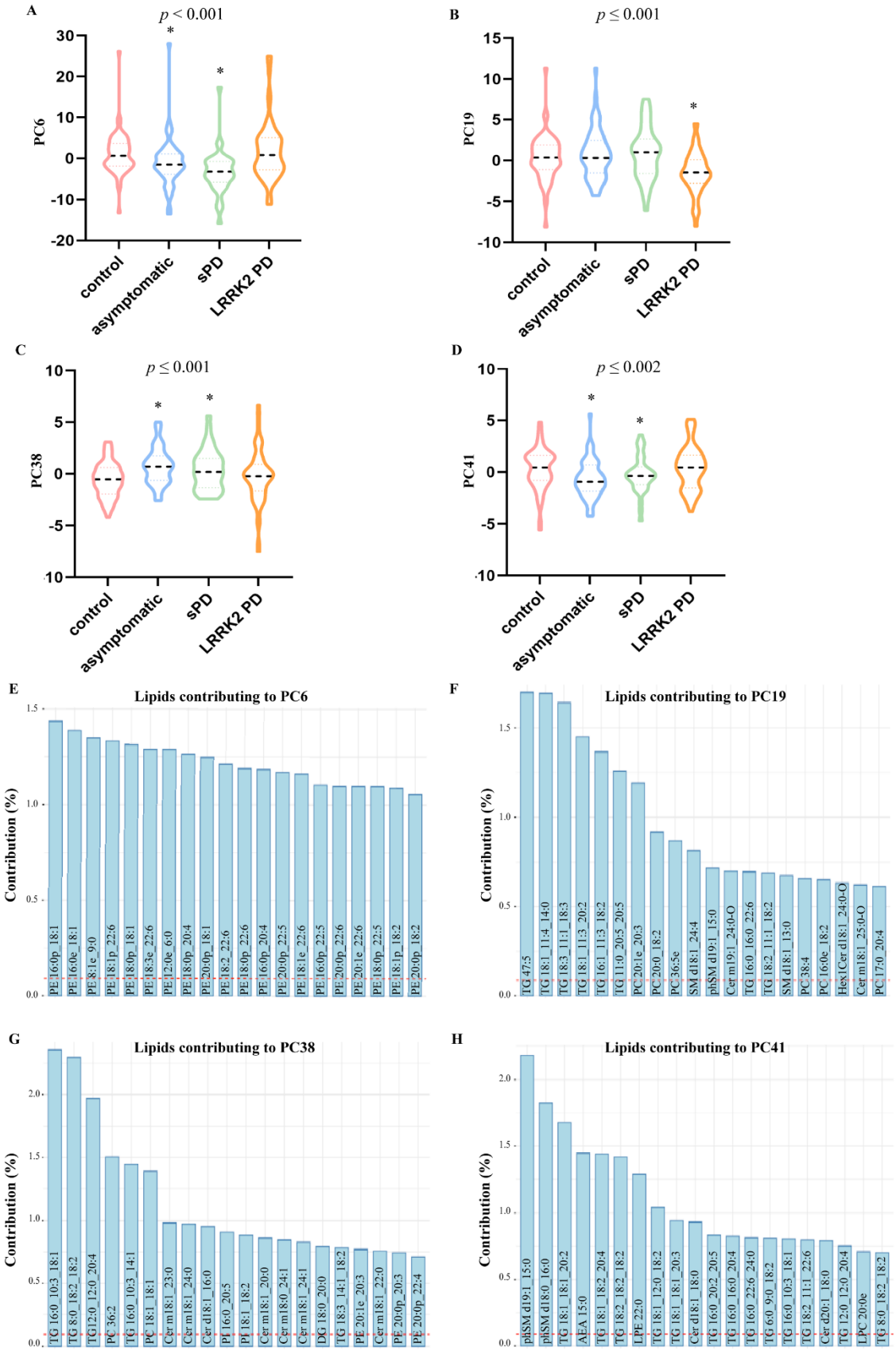
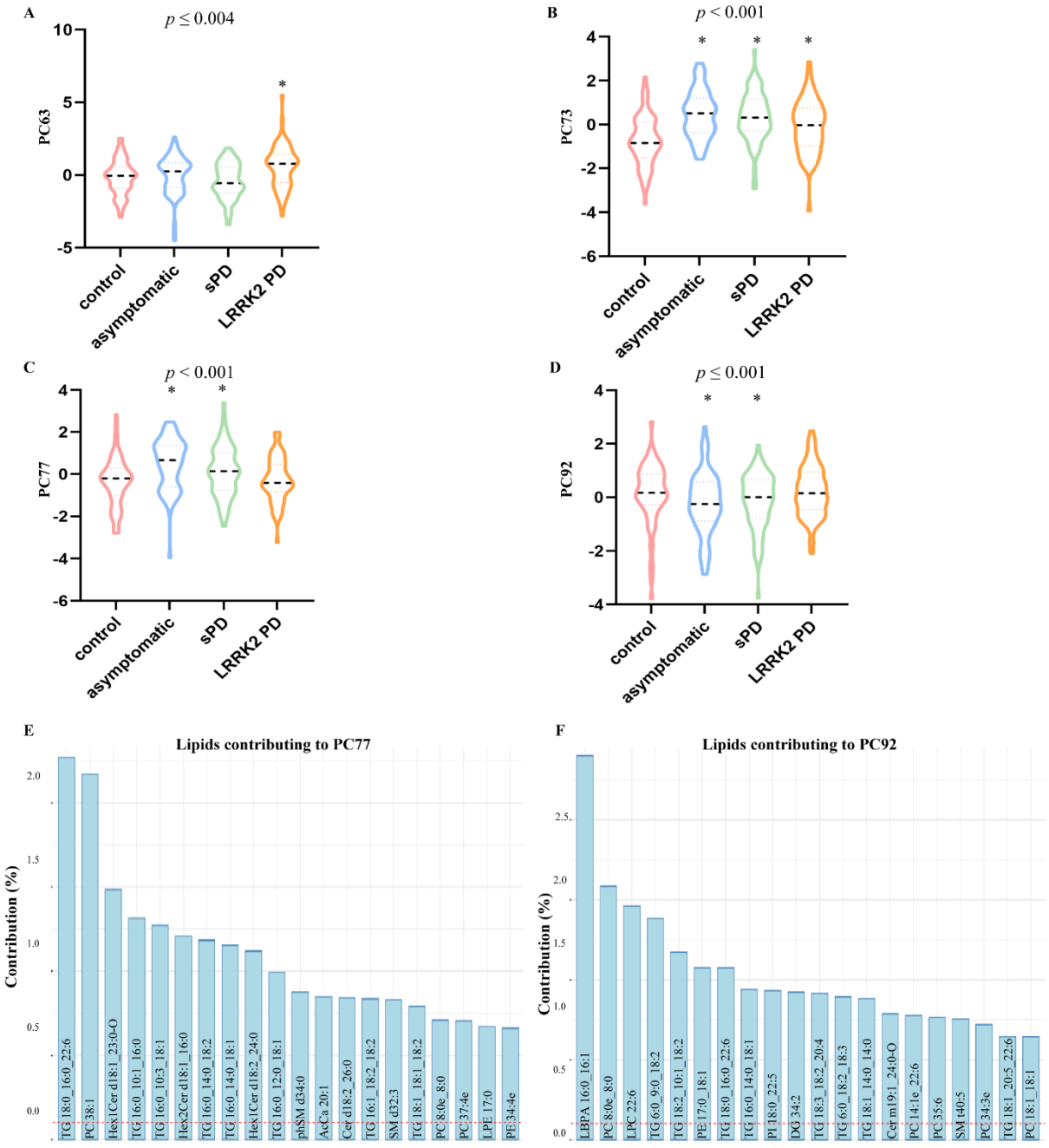


Supplementary Figure 1 Serum lipid profiles from asymptomatic *LRRK2* mutation carriers, *LRRK2* PD and sporadic PD are different from controls. To determine if lipid profiles were affected in serum from sub-groups of the multiethnic cohort (asymptomatic *LRRK2* mutation carriers, *LRRK2* PD and sporadic PD), linear discriminant analysis (LDA) on identified principal components was performed. (**A**) - (**D**) Two factor multivariate

analysis of variance covarying for age and sex identified four principal components, (**A**) PC6, (**B**) PC19, (C) PC38 and (D) PC41, which were significantly affected by an interaction between *LRRK2* and PD status. *Significantly different to control. (**E**) - (**H**) The top twenty lipid species that contributed to the four principal components which significantly distinguished between groups. The dashed red line represents the expected value if the contribution of lipids were uniform. *N* = 221. s*PD* sporadic Parkinson's disease.



Supplementary Figure 2 Serum lipid profiles from asymptomatic *LRRK2* mutation carriers, *LRRK2* PD and sporadic PD are different from controls in the *LRRK2* Ashkenazi Jewish Cohort. To determine if lipid profiles were affected in serum from sub-groups of the Ashkenazi Jewish cohort (asymptomatic *LRRK2* mutation carriers, *LRRK2* PD and sporadic PD), linear discriminant analysis (LDA) on identified principal components was performed. (**A**) - (**D**) Two factor multivariate analysis of variance covarying for age and sex identified four principal components, (**A**) PC63, (**B**) PC73, (C) PC77 and (D) PC92, which were significantly affected by an interaction between *LRRK2* and PD status. *Significantly different to control. (**E**) - (**F**) The top twenty lipid species that contributed to the four principal components which significantly distinguished between groups. The dashed red line represents the expected value if the contribution of lipids were uniform. *N* = 221. s*PD* sporadic Parkinson's disease.

Supplementary Table 1 Demographic data for the LRRK2 multiethnic cohort

	Controls	PD without LRRK2 G2019S	PD with LRRK2 G2019S	LRRK2 G2019S without PD
N (serum)	63	37	65	56
Age	57.5 ± 1.5	61.6 ± 2	61.4 ± 1.3	51.8 ± 1.9*
Sex (M/F)	18/45	21/16#	36/29#	23/33
Age at diagnosis	-	54 ± 2	51.6 ± 1.4	-
MoCA	26.4 ± 0.4	26.1 ± 0.8	23.3 ± 0.6*	26.7 ± 0.4
UPDRS III	0.5 ± 0.2	28.4 ± 1.6*	19.1 ± 1.5*	3.1 ± 0.9
Epworth Sleep	6.7 ± 0.5	6.4 ± 0.6	8.9 ± 0.8*	6.4 ± 0.5
Depression	2.6 ± 0.4	2.6 ± 0.4	4 ± 0.5*	2.5 ± 0.4
Daily Living	99.1 ± 4.3	82.4 ± 2.6#	83.1 ± 1.7#	98 ± 1.2
SCOPA-AUT	9.7 ± 1	14.9 ± 2.1#	15.5 ± 1.3#	9.9 ± 1
REM sleep	2 ± 0.3	4.2 ± 0.5*	2.5 ± 0.3	2 ± 0.3
UPSIT	31.2 ± 0.6	17.7 ± 1.5*	20.8 ± 0.9*	30.9 ± 0.9
BP meds (N/Y)	54/8	26/10	51/8	45/5
On aspirin (N/Y)	58/2	25/2	54/3	41/2
On ibuprofen (N/Y)	57/3	23/4	57/0	37/6

A comparison of clinical variables across groups was assessed by one-way ANOVAs with least-significant difference post hoc. Chi-squared was performed for sex and Kruskal-Wallis followed by Mann–Whitney was performed for BP meds.

*$p < 0.05$ compared to all other groups.

#$p < 0.05$ compared to controls.

Values are mean ± SEM. MoCA Montreal Cognitive Assessment, UPDRS III Unified Parkinson's Disease Rating Scale part 3, Depression Geriatric Depression Scale, Daily Living Schwab and England Activities of Daily Living Scale, SCOPA-AUT Scales for Outcomes in Parkinson's Disease - Autonomic dysfunction, UPSIT University of Pennsylvania Smell Identification Test. BP meds blood pressure medication.

Supplementary Table 2 Demographic data for the LRRK2 Ashkenazi Jewish cohort

	Controls	PD without LRRK2 G2019S	PD with LRRK2 G2019S	LRRK2 G2019S without PD
N	77	79	79	80
Age	59.8 ± 1.9*	68 ± 1.1#	69.4 ± 0.9#	55.8 ± 1.4*
Sex (M/F)	33/44	55/24*	39/40	35/45
Age at diagnosis	-	58.1 ± 1	57.3 ± 1.2	-
MoCA	26.7 ± 0.3	25.1 ± 0.6#	25.1 ± 0.5#	27.3 ± 0.4
UPDRS III	1.8 ± 0.3	24.8 ± 1.9*	20.7 ± 1.6*	2.2 ± 0.4
Epworth Sleep	5.7 ± 0.4	8.8 ± 0.7#	8.5 ± 0.6#	5.7 ± 0.6
Depression	2 ± 0.4	3.9 ± 0.5#	4.4 ± 0.5#	1.2 ± 0.2
Daily Living	98.9 ± 0.8	76.1 ± 3.1#	77.2 ± 2.6#	99.2 ± 0.6
SCOPA-AUT	13.5 ± 1.5	23.1 ± 1.6#	22.2 ± 1.7#	12.5 ± 1.4
REM sleep	2 ± 0.3	4.7 ± 0.5*	3.2 ± 0.4*	2.1 ± 0.4
UPSIT	31.8 ± 1	17.4 ± 1*	23.3 ± 1.3*	32.6 ± 1.5

A comparison of clinical variables across groups was assessed by one-way ANOVAs with least-significant difference post hoc. Chi-squared was performed for sex. Values are mean ± SEM.
*$p < 0.05$ compared to all other groups
#$p < 0.05$ compared to controls. MoCA Montreal Cognitive Assessment, UPDRS III Unified Parkinson's Disease Rating Scale part 3, Depression Geriatric Depression Scale, H & Y Hoehn & Yahr, Daily Living Schwab and England Activities of Daily Living Scale, SCOPA-AUT Scales for Outcomes in Parkinson's Disease - Autonomic dysfunction, UPSIT University of Pennsylvania Smell Identification Test.

Supplementary Table 3 LRRK2 multiethnic cohort serum lipids

Lipid name	Abbreviation	Number
Glycerolipids		
Diacylglycerol	DG	28
Monogalactosyldiacylglycerol	MGDG	2
Triacylglycerol	TG	474
Glycerophospholipids		
Cyclic phosphatidic acid	cPA	1
Lysophosphatidic acid	LPA	1
Lysophosphatidylcholine	LPC	44
Lysophosphatidylethanolamine	LPE	15
Phosphatidylcholine	PC	190
Phosphatidylethanolamine	PE	75
Phosphatidylglycerol	PG	1
Phosphatidylinositol	PI	19
Phosphatidylserine	PS	2
Sphingolipids		
Ceramide	Cer	83
Trihexosyl N-acetylhexosyl ceramide	CerG3GNAc1	1
Ceramide phosphate	CerP	1
Hexosylceramide	Hex1Cer	29
Dihexosylceramide	Hex2Cer	10
Trihexosylceramide	Hex3Cer	4
Sphingomyelin	SM	56
Sphingomyelin(phytosphingosine)	phSM	2
Sulfatide	ST	2
Sterol lipids		
Cholesterol ester	ChE	13
Acyl hexosyl cholesterol ester	AcHexChE	1
Campesterol ester	CmE	3
Sitosterol ester	SiE	1
Fatty Acyls		
Acyl carnitine	AcCa	35
N-Acylethanolamine	AEA	2
Platelet-activating factor	PAF	18
Prenol lipids		
Coenzyme Q8	CoQ8	1
Coenzyme Q9	CoQ9	1
Coenzyme Q10	CoQ10	1

Lipids sub-classes and the number of individual species detected in serum from the LRRK2 multiethnic cohort (n = 221).

Supplementary Table 4 Summary of canonical discriminant functions in the multiethnic cohort

Eigenvalues

Function	Eigenvalue	% of variance	Cumulative %	Canonical correlation
1	12.602	41.8	41.8	0.963
2	10.233	33.9	75.7	0.954
3	7.326	24.3	100.0	0.938

Wilks' Lambda

Test of Function(s)	Wilks' Lambda	Chi-square	df	Sig.
1 through to 3	0.001	1111.587	357	2.2×10^{-78}
2 through to 3	0.011	705.700	236	2.5×10^{-48}
3	0.120	329.563	117	4.0×10^{-22}

Serum lipid profiles from Parkinson's disease patients, *LRRK2* mutation carriers and controls from the multiethnic cohort were transformed by principal component analysis. Using linear discriminant analysis (LDA) on these principal components, three canonical functions were generated that could significantly discriminate the groups.

Supplementary Table 5 LRRK2 Ashkenazi Jewish cohort serum lipids

Lipid name	Abbreviation	Number
Glycerolipids		
Diacylglycerol	DG	43
Monogalactosyldiacylglycerol	MGDG	2
Triacylglycerol	TG	247
Glycerophospholipids		
Bis(monoacylglycerol)phosphate	BMP	2
Lysophosphatidylcholine	LPC	37
Lysophosphatidylethanolamine	LPE	22
Phosphatidic acid	PA	1
Phosphatidylcholine	PC	207
Phosphatidylethanolamine	PE	79
Phosphatidylethanol	PEt	2
Phosphatidylglycerol	PG	18
Phosphatidylinositol	PI	19
Phosphatidylserine	PS	13
Sphingolipids		
Ceramide	Cer	52
Dihexosyl N-acetylhexosyl ceramide	CerG2GNAc1	1
Trihexosyl N-acetylhexosyl ceramide	CerG3GNAc1	1
Ceramide phosphoethanolamine	CerPE	2
Hexosylceramide	Hex1Cer	29
Dihexosylceramide	Hex2Cer	9
Sphingomyelin	SM	129
Sphingomyelin(phytosphingosine)	phSM	14
Sterol lipids		
Cholesterol ester	ChE	15
Acyl hexosyl cholesterol ester	AcHexChE	3
Acyl hexosyl stigmasterol ester	AcHexStE	1
Acyl hexosyl zymosterol ester	AcHexZyE	1
Campesterol ester	CmE	4
Zymosterol ester	ZyE	2
Fatty Acyls		
Acyl carnitine	AcCa	17
Fatty acid	FA	2
O-Acyl-(gamma-hydroxy) fatty acid	OAHFA	2
Prenol lipids		
Coenzyme Q8	CoQ8	1
Coenzyme Q10	CoQ10	1

Lipid sub-classes and the number of individual species detected in serum from the LRRK2 Ashkenazi Jewish cohort (n = 315).

Supplementary Table 6 Summary of canonical discriminant functions in the Ashkenazi Jewish cohort

Eigenvalues

Function	Eigenvalue	% of variance	Cumulative %	Canonical correlation
1	4.112	47.3	47.3	0.897
2	2.861	32.9	80.2	0.861
3	1.723	19.8	100	0.795

Wilks' Lambda

Test of Function(s)	Wilks' Lambda	Chi-square	df	Sig.
1 through to 3	0.019	1035.907	312	1.8×10^{-78}
2 through to 3	0.095	611.676	206	7.7×10^{-42}
3	0.367	260.467	102	8.0×10^{-16}

To determine if lipid profiles could distinguish between groups in a second cohort, serum lipid profiles from Parkinson's disease patients, *LRRK2* mutation carriers and controls from the multiethnic cohort were transformed by principal component analysis. Using linear discriminant analysis (LDA) on these principal components, three canonical functions were generated that could significantly discriminate the groups.

Supplementary Table 7 Demographic data for the CSF cohort

	Controls	PD without LRRK2 G2019S	PD with LRRK2 G2019S	LRRK2 G2019S without PD
n	20	29	19	20
Age	53.5 ± 3.5	58.2 ± 2.2	64.2 ± 2.9#	52 ± 3
Sex (M/F)	10/10	19/10	8/11	11/9
Age at diagnosis	-	52.4 ± 2.4	55.2 ± 3.3	-
MoCA	27.3 ± 0.5	26.9 ± 0.5	23.7 ± 1*	26.4 ± 0.5
UPDRS III	0.3 ± 0.3	27.1 ± 1.9#	22.8 ± 3.5#	3.1 ± 1.4*
Epworth Sleep	7.1 ± 0.7	5.4 ± 0.5	6.9 ± 1.1	5.4 ± 0.9
Depression	3.4 ± 1	2.1 ± 0.4	3 ± 0.7	1.9 ± 0.6
Daily Living	99.5 ± 0.5	87.1 ± 1.8*	80 ± 4*	99.5 ± 0.5
SCOPA-AUT	8.9 ± 1.7	10.5 ± 1.2	14.1 ± 1.7#	7.1 ± 1.4
REM sleep	1.9 ± 0.4	3.6 ± 0.6#	1.8 ± 0.5	2.2 ± 0.5
UPSIT	33.6 ± 0.8	17.7 ± 1.6*	22 ± 2*	31 ± 0.8
BP meds (N/Y)	16/4	21/7	18/1	18/0
On aspirin (N/Y)	16/1	20/1	15/0	15/0
Inflammatory meds (N/Y)	15/2	20/1	15/0	15/0
On ibuprofen (N/Y)	17/0	19/2	15/0	15/0

A comparison of scale clinical variables across groups was assessed by one-way ANOVAs with least-significant difference post hoc. Chi-squared was performed for sex and Kruskal-Wallis followed by Mann–Whitney tests were performed for medication use. Values are mean ± SEM.

*$p < 0.05$ compared to all groups.

#$p < 0.05$ compared to controls.

MoCA Montreal Cognitive Assessment, UPDRS III Unified Parkinson's Disease Rating Scale Part 3, Depression Geriatric Depression Scale, Daily Living Schwab and England Activities of Daily Living scale, SCOPA-AUT Scales for Outcomes in Parkinson's Disease - Autonomic dysfunction, UPSIT University of Pennsylvania Smell Identification Test. BP meds blood pressure medication. Inflammatory meds Regular use of other inflammatory medication.

Supplementary Table 8 CSF cohort serum lipids

Lipid name	Abbreviation	Number
Glycerolipids		
Diacylglycerol	DG	7
Monoacylglycerol	MG	3
Triacylglycerol	TG	76
Glycerophospholipids		
Bis(monoacylglycerol)phosphate	BMP	1
Lysophosphatidylcholine	LPC	2
Phosphatidylcholine	PC	45
Phosphatidylethanolamine	PE	11
Phosphatidylglycerol	PG	2
Phosphatidylinositol	PI	1
Sphingolipids		
Ceramide	Cer	7
Ceramide phosphate	CerP	1
Hexosylceramide	Hex1Cer	5
Sphingomyelin	SM	20
Sterol lipids		
Cholesterol ester	ChE	2
Fatty Acyls		
N-Acylethanolamine	AEA	1
Prenol lipids		
Coenzyme Q10	CoQ10	1

Lipid sub-classes and individual species detected in cerebrospinal fluid from the LRRK2 multiethnic cohort (n = 88).

Supplementary Table 9 Pathways altered in Parkinson's disease patients and *LRRK2* mutation carrier CSF

	ID	Lipids
Pathway altered in Parkinson's disease		
Sphingolipid metabolism	[map00600]	CerP, Hex1Cer
Glycogen production, GLUT4 translocation and glucose uptake (Insulin resistance)	[map04931]	DG, TG
Oxidative phosphorylation and thermogenesis	[map04714]	DG, TG
Glycerolipid metabolism	[map00561]	DG, TG
Regulation of lipolysis in adipocytes	[map04923]	DG, TG
Fat digestion and absorption	[map04975]	DG, TG
Pathways altered in *LRRK2* G2019S mutation carriers		
Sphingolipid metabolism	[map00600]	Cer, Hex1Cer
Glycogen production, GLUT4 translocation and glucose uptake (Insulin resistance)	[map04931]	Cer, DG
Adipocytokine signalling pathway	[map04920]	Cer, DG
Sphingolipid signalling	[map04071]	Cer, DG
Neurotrophin signalling pathway	[map04722]	Cer, DG
Advanced glycation end products (AGE) signalling	[map04933]	Cer, DG

Lipid sub-classes of interest from the CSF analyses were searched in the online KEGG compound/pathway database (Kanehisa et al., 2020) to identify whether lipids of interest were enriched in certain pathways. Pathways that were shared by at least two lipids are listed above. GLUT4 Glucose transporter type 4, insulin-responsive. Glycogen production, GLUT4 translocation and glucose uptake are sub-pathways in an "insulin resistance" pathway. Oxidative phosphorylation and thermogenesis is from "thermogenesis" pathway. *Glucosylceramide and galactosylceramide were entered as the search terms for monohexoylceramide (Hex1Cer) since the data obtained from LC-MS/MS does not allow these to be discriminated.

Supplementary Table 10 Serum lipid directions of change

	Multiethnic		Ashkenazi Jewish		Multiethnic		Ashkenazi Jewish	
	PC		**PC**		**SM**		**SM**	
	G2019S	**PD**	**G2019S**	**PD**	**G2019S**	**PD**	**G2019S**	**PD**
P value	.0004	2 x 10-5	2.3 x 10-5	1.1 x 10-10	2.1 x 10-11	5.3 x 10-8	1.1 x 10-32	2.2 x 10-12
Lipids up	6	54	5	8	1	4	0	5
Lipids down	10	2	14	2	8	3	9	5
	Cer		**Cer**		**PE**		**PE**	
	G2019S	**PD**	**G2019S**	**PD**	**G2019S**	**PD**	**G2019S**	**PD**
P value	2.9 x 10-13	6.1 x 10-11	ns	1 x 10-5	.021	2 x 10-5	.002	2.4 x 10-8
Lipids up	0	1	-	0	3	5	6	1
Lipids down	17	9	-	9	0	2	1	5
	LPE		**LPE**		**AcCa**		**AcCa**	
	G2019S	**PD**	**G2019S**	**PD**	**G2019S**	**PD**	**G2019S**	**PD**
P value	ns	.008	ns	ns	ns	ns	ns	ns
Lipids up	-	0	-	-	-	-	-	-
Lipids down	-	0	-	-	-	-	-	-
	MGDG		**MGDG**		**TG**		**TG**	
	G2019S	**PD**	**G2019S**	**PD**	**G2019S**	**PD**	**G2019S**	**PD**
P value	.01	2 x 10-6	ns	ns	1.5 x 10-8	5 x 10-6	3.1 x 10-5	0.0009
Lipids up	1	1	-	-	6	15	5	6
Lipids down	0	0	-	-	106	21	11	5
	LPC		**LPC**		**Hex1Cer**		**Hex1Cer**	
	G2019S	**PD**	**G2019S**	**PD**	**G2019S**	**PD**	**G2019S**	**PD**
P value	.032	1 x 10-6	ns	ns	ns	0.023	ns	8.3 x 10-7
Lipids up	0	9	-	-	-	1	-	2
Lipids down	10	0	-	-	-	0	-	0
	DG		**DG**					
	G2019S	**PD**	**G2019S**	**PD**				
P value	ns	.004	ns	0.004				
Lipids up	-	-	-	2				
Lipids down	-	14	-	0				

For both the Ashkenazi Jewish and multiethnic cohort serum, lipid sub-classes in Figure 6 were analysed via 2 factor multivariate analysis covarying for age and sex (and batch for the AJ cohort). P-value represents Wilks' Lambda from the multivariate analysis. A significant effect of either PD status or LRRK2 G2019S mutation status on each lipid sub-class are reported. Serum triacylglycerol (TG) and phosphatidylcholine (PC) analyses were performed grouped by carbon/double bond number (multiethnic: TG 31:0-TG 50:2, TG 50:2e-TG 56:6e and TG 56:7-TG 66:7, AJ: TG 29:0-TG 52:7 and TG 52:8 - TG 66:7; PC 16:0e-PC 37:6, PC 38:6-PC 48:2).