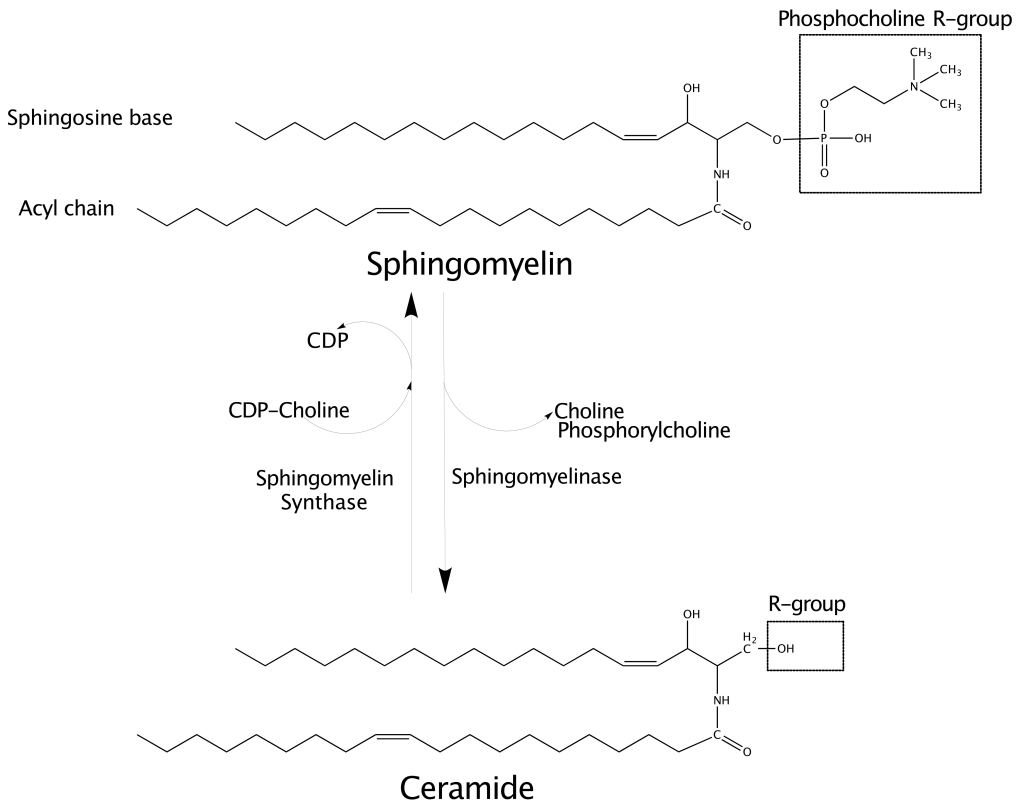
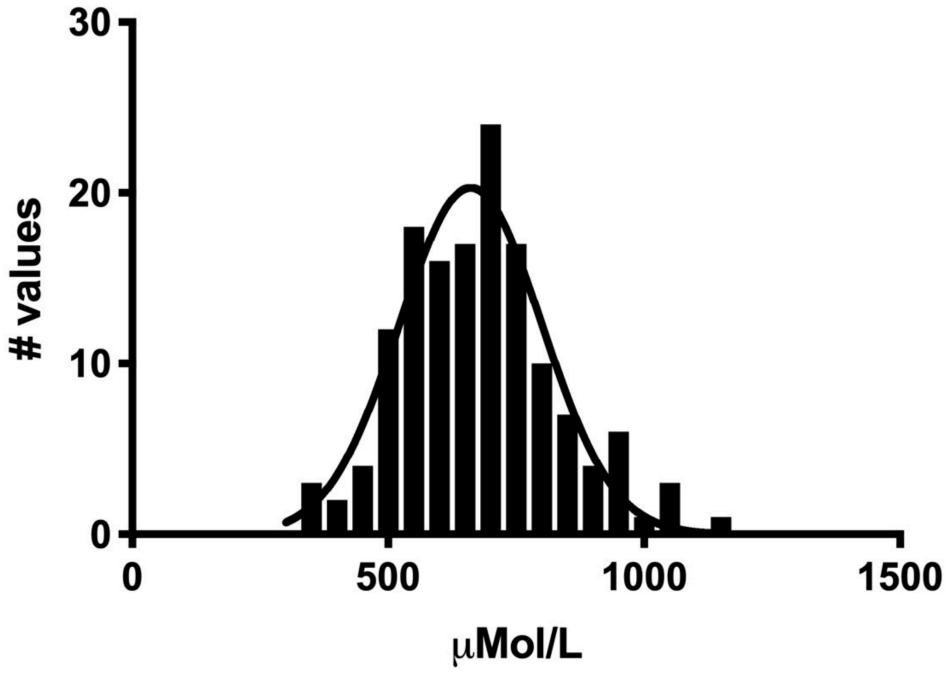
Supplementary Material

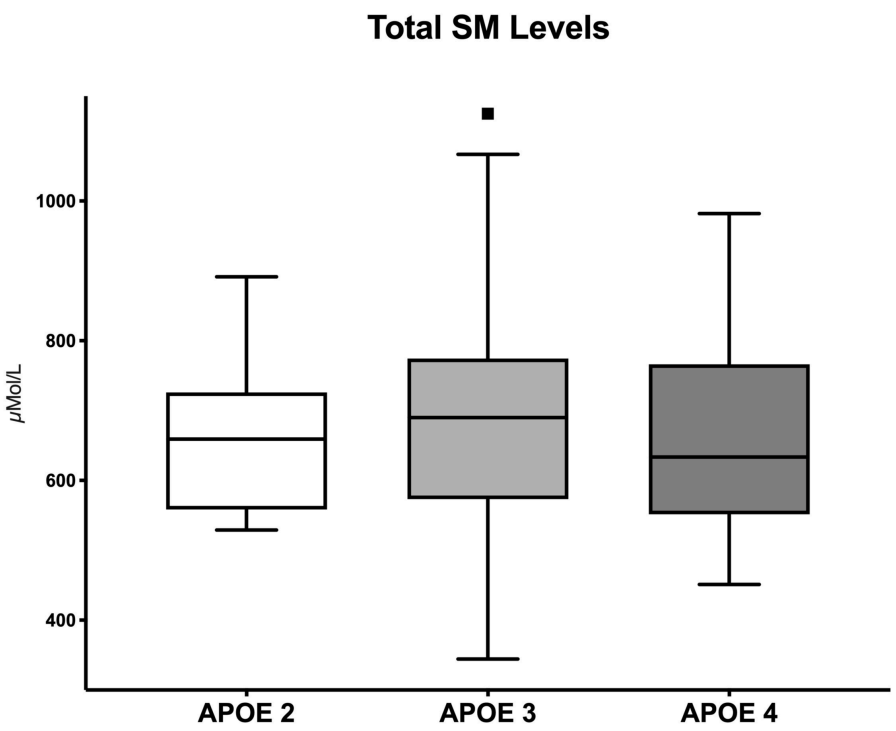
Plasma Sphingomyelins in Late-Onset Alzheimer's Disease



Supplementary Figure 1. Synthesis and structure of sphingomyelin species. Addition of a choline group to ceramide by sphingomyelin synthase produces a sphingomyelin. Removal of that group from SM is facilitated by sphingomyelinase. The length, saturation, and hydroxylation status of the acyl chain generates structural variability between SM species.



Supplementary Figure 2. Histogram of total SM, the sum of all measured plasma SM levels.



Supplementary Figure 3. Total plasma SM levels in µMol/L separated by *APOE* status. Individuals carrying at least one copy of *APOE* 2 or *APOE* 4 were grouped together respectively, while *APOE* 3 represents carriers of two copies of *APOE* 3. Includes individuals in all three disease states. Box plot center line represents mean, upper and lower bounds and whiskers generated by Tukey method; outliers plotted as points beyond whiskers.

Supplementary Table 1. Literature review of sphingolipid dysregulation in AD. Increase in sphingolipid or enzyme levels or activity is indicated in pink, whereas decreases in levels or activity are indicated in blue. Where results were equivocal in direction, cell is not colored and explanation is found in the notes column.

First Author	Date	Sphingolipid	Subjects	Tissue	Notes
Li et al.	2019	SM	Human	Plasma	High SMs association with higher total brain volume on MRI
Li et al.	2017	SM	Human	Plasma	Prospective association of high SM with dementia in African Americans
Mielke et al.	2017	SM	Human	Plasma	High SM in men increases risk of AD, whereas high SM in women decreases risk of AD
Mielke et al.	2011	SM	Human	Plasma	
Han et al.	2011	SM	Human	Plasma	Early AD metabolomics
Oberacher et al.	2017	SM	Human	Platelets	SM(OH)C14:1 is part of lipidomic model to differentiate normal control from MCI patients
Torretta et al.	2018	SM	Human	Serum	
Toledo et al.	2017	SM	Human	Serum	Risk of conversion from MCI to AD positively associated with SMOH C 14:1 and SM C16:0
Oresic et al.	2011	SM	Human	Serum	
Torretta et al.	2018	SM	Human	CSF	SM C24:1
Koal et al.	2015	SM	Human	CSF	
Fonteh et al.	2015	SM	Human	CSF	
Mielke et al.	2014	SM	Human	CSF	
Kosicek et al.	2012	SM	Human	CSF	Levels correlate with amyloid and tau
Varma et al.	2018	SM	Human	Brain	Increased risk of conversion to incident AD associated with: SM C 16:0, SMC 16:1, SM OH C 14:1, SM C 18:1
Diaz et al.	2015	SM	Human	Brain	More highly saturated in lipid rafts in cortex and cerebellum
Chan et al.	2012	SM	Human	Brain	
He et al.	2010	SM	Human	Brain	
Bandaru et al.	2009	SM	Human	Brain	In grey matter of *APOE4* AD verses *APOE3* AD
Soderberg et al.	1992	SM	Human	Brain	
Bandaru et al.	2009	SM	Human	Brain	Grey mater
Pettegrew et al.	2001	SM	Human	Brain	
Lin et al.	2017	SM	Rat	Plasma	Metabolomics identified sphingolipid metabolism as dysregulated, SM 18:1/24:1 and SM 18:0/2:0 decreased
Tajima et al.	2013	SM	Mouse	Plasma	

Tajima et al.	2013	SM	Mouse	Brain	
Gonzalez-Dominguez et al.	2014	SM	Mouse	Brain	Saturated SMs increase in hippocampus, unsaturated decreased in cortex, long chain SMs decreased
Fabelo et al.	2012	SM	Mouse	Brain	Within lipid rafts
Kim et al.	2018	Cer	Human	Plasma	Lipid species found in plasma HDL and LDL/VLDL
Kim et al.	2017	Cer	Human	Plasma	
Mielke et al.	2017	Cer	Human	Plasma	High Cer increases AD risk in men
Mielke et al.	2011	Cer	Human	Plasma	Not significant but higher trended towards disease progression
Han et al.	2011	Cer	Human	Plasma	
Mielke et al.	2010	Cer	Human	Plasma	Ceramides decreased in MCI versus NC, but in MCI group higher Cers were predictive of cognitive decline
Torretta et al.	2018	Cer	Human	Serum	
Mielke et al.	2012	Cer	Human	Serum	Increased serum ceramides increases risk of AD in women
Fonteh et al.	2015	Cer	Human	CSF	Increased in prodromal disease, decreased with memory impairment
de Wit et al.	2017	Cer	Human	Brain	Cer increased in astrocytesin AD with capillary cerebral amyloid angiopathy compared to AD brain
Filippov et al.	2012	Cer	Human	Brain	
He et al.	2010	Cer	Human	Brain	
Bandaru et al.	2009	Cer	Human	Brain	White matte
Bandaru et al.	2009	Cer	Human	Brain	In grey matter of *APOE4* AD verses *APOE3* AD
Cutler	2004	Cer	Human	Brain	Advanced AD
Han et al.	2002	Cer	Human	Brain	Cers elevated early in AD, decline in late stages of AD
den Hoedt	2017	Cer	Mouse	Brain	In transgenic human *APOE4* mice, compared to WT
Fonteh et al.	2015	aSMase	Human	CSF	
de Wit et al.	2017	aSMase	Human	Brain	aSMase increased in microglia in AD brain with capillary cerebral amyloid angiopathy compared to AD brain
He et al.	2010	aSMase	Human	Brain	
Lee et al.	2014	aSMase	Mouse	Blood	
Lee et al.	2014	aSMase	Mouse	Brain	
Lu et al.	2019	SM synthase	Mouse	Brain	Inhibition of SM synthase 1 ameliorates Aβ in mouse
Hsiao et al.	2013	SM synthase	Human	Brain	Elevated SM synthase activity increases Aβ
Lin et al.	2017		Rat	Brain	Metabolomics identified sphingolipid metabolism as dysregulated

Supplementary Table 2. Frequency of *APOE* genotypes in each disease state. Percentage of each genotype overall is in farthest right column, and percentage within each group in parentheses.

APOE Genotype Frequency				
APOE	Normal Control (n=71)	Pre-converter (n=28)	MCI/AD (n=46)	% of Total
2/2	1 (1.4%)	0	1 (2.2%)	1.38
2/3	0	0	4 (8.7%)	2.76
3/3	42 (59%)	23 (82%)	21 (46%)	59.31
3/4	16 (23%)	5 (18%)	18 (39%)	26.90
4/4	1 (1.4%)	0	0	1.38
2/4	1 (1.4%)	0	1 (2.2%)	1.38