



















- [11] Casanova R, Varma S, Simpson B, Kim M, An Y, Saldana S, Riveros C, Moscato P, Griswold M, Sonntag D, Wahrheit J, Klavins K, Jonsson PV, Eiriksdottir G, Aspelund T, Launer LJ, Gudnason V, Quigley CL, Thambisetty M (2016) Blood metabolite markers of preclinical Alzheimer's disease in two longitudinally followed cohorts of older individuals. *Alzheimers Dement* **12**, 815-822.
- [12] Proitsi P, Kim M, Whitley L, Pritchard M, Leung R, Soininen H, Kloszewska I, Mecocci P, Tsolaki M, Vellas B, Sham P, Lovestone S, Powell JF, Dobson RJ, Legido-Quigley C (2015) Plasma lipidomics analysis finds long chain cholesteryl esters to be associated with Alzheimer's disease. *Transl Psychiatry* **5**, e494.
- [13] Proitsi P, Kim M, Whitley L, Simmons A, Sattlecker M, Velayudhan L, Lupton MK, Soininen H, Kloszewska I, Mecocci P, Tsolaki M, Vellas B, Lovestone S, Powell JF, Dobson RJ, Legido-Quigley C (2016) Association of blood lipids with Alzheimer's disease: A comprehensive lipidomics analysis. *Alzheimers Dement*, doi: 10.1016/j.jalz.2016.08.003
- [14] Lovestone S, Francis P, Strandgaard K (2007) Biomarkers for disease modification trials—the innovative medicines initiative and AddNeuroMed. *J Nutr Health Aging* **11**, 359-361.
- [15] Whitley L, Godzien J, Ruperez FJ, Legido-Quigley C, Barbas C (2012) In-vial dual extraction for direct LC-MS analysis of plasma for comprehensive and highly reproducible metabolic fingerprinting. *Anal Chem* **84**, 5992-5999.
- [16] Astarita G, Jung KM, Vasilevko V, Dipatrizio NV, Martin SK, Cribbs DH, Head E, Cotman CW, Piomelli D (2011) Elevated stearoyl-CoA desaturase in brains of patients with Alzheimer's disease. *PLoS One* **6**, e24777.
- [17] Chan RB, Oliveira TG, Cortes EP, Honig LS, Duff KE, Small SA, Wenk MR, Shui G, Di Paolo G (2012) Comparative lipidomic analysis of mouse and human brain with Alzheimer disease. *J Biol Chem* **287**, 2678-2686.
- [18] Engelborghs S, Maertens K, Vloeberghs E, Beerts T, Somers N, Marien P, De Deyn PP (2006) Neuropsychological and behavioural correlates of CSF biomarkers in dementia. *Neurochem Int* **48**, 286-295.
- [19] Kester MI, Goos JDC, Teunissen CE, Benedictus MR, Bouwman FH, Wattjes MP, Barkhof F, Scheltens P, van der Flier WM (2014) Associations between cerebral small-vessel disease and Alzheimer disease pathology as measured by cerebrospinal fluid biomarkers. *JAMA Neurol* **71**, 855-862.
- [20] Filippov V, Song MA, Zhang KL, Vinters HV, Tung S, Kirsch WM, Yang J, Duerksen-Hughes PJ (2012) Increased ceramide in brains with Alzheimer's and other neurodegenerative diseases. *J Alzheimers Dis* **29**, 537-547.
- [21] Malaplate-Armand C, Florent-Bechard S, Youssef I, Koziel V, Sponne I, Kriem B, Leininger-Muller B, Olivier JL, Oster T, Pillot T (2006) Soluble oligomers of amyloid-beta peptide induce neuronal apoptosis by activating a cPLA2-dependent sphingomyelinase-ceramide pathway. *Neurobiol Dis* **23**, 178-189.
- [22] Ogretmen B, Hannun YA (2004) Biologically active sphingolipids in cancer pathogenesis and treatment. *Nat Rev Cancer* **4**, 604-616.
- [23] Ellis B, Hye A, Snowden SG (2015) Metabolic modifications in human biofluids suggest the involvement of sphingolipid, antioxidant, and glutamate metabolism in Alzheimer's disease pathogenesis. *J Alzheimers Dis* **46**, 313-327.
- [24] Morad SAF, Cabot MC (2013) Ceramide-orchestrated signalling in cancer cells. *Nat Rev Cancer* **13**, 51-65.
- [25] Puglielli L, Ellis BC, Saunders AJ, Kovacs DM (2003) Ceramide stabilizes beta-site amyloid precursor protein-cleaving enzyme 1 and promotes amyloid beta-peptide biogenesis. *J Biol Chem* **278**, 19777-19783.
- [26] Swerdlow RH (2007) Is aging part of Alzheimer's disease, or is Alzheimer's disease part of aging? *Neurobiol Aging* **28**, 1465-1480.
- [27] Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ (2013) Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. *Lancet Neurol* **12**, 207-216.
- [28] Mielke MM, Haughey NJ, Bandaru VVR, Schech S, Carrick R, Carlson MC, Morrison Miller MI, Ceritoglu C, Brown T, Albert M, Lyketsos CG (2010) Plasma ceramides are altered in mild cognitive impairment and predict cognitive decline and hippocampal volume loss. *Alzheimers Dement* **6**, 378-385.
- [29] Simpson BN, Kim M, Chuang Y-F, Beason-Held L, Kitner-Triolo M, Kaut M, Lirette ST, Windham BG, Griswold ME, Legido-Quigley C, Thambisetty M (2016) Blood metabolite markers of cognitive performance and brain function in aging. *J Cereb Blood Flow Metab* **36**, 1212-1223.
- [30] Fitzpatrick AL, Irizarry MC, Cushman M, Jenny NS, Chi GC, Koro C (2014) Lipoprotein-associated phospholipase A2 and risk of dementia in the Cardiovascular Health Study. *Atherosclerosis* **235**, 384-391.
- [31] Nguyen LN, Ma D, Shui G, Wong P, Cazenave-Gassiot A, Zhang X, Wenk MR, Goh EL, Silver DL (2014) Mfsd2a is a transporter for the essential omega-3 fatty acid docosahexaenoic acid. *Nature* **509**, 503-506.
- [32] Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT (2015) MIND diet associated with reduced incidence of Alzheimer's disease. *Alzheimers Dement* **11**, 1007-1014.
- [33] Tully AM, Roche HM, Doyle R, Fallon C, Bruce I, Lawlor B, Coakley D, Gibney MJ (2003) Low serum cholesteryl ester-docosahexaenoic acid levels in Alzheimer's disease: A case-control study. *Br J Nutr* **89**, 483-489.
- [34] Kidd PM (2007) Omega-3 DHA and EPA for cognition, behavior, and mood: Clinical findings and structural-functional synergies with cell membrane phospholipids. *Altern Med Rev* **12**, 207-227.
- [35] Yu Z, Zhai G, Singmann P, He Y, Xu T, Prehn C, Romisch-Margl W, Lattka E, Gieger C, Soranzo N, Heinrich J, Standl M, Thiering E, Mittelstrass K, Wichmann HE, Peters A, Suhre K, Li Y, Adamski J, Spector TD, Illig T, Wang-Sattler R (2012) Human serum metabolic profiles are age dependent. *Aging Cell* **11**, 960-967.
- [36] Das U (2011) Essential fatty acids—biochemistry, physiology and clinical significance. In *Molecular Basis of Health and Disease*, Springer, Netherlands, pp. 101-151.
- [37] Di Marzo V, Stella N, Zimmer A (2015) Endocannabinoid signalling and the deteriorating brain. *Nat Rev Neurosci* **16**, 30-42.