Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

General Psychiatry

Supplementary Materials

Table S1. Accuracy of blood-based biomarkers for detecting brain amyloid pathology.

Biomarkers	Method	Subjects	Standard	AUC (Aβ+/Aβ-)	References
Aβ42	SIMOA	274 NC, 174 SCD, 214 MCI, 57 AD	CSF	0.65	Janelidze et al. 2016 [1]
	SIMOA	248 SCD	CSF, PET	CSF: 0.66; PET: 0.66	Verberk et al. 2018 [2]
	SIMOA	276 SMC	PET	0.68	Vergallo et al. 2019 [3]
	SIMOA	441 non-dementia	PET	0.59	Keshavan et al. 2021 [4]
	SIMOA	238 NC, 118 SCD, 135 MCI, 118 Dementia	PET	0.59	Pan et al. 2023 [5]
	IP-MS	218 NC, 97 MCI, 58 AD	PET	Cohort 1: 0.87 Cohort 2: 0.72	Nakamura et al. 2018 [6]
Aβ42/40	SIMOA	441 non-dementia	PET	0.62	Keshavan et al. 2021 [4]
	SIMOA	14 NC, 30 CIND, 9 VaD, 15 AD	PET	0.82	Tanaka et al. 2021 [7]
	SIMOA	182 NC, 104 MCI	CSF, PET	CSF: 0.69; PET: 0.65	Janelidze et al. 2021 [8]
	SIMOA	248 SCD	CSF, PET	CSF: 0.77; PET: 0.68	Verberk et al. 2018 [2]
	SIMOA	161 NC, 38 MCI	PET	0.79	De Meyer et al. 2020 [9]
	SIMOA	276 SMC	PET	0.79	Vergallo et al. 2019 [3]
	SIMOA	274 NC, 174 SCD, 214 MCI, 57 AD	CSF	0.68	Janelidze et al. 2016 [1]
	SIMOA	238 NC, 118 SCD, 135 MCI, 118 Dementia	PET	0.65	Pan et al. 2023 [5]
	IP-MS	182 NC, 104 MCI	CSF, PET	CSF: 0.85; PET: 0.83	Janelidze et al. 2021 [8]
	IP-MS	218 NC, 97 MCI, 58 AD	PET	Cohort 1: 0.97 Cohort 2: 0.84	Nakamura et al. 2018 [10]
	IP-MS	158 NC	PET	0.88	Schindler et al. 2019 [11]
P-tau181	SIMOA	441 non-dementia	PET	0.70	Keshavan et al. 2021 [4]
	SIMOA	400 NC, 558 MCI, 219 AD	PET	0.77	Karikari et al. 2021 [12]
	SIMOA	113 NC, 45 MCI,	PET	0.88	Karikari et al. 2020 [13]

		33 AD, 8 non-AD, 27 young adult			
	SIMOA	69 NC, 47 MCI, 56 AD, 190 non-AD	PET	0.91	Thijssen et al. 2020 [14]
	SIMOA	238 NC, 118 SCD, 135 MCI, 118 Dementia	PET	0.70	Pan et al. 2023 [5]
	MSD	172 NC, 57 MCI, 40 AD	PET	0.80	Mielke et al. 2018 [15]
	MSD	219 NC, 125 MCI,	PET	0.81	Janelidze et al. 2020 [16]
	IP-MS	73 NC, 45 MCI, 8 AD	PET	Cohort 1: 0.95 Cohort 2: 0.72	Barthelemy et al. 2020 [17]
P-tau217	MSD	301 NC, 178 MCI, 121 AD, 99 non-AD	PET	0.87	Palmqvist et al. 2020 [18]
P-tau231	SIMOA	159 NC, 54 MCI	PET	NC: 0.83; MCI: 0.80	Ashton et al. 2021 [19]

Note: Aβ+ = amyloid-β positive; Aβ- = amyloid-β negative; AD, Alzheimer's disease; AUC, area under the receiver operating characteristic curves; CIND, cognitive impairment - no dementia; CSF, cerebrospinal fluid; IP-MS, Immunoprecipitation followed by mass spectrometry; MCI, mild cognitive impairment; MSD, Meso Scale Discovery; NC, cognitively normal adults; PET, positron emission tomography; SCD, subjective cognitive decline; SIMOA, single molecule array; SMC, subjective memory complaint; VaD, vascular dementia.

Table S2. Microbial metabolites associated with AD.

Biomarkers	Male	Female	References
Bile acid	NC versus AD: T-β-muricholic acid↓ NC versus AD: lithocholic acid↓	NC versus AD: glycoursodeoxycholic acid, glycodeoxycholic acid, α-muricholic acid, β-muricholic acid, and ω-muricholic acid↑	Wu et al. 2020 [20]
Short chain fatty acid	MCI versus AD: formic acid, acetic acid, propanoic acid, 2-methylbutyric acid, and isovaleric acid↓ NC versus MCI or AD: formic acid, acetic acid, propanoic acid, 2-methylbutyric acid, Butyric acid, Isovaleric acid, Valeric acid↓		Wu et al. 2021 [21]
Neurotransmitter	NC versus AD: serotonin, 5-methoxytryptophan, indole derivatives↓; indole-3-pyruvic acid↑		Wu et al. 2021 [21]
Steroid	NC versus AD: 19-Oxoandrost-4-ene-3,17-dione, 1α,25-vitamin D3↓; Trigofoenoside F, Angeloylbarringtogenol C, Sagittariol↑		Tynkkynen et al. 2018 [22]

Note: ↑ = increased in MCI and/or AD compared to control group; ↓ = Decreased in MCI and/or AD compared to control group.

Abbreviations: AD = Alzheimer's disease, MCI = mild cognitive impairment, NC = cognitively normal adults.

Table S3. Comparison of effectiveness of ERP components in differentiating cognitive decline stages.

ERP components	Comparison	Sensitivity	Specificity	References
P50 amplitude	MCI versus AD	81%	77%	Kozlowska et al. 2016 [23]
P200 latency	Progressive MCI versus stable MCI	88%	77%	Lijffijt et al. 2009 [24]
N2b latency	Progressive MCI versus stable MCI	75%	69%	Missonnier et al. 2007 [25]
N2b latency	NC versus mdaMCI	83%	81%	Fernandez et al. 2013 [26]
N2pc latency	NC versus mdaMCI	92%	84%	Cespón et al. 2015 [27]
P3b latency	NC versus MCI	80%	100%	Cespón et al. 2015 [28]
N400 amplitude	NC versus AD	55%	91%	Parra et al. 2012 [29]

Abbreviations: AD = Alzheimer's disease, ERP = Event Related Potential, MCI = mild cognitive impairment, mdaMCI = multiple-domain amnestic MCI, NC = cognitively normal adults.
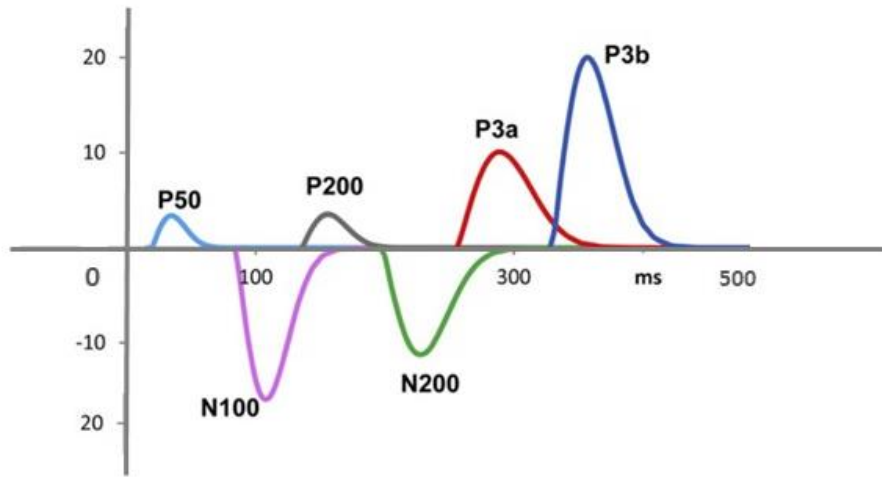
Figure S1. Diagram of Event Related Potential (ERP) Components.
The waveforms and latencies of common ERP components related to early
recognition of cognitive decline.

References:

[1] Janelidze S, Stomrud E, Palmqvist S, Zetterberg H, van Westen D, Jeromin A, Song L, Hanlon D, Tan Hehir CA, Baker D, Blennow K, Hansson O (2016) Plasma β-amyloid in Alzheimer's disease and vascular disease. *Sci Rep* **6**, 26801.

[2] Verberk IMW, Slot RE, Verfaillie SCJ, Heijst H, Prins ND, van Berckel BNM, Scheltens P, Teunissen CE, van der Flier WM (2018) Plasma Amyloid as Prescreener for the Earliest Alzheimer Pathological Changes. *Ann Neurol* **84**, 648–658.

[3] Vergallo A, Mégret L, Lista S, Cavedo E, Zetterberg H, Blennow K, Vanmechelen E, De Vos A, Habert M-O, Potier M-C, Dubois B, Neri C, Hampel H, INSIGHT-preAD study group, Alzheimer Precision Medicine Initiative (APMI) (2019) Plasma amyloid β 40/42 ratio predicts cerebral amyloidosis in cognitively normal individuals at risk for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* **15**, 764–775.

[4] Keshavan A, Pannee J, Karikari TK, Rodriguez JL, Ashton NJ, Nicholas JM, Cash DM, Coath W, Lane CA, Parker TD, Lu K, Buchanan SM, Keuss SE, James S-N, Murray-Smith H, Wong A, Barnes A, Dickson JC, Heslegrave A, Portelius E, Richards M, Fox NC, Zetterberg H, Blennow K, Schott JM (2021) Population-based blood screening for preclinical Alzheimer's disease in a British birth cohort at age 70. *Brain: A Journal of Neurology* **144**, 434–449.

[5] Pan F, Huang Y, Cai X, Wang Y, Guan Y, Deng J, Yang D, Zhu J, Zhao Y, Xie F, Fang Z, Guo Q (2023) Integrated algorithm combining plasma biomarkers and cognitive assessments accurately predicts brain β-amyloid pathology. *Communications Medicine* **3**, 65.

[6] Nakamura A, Kaneko N, Villemagne VL, Kato T, Doecke J, Doré V, Fowler C, Li Q-X, Martins R, Rowe C, Tomita T, Matsuzaki K, Ishii K, Ishii K, Arahata Y, Iwamoto S, Ito K, Tanaka K, Masters CL, Yanagisawa K (2018) High performance plasma amyloid-β biomarkers for Alzheimer's disease. *Nature* **554**, 249–254.

[7] Tanaka T, Ruifen JC, Nai Y-H, Tan CH, Lim CZJ, Zhang Y, Stephenson MC, Hilal S, Saridin FN, Gyanwali B, Villaraza S, Robins EG, Ihara M, Schöll M, Zetterberg H, Blennow K, Ashton NJ, Shao H, Reilhac A, Chen C (2021) Head-to-head comparison of amplified plasmonic exosome Aβ42 platform and single-molecule array immunoassay in a memory clinic cohort. *Eur J Neurol* **28**, 1479–1489.

[8] Janelidze S, Teunissen CE, Zetterberg H, Allué JA, Sarasa L, Eichenlaub U, Bittner T, Ovod V, Verberk IMW, Toba K, Nakamura A, Bateman RJ, Blennow K, Hansson O (2021) Head-to-Head Comparison of 8 Plasma Amyloid-β 42/40 Assays in Alzheimer Disease. *JAMA Neurol* **78**, 1375–1382.

[9] De Meyer S, Schaeverbeke JM, Verberk IMW, Gille B, De Schaepdryver M, Luckett ES, Gabel S, Bruffaerts R, Mauroo K, Thijssen EH, Stoops E, Vanderstichele HM, Teunissen CE, Vandenberghe R, Poesen K (2020) Comparison of ELISA- and SIMOA-based quantification of plasma Aβ ratios for early detection of cerebral amyloidosis. *Alzheimer's Research & Therapy* **12**, 162.

[10] Nakamura A, Kaneko N, Villemagne VL, Kato T, Doecke J, Doré V, Fowler C, Li Q-X, Martins R, Rowe C, Tomita T, Matsuzaki K, Ishii K, Ishii K, Arahata Y, Iwamoto S, Ito K, Tanaka K, Masters CL, Yanagisawa K (2018) High performance plasma amyloid-β biomarkers for Alzheimer's disease. *Nature* **554**, 249–254.

[11] Schindler SE, Bollinger JG, Ovod V, Mawuenyega KG, Li Y, Gordon BA, Holtzman DM, Morris JC, Benzinger TLS, Xiong C, Fagan AM, Bateman RJ (2019) High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. *Neurology* **93**, e1647–e1659.

[12] Karikari TK, Benedet AL, Ashton NJ, Lantero Rodriguez J, Snellman A, Suárez-Calvet M, Saha-Chaudhuri P, Lussier F, Kvartsberg H, Rial AM, Pascoal TA, Andreasson U, Schöll M, Weiner MW, Rosa-Neto P, Trojanowski JQ, Shaw LM, Blennow K, Zetterberg H, Alzheimer's Disease Neuroimaging Initiative (2021) Diagnostic performance and prediction of clinical progression of plasma phospho-tau181 in the Alzheimer's Disease Neuroimaging Initiative. *Mol Psychiatry* **26**, 429–442.

[13] Karikari TK, Pascoal TA, Ashton NJ, Janelidze S, Benedet AL, Rodriguez JL, Chamoun M, Savard M, Kang MS, Therriault J, Schöll M, Massarweh G, Soucy J-P, Höglund K, Brinkmalm G, Mattsson N, Palmqvist S, Gauthier S, Stomrud E, Zetterberg H, Hansson O, Rosa-Neto P, Blennow K (2020) Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *The Lancet Neurology* **19**, 422–433.

[14] Thijssen EH, La Joie R, Wolf A, Strom A, Wang P, Iaccarino L, Bourakova V, Cobigo Y, Heuer H, Spina S, VandeVrede L, Chai X, Proctor NK, Airey DC, Shcherbinin S, Duggan Evans C, Sims JR, Zetterberg H, Blennow K, Karydas AM, Teunissen CE, Kramer JH, Grinberg LT, Seeley WW, Rosen H, Boeve BF, Miller BL, Rabinovici GD, Dage JL, Rojas JC, Boxer AL, Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) investigators (2020) Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. *Nat Med* **26**, 387–397.

[15] Mielke MM, Hagen CE, Xu J, Chai X, Vemuri P, Lowe VJ, Airey DC, Knopman DS, Roberts RO, Machulda MM, Jack CR, Petersen RC, Dage JL (2018) Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association* **14**, 989–997.

[16] Janelidze S, Mattsson N, Palmqvist S, Smith R, Beach TG, Serrano GE, Chai X, Proctor NK, Eichenlaub U, Zetterberg H, Blennow K, Reiman EM, Stomrud E, Dage JL, Hansson O (2020) Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. *Nat Med* **26**, 379–386.

[17] Barthélemy NR, Horie K, Sato C, Bateman RJ (2020) Blood plasma phosphorylated-tau isoforms track CNS change in Alzheimer's disease. *J Exp Med* **217**, e20200861.

[18] Palmqvist S, Janelidze S, Quiroz YT, Zetterberg H, Lopera F, Stomrud E, Su Y, Chen Y, Serrano GE, Leuzy A, Mattsson-Carlgren N, Strandberg O, Smith R, Villegas A, Sepulveda-Falla D, Chai X, Proctor NK, Beach TG, Blennow K, Dage JL, Reiman EM, Hansson O (2020) Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders. *Jama* **324**, 772–781.

[19] Ashton NJ, Pascoal TA, Karikari TK, Benedet AL, Lantero-Rodriguez J, Brinkmalm G, Snellman A, Schöll M, Troakes C, Hye A, Gauthier S, Vanmechelen E, Zetterberg H, Rosa-Neto P, Blennow K (2021) Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. *Acta Neuropathol* **141**, 709–724.

[20] Wu J, Zhu X, Lin H, Chen Z, Tang H, Wang Y (2020) Gender differences in the bile acid profiles of APP/PS1 transgenic AD mice. *Brain Res Bull* **161**, 116–126.

[21] Wu L, Han Y, Zheng Z, Peng G, Liu P, Yue S, Zhu S, Chen J, Lv H, Shao L, Sheng Y, Wang Y, Li L, Li L, Wang B (2021) Altered Gut Microbial Metabolites in Amnestic Mild Cognitive Impairment and Alzheimer's Disease: Signals in Host-Microbe Interplay. *Nutrients* **13**, 228.

[22] Tynkkynen J, Chouraki V, van der Lee SJ, Hernesniemi J, Yang Q, Li S, Beiser A, Larson MG, Sääksjärvi K, Shipley MJ, Singh-Manoux A, Gerszten RE, Wang TJ, Havulinna AS, Würtz P, Fischer K, Demirkan A, Ikram MA, Amin N, Lehtimäki T, Kähönen M, Perola M, Metspalu A, Kangas AJ, Soininen P, Ala-Korpela M, Vasan RS, Kivimäki M, van Duijn CM, Seshadri S, Salomaa V (2018) Association of branched-chain amino acids and other circulating metabolites with risk of incident dementia and Alzheimer's disease: A prospective study in eight cohorts. *Alzheimers Dement* **14**, 723–733.

[23] Kozlowska K, Melkonian D, Spooner CJ, Scher S, Meares R (2017) Cortical arousal in children and adolescents with functional neurological symptoms during the auditory oddball task. *Neuroimage Clin* **13**, 228–236.

[24] Lijffijt M, Lane SD, Meier SL, Boutros NN, Burroughs S, Steinberg JL, Moeller FG, Swann AC (2009) P50, N100, and P200 sensory gating: relationships with behavioral inhibition, attention, and working memory. *Psychophysiology* **46**, 1059–1068.

[25] Missonnier P, Deiber M-P, Gold G, Herrmann FR, Millet P, Michon A, Fazio-Costa L, Ibañez V, Giannakopoulos P (2007) Working memory load-related electroencephalographic parameters can differentiate progressive from stable mild cognitive impairment. *Neuroscience* **150**, 346–356.

[26] Fernandez R, Monacelli A, Duffy CJ (2013) Visual motion event related potentials distinguish aging and Alzheimer's disease. *J Alzheimers Dis* **36**, 177–183.

[27] Cespón J, Galdo-Álvarez S, Pereiro AX, Díaz F (2015) Differences between mild cognitive impairment subtypes as indicated by event-related potential correlates of cognitive and motor processes in a Simon task. *J Alzheimers Dis* **43**, 631–647.

[28] Cespón J, Galdo-Álvarez S, Díaz F (2015) Inhibition deficit in the spatial tendency of the response in multiple-domain amnestic mild cognitive

Supplemental material

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance placed on this supplemental material which has been supplied by the author(s)

General Psychiatry

impairment. An event-related potential study. *Front Aging Neurosci* **7**, 68.

[29] Parra MA, Ascencio LL, Urquina HF, Manes F, Ibáñez AM (2012) P300 and neuropsychological assessment in mild cognitive impairment and Alzheimer dementia. *Front Neurol* **3**, 172.