

# Plasma neurofilament light chain protein is not increased in treatment-resistant schizophrenia and first-degree relatives

## SUPPLEMENTARY MATERIAL

Control percentile <sup>a,b</sup>	TRS (n=82)	P-value (TRS vs C) <sup>c</sup>	NON-CLOZ (n=13)	P-value (NON-CLOZ vs C) <sup>c</sup>	Siblings (n=21)	P-value (siblings vs C) <sup>c</sup>
80 <sup>th</sup> percentile, n (%)	22 (27%)	0.223	1 (8%)	0.676	8 (38%)	0.07
90 <sup>th</sup> percentile, n (%)	19 (23%)	<b><u>0.039</u></b>	1 (8%)	1.000	8 (38%)	<b><u>&lt;0.001</u></b>
95 <sup>th</sup> percentile, n (%)	8 (10%)	0.195	0	1.000	3 (14%)	0.114
98 <sup>th</sup> percentile, n (%)	3 (4%)	0.642	0	1.000	0	1.000

### **Supplementary Table 1. Additional analyses to explore percentile distributions in different groups.**

Underlined and bold values show  $p < 0.05$ .

a: 80<sup>th</sup> percentile: 7.3pg/mL, 90<sup>th</sup> percentile: 8.0pg/mL, 95<sup>th</sup> percentile: 11.3pg/mL, 98<sup>th</sup> percentile: 13.7pg/mL, 99<sup>th</sup> percentile: N/A

b: excluding extreme outlier in control group

c: Fisher's Exact Test used to compare numbers in each percentile allocation in TRS, NON-CLOZ and siblings, compared to controls.

C: control; NON-CLOZ: non-clozapine treated schizophrenia; TRS: treatment-resistant schizophrenia

Comparison	Levene's test	Student's t-test	Welch's t-test	Robust group term
TRS vs control	<b><u>0.003</u></b>	0.43	0.38	0.34 [-0.61, 1.29]
NON-CLOZ vs control	0.53	0.17	0.10	0.79 [-0.16, 1.74]
Sibling vs control	<b><u>0.003</u></b>	0.15	0.24	0.56 [-0.73, 1.85]
Parent vs control	<b><u>&lt;0.001</u></b>	<b><u>&lt;0.001</u></b>	<b><u>&lt;0.001</u></b>	2.33 [-0.21, 4.87]
NON-CLOZ vs TRS	0.06	0.23	0.04	0.83 [-0.48, 2.15]

**Supplementary Table 2. Additional sensitivity analyses to determine impact of heterogeneity of variances on group differences.**

Underlined and bold values show  $p < 0.05$ . As described in the text, taken together, these sensitivity analyses suggest that heterogeneity of variances does not explain the lack of statistically significant group differences.

NON-CLOZ: non-clozapine treated schizophrenia; TRS: treatment-resistant schizophrenia

Confidence Intervals of Spearman's rho in TRS group			
	Spearman's rho	95% Confidence Intervals (2-tailed) <sup>a,b</sup>	
		Lower	Upper
NfLValue - AgeAtSample	0.674*	0.531	0.78
NfLValue - SexFEMALE	0.178	-0.047	0.386
NfLValue - Duration of Illness	0.467*	0.267	0.629
NfLValue - PANSSPositiveScale	-0.016	-0.24	0.209
NfLValue - PANSSNegativeScale	-0.06	-0.281	0.166
NfLValue - PANSSGeneral	0.108	-0.12	0.325
NfLValue - school_years	-0.029	-0.251	0.197
NfLValue - CurrentSmokerYesNo	-0.175	-0.392	0.061
NfLValue - Alcohol use disorder	-0.199	-0.404	0.025
NfLValue - HTN	0.202	-0.027	0.411
NfLValue - Diabetes	0.115	-0.117	0.335
NfLValue - Dyslipidaemia	0.273*	0.053	0.468
NfLValue - BMI_calculated	-0.264*	-0.48	-0.019
NfLValue - weight	-0.316*	-0.516	-0.082
NfLValue - wasi_iq	0.139	-0.096	0.36
NfLValue - ClozapineLevel	0.258*	0.034	0.457
NfLValue - SOFAS	-0.039	-0.266	0.191
NfLValue - head_injury	-0.084	-0.303	0.143
NfLValue - epil	0.036	-0.191	0.26
NfLValue - NeurologicalDisorderDiagnosis	-0.037	-0.259	0.187
NfLValue - ECT	-0.076	-0.3	0.155

**Supplementary Table 3. Exploratory analyses of associations between NfL and clinical variables in the treatment-resistant schizophrenia group**

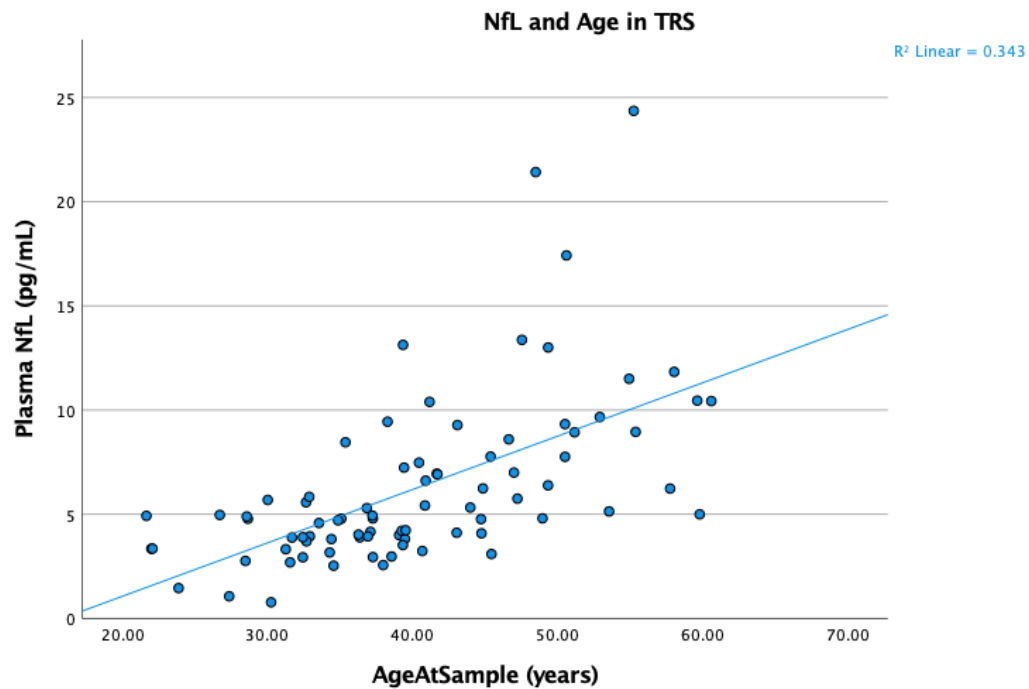
**\*: Statistically significant (Spearman's rho 95% confidence intervals don't include zero)**

BMI: body mass index; ECT: electroconvulsive therapy; GAF: Global Assessment of Functioning scale; NfL: neurofilament light; PANSS: Positive and Negative Syndrome Scale; SOFAS: Social and Occupational Functioning Assessment Scale

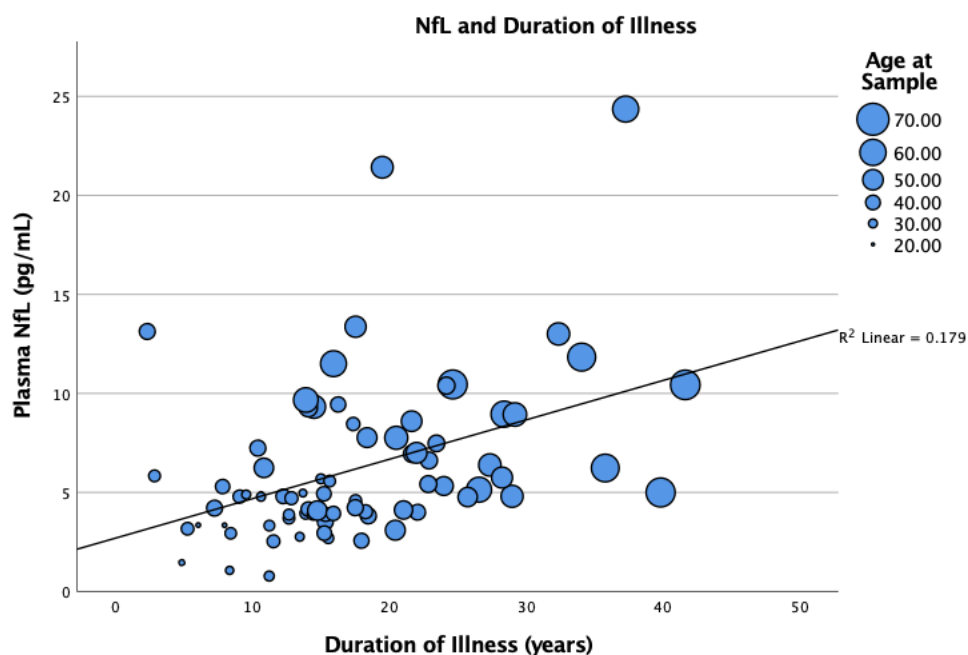
**a: Estimation is based on Fisher's r-to-z transformation.**

**b: Estimation of standard error is based on the formula proposed by Fieller, Hartley, and Pearson.**

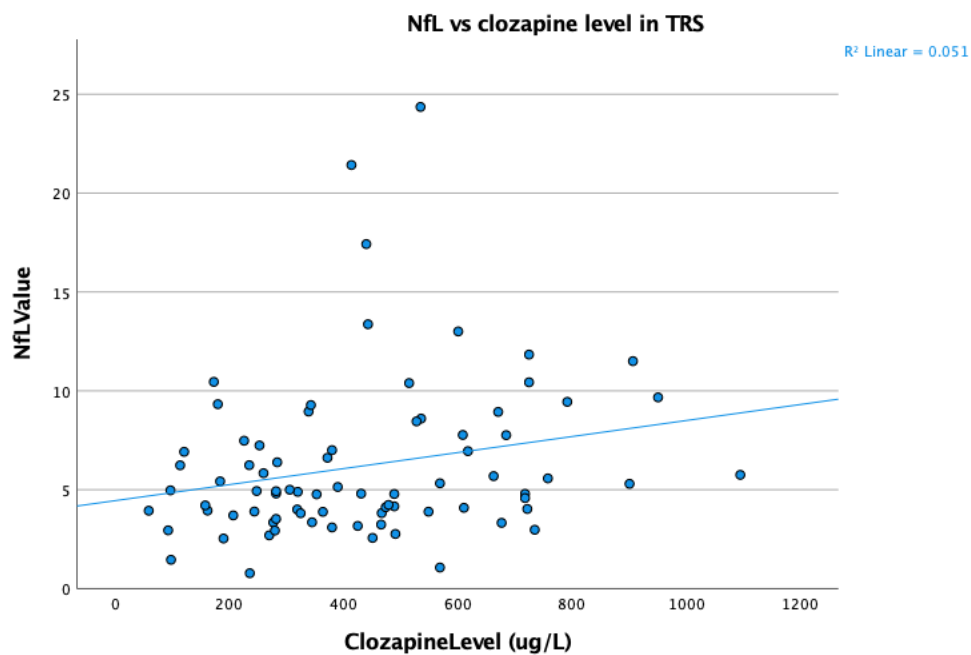
## Figures



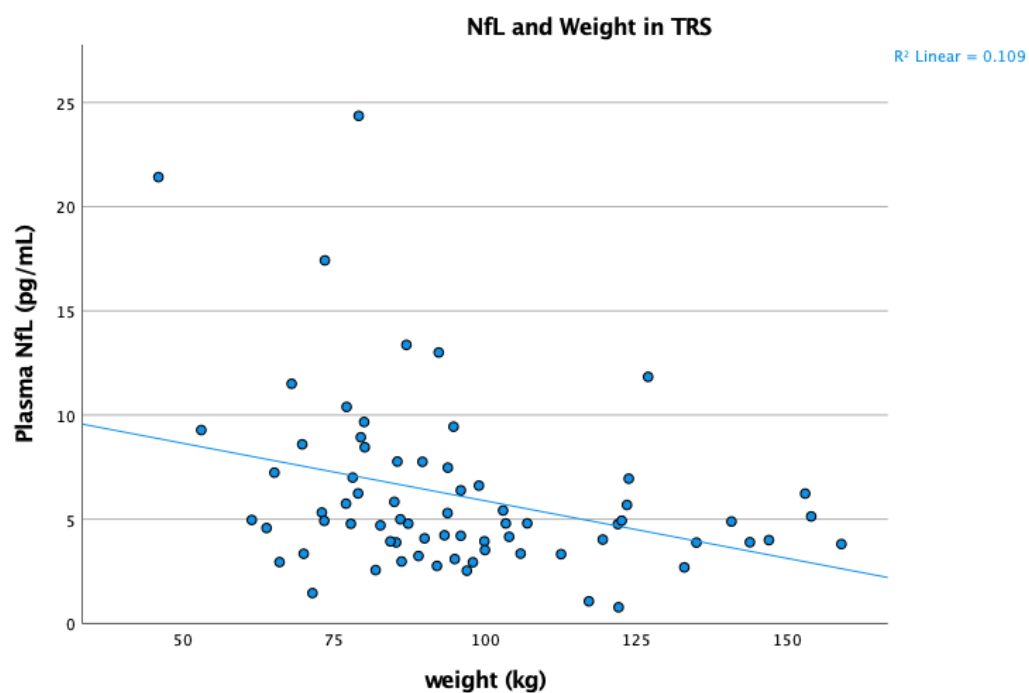
**Supplementary Figure 1. Plasma neurofilament light versus age at blood sample in the treatment-resistant schizophrenia group**



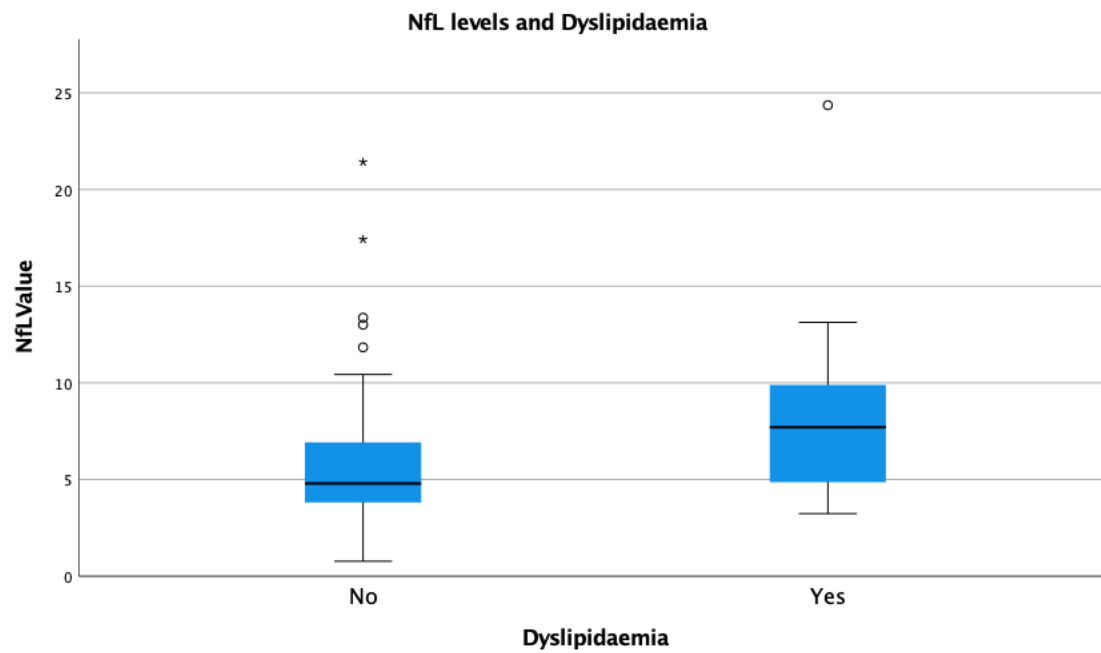
**Supplementary Figure 2. Plasma neurofilament light versus duration of illness in the treatment-resistant schizophrenia group**



**Supplementary Figure 3. Plasma neurofilament light versus clozapine level in the treatment-resistant schizophrenia group**



**Supplementary Figure 4. Plasma neurofilament light versus weight in the treatment-resistant schizophrenia group**



**Supplementary Figure 5. Plasma neurofilament light levels in people with and without dyslipidaemia in the treatment-resistant schizophrenia group**

## APPENDIX 1

### **COLLABORATORS:**

#### **On behalf of others in The MiND Study Group:**

<b>Name</b>	<b>Affiliations (separated by semi colon)</b>	<b>Title</b>	<b>Highest qualification</b>
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