2)	23.5 (15.6-32.2)	95.6 (93.3-97.8)
	GFAP+ NfL	66.8 (58.8-75.1)	72.9 (68.6-77.2)	59.3 (43.9-75.0)	74.2 (69.8-78.6)	18.3 (11.9-25.8)	94.9 (92.3-97.3)

Supplementary Table 9. Predictive performance measures of blood biomarkers of AD for detecting 10-year all-cause and AD dementia in SNAC-K participants with memory complaints

Biomarker	AUC (95%CI)	Correctly classified participants (accuracy) (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
All-cause dementia						
A β 42/40	66.4 (58.3-73.9)	52.2 (46.5-57.8)	74.5 (62.5-86.0)	47.6 (41.4-54.0)	22.45 (16.5-28.7)	90.2 (84.9-94.9)
P-tau181, pg/mL	81.6 (75.9-87.0)	72.1 (67.1-77.1)	80.4 (68.6-90.9)	70.4 (64.6-75.9)	35.7 (27.1-44.6)	94.6 (91.2-97.8)
P-tau217, pg/mL	80.2 (73.8-86.0)	71.4 (66.5-76.4)	76.5 (64.2-87.8)	70.4 (64.8-75.9)	34.5 (25.9-43.6)	93.6 (89.9-96.9)
T-tau, pg/mL	68.8 (60.5-76.5)	57.1 (51.5-62.8)	76.5 (64.6-88.0)	53.2 (47.1-59.3)	25.0 (18.5-31.9)	91.7 (86.9-96.0)
NfL, pg/mL	80.1 (73.9-85.8)	67.8 (62.5-72.8)	88.2 (78.7-96.3)	63.6 (57.7-69.4)	33.1 (25.3-41.1)	96.4 (93.3-98.8)
GFAP, pg/mL	74.9 (67.3-81.7)	65.1 (59.5-70.4)	78.4 (66.7-89.3)	62.4 (56.2-68.1)	29.9 (22.2-37.8)	93.4 (89.4-96.9)
AD-dementia						
A β 42/40	61.9 (52.9-70.6)	53.6 (47.9-59.6)	71.4 (53.6-87.5)	51.6 (45.5-57.8)	14.0 (8.6-20.0)	94.2 (90.0-97.8)
P-tau181, pg/mL	73.3 (64.9-81.5)	60.3 (54.6-66.0)	78.6 (62.5-93.3)	58.3 (52.2-64.3)	17.2 (10.9-23.9)	96.1 (93.0-98.8)
P-tau217, pg/mL	75.9 (67.0-84.4)	66.0 (60.6-71.3)	71.4 (54.2-88.0)	65.4 (59.4-71.2)	18.5 (11.4-26.1)	95.4 (92.1-98.3)
T-tau, pg/mL	54.7 (44.1-64.7)	48.9 (43.3-54.6)	67.9 (50.0-84.4)	46.9 (40.7-53.0)	12.3 (7.4-17.6)	93.0 (88.1-97.0)
NfL, pg/mL	69.0 (58.7-78.5)	62.1 (56.4-67.4)	67.9 (50.0-84.6)	61.4 (55.4-67.3)	16.2 (9.6-23.1)	94.6 (90.9-97.6)
GFAP, pg/mL	74.7 (65.6-82.7)	65.6 (59.9-70.9)	82.1 (66.7-95.8)	63.8 (57.8-69.6)	20.0 (12.8-27.4)	97.0 (94.3-99.4)

Supplementary Table 10. Analytical validation and compatibility assessment of Simoa ALZpath p-Tau 217 in SRX

Test	Internal Result SR-X *	Compatibility report with SR-X**	Validation report HD-X***
LOD	0.0003-0.0004 pg/ml	0.0004 pg/mL	0.0003-0.0021 pg/ml
Analytical LLOQ	0.0020-0.0030 pg/ml	0,00433 pg/mL	0.00326 pg/mL
Functional LLOQ	0.0060-0.0090 pg/mL	0,01299 pg/mL	0,00978 pg/mL
Precision profile	Mean Total CV (%) Within Run CV (%): 11 Between Run CV (%):13.4 Cohort Within 39 Run CV (%): 13.3 Cohort Between 39 Run CV (%): 17.6 Control1/2 Within 39 Run CV (%): 8.8/6.1 Controls1/2 Between 39 Run CV (%): 12/11.2		Mean Total CV (%):5.3 Within Run CV (%): 4 Between Run CV (%):10
Spike and Recovery	EDTA plasma, peptide spike: 31 % range: 38-43% EDTA plasma, CSF spike: 54%, range 51-57% Serum, peptide spike: 37 % range:31-40% Serum, CSF spike: 49%, range 47-51%		EDTA plasma, peptide spike: 22% range:17-28% EDTA plasma, CSF spike: 50%, range 41-63%
Dilution Linearity	EDTA plasma 3x-24x: 100% (range: 80-120%) Serum 3x-24x: 101% (range 93-108%)		EDTA plasma 3x-24x: 125% (range 101-151%)

Internal Result SR-X*: analytical parameters generated at the Affinity Proteomics Unit, are compared with the reports generated by Quanterix and available online: <https://www.quanterix.com/simoa-assay-kits/simoa-alzpath-p-tau-217-assay/>

Compatibility report with SR-X:** data from the report published by Quanterix

Validation report HD-X*:** data from the report published by Quanterix .

Supplementary Table 11. Intra and inter assay precision expressed as coefficient of variation (% CV).

	Sample pool			Control 1			Control 2		
	Conc	Within run	Between run	Conc	Within run	Between run	Conc	Within run	Between run
Aβ-40	120.4	2.2	5.2	10.1	3.8	6.8	156.1	1.6	3.7
Aβ-42	6.6	4.8	7.4	3.4	6.1	8.2	76.8	2.1	4.7
p-tau 181	1.5	9.2	13.6	3.6	4.9	7.9	98.0	3.2	5.9
p-tau 217	0.14	13.3	17.6	0.8	8.8	12.0	7.7	6.1	11.2
t-tau	0.9	10.7	12.3	1.6	5.3	8.5	61.7	2.0	5.2
NfL	24.1	7.6	11.6	4.1	11.5	17.6	409.8	4.5	7.4
GFAP	194	13.1	21.4	89.8	11.4	17.4	10311	5.8	9.7

Conc: average of the concentrations (pg/mL) obtained in 39 runs.

Within run: CV (%) calculated on the triplicate pool, control 1 and control 2 included in each run (plate). The average CV for all runs is reported.

Between run: CV (%) calculated on the concentration values obtained for pool, control 1 and control 2 across all the runs (plate).

