

MiSBIE symposium —

Immune cell mitochondrial phenotypes, mood disorder symptoms and adversity in MiSBIE

12.12.25

Cynthia Liu

Immune cell mitochondrial phenotypes

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- Specific immune cell subtypes possess distinct mitochondrial and OxPhos profiles
(Chacko et al., 2013; Kramer et al., 2014; Maianski et al., 2004; Rausser et al., 2021; Weiss et al., 2022)
- In Mitochondrial Disease (MitoD):
 - Respiratory track infections are a leading cause of death in MitoD – immune dysfunction in MitoD (Barends et al. 2015)
 - Purifying MitoD-causing mtDNA mutations occurs in immune cell types → decreasing mutation load as these cells mature (esp. in lymphoid cells)
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Mitochondrial respiratory capacity (MRC)

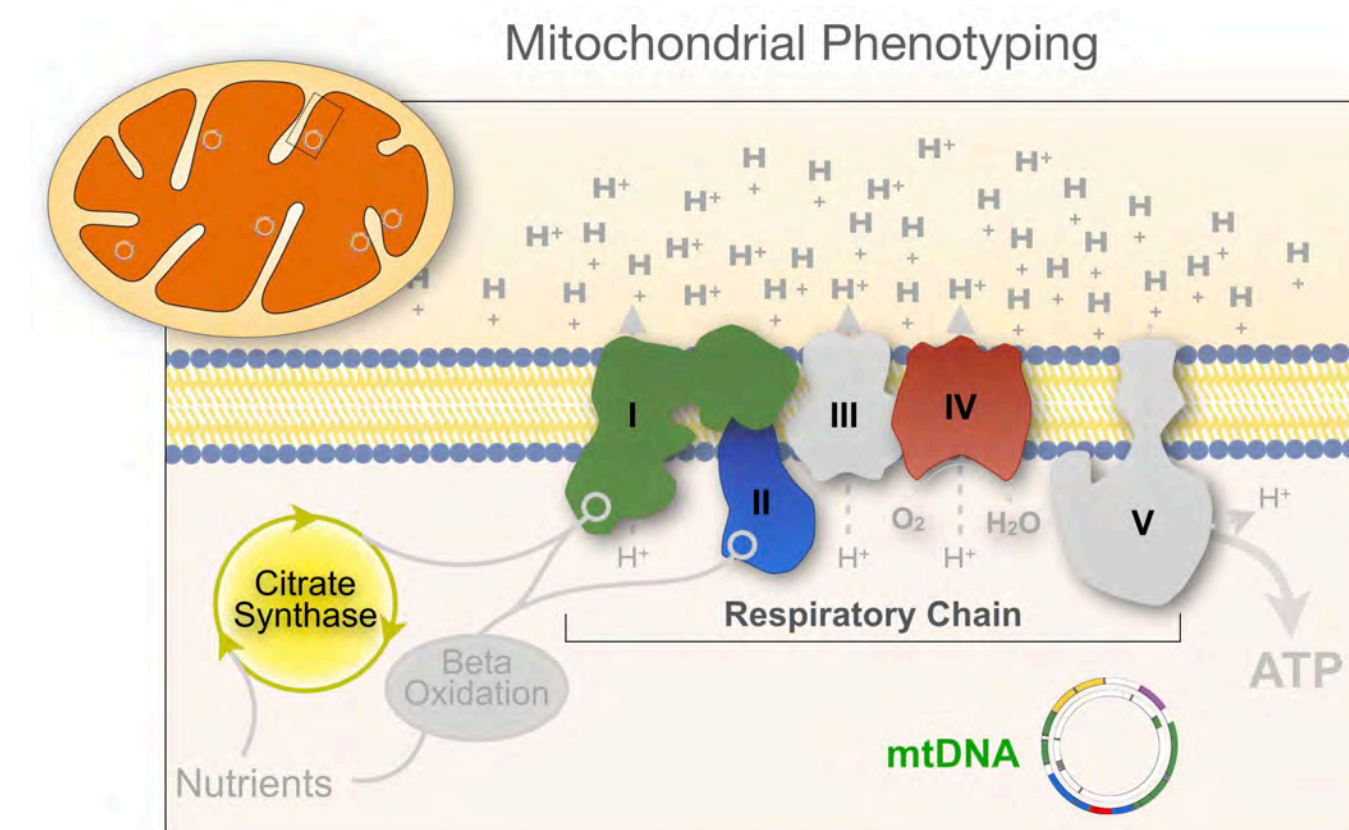
measures respiratory capacity on a per mitochondrion basis in tissue/cell homogenates

measures of respiratory capacity:

- Complex I activity
- Complex II (SDH) activity
- Complex IV (COX) activity

Measures of mitochondrial content:

- Citrate Synthase (CS) activity
- mtDNAcn



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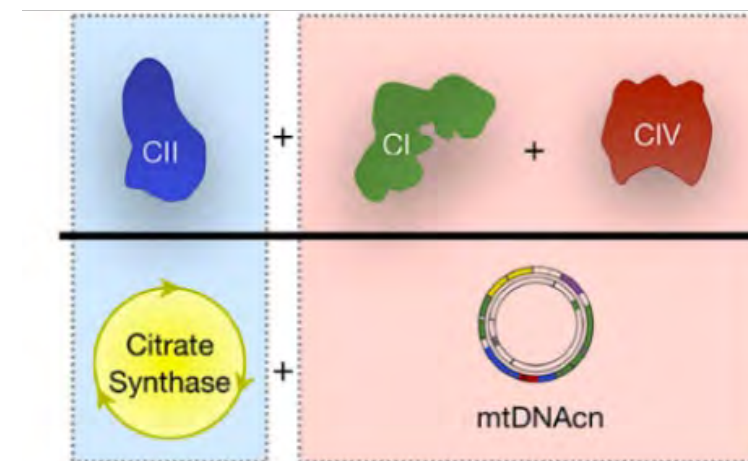
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$$MRC = \frac{TRC}{MitoD}$$
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TRC = tissue respiratory capacity

MitoD = mitochondria tissue density

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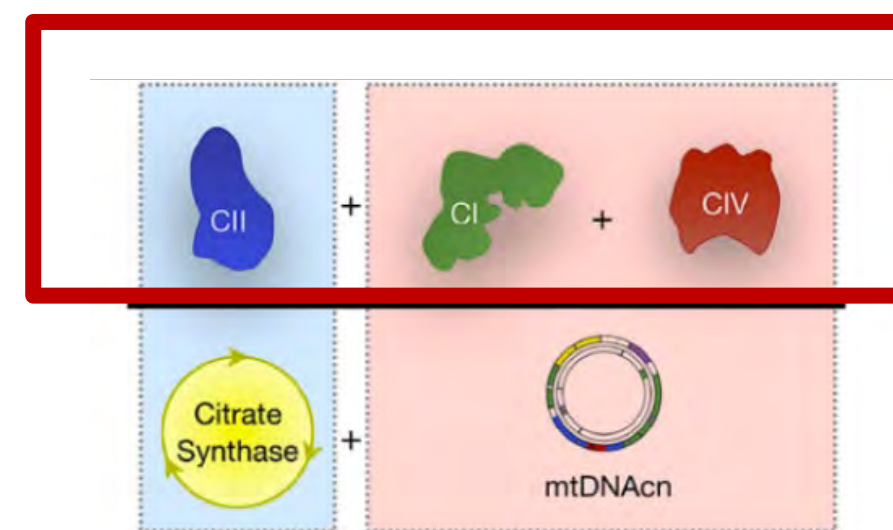
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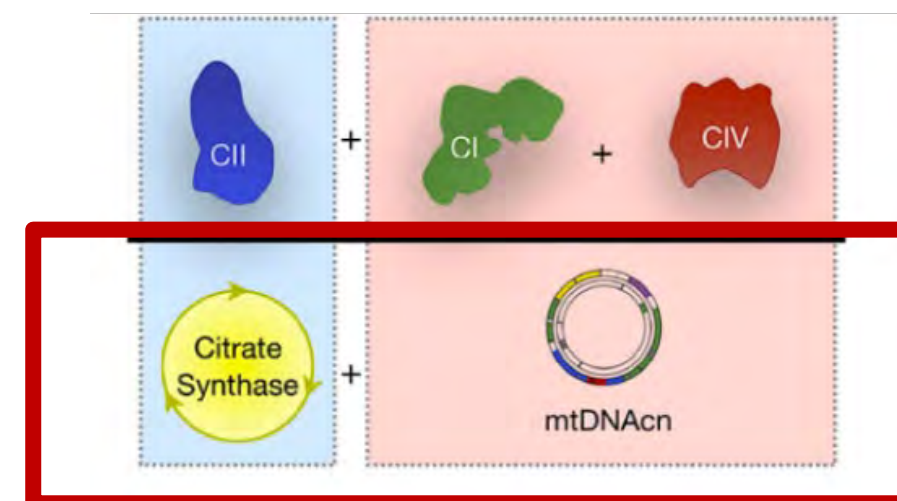
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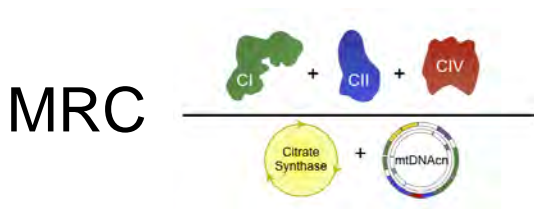
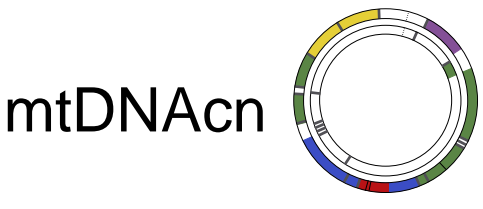
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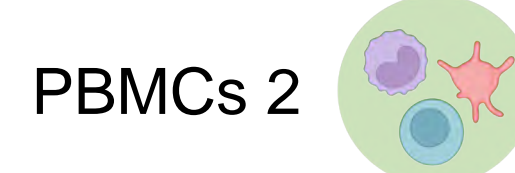
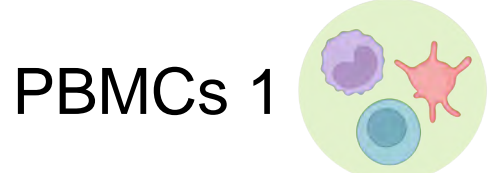
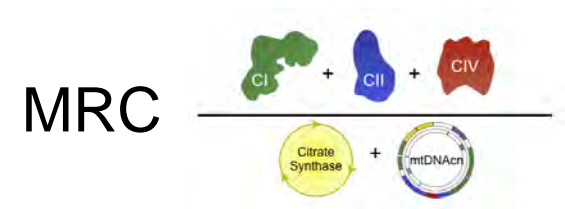
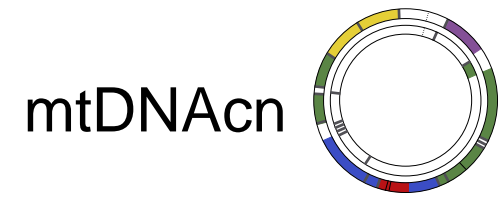
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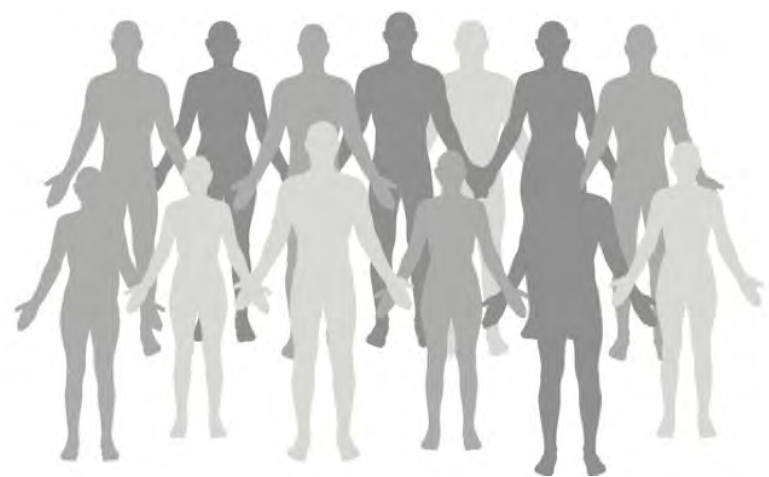
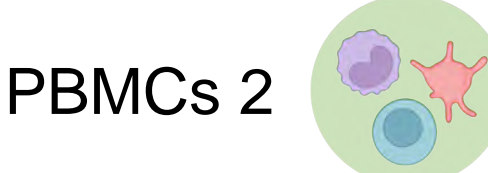
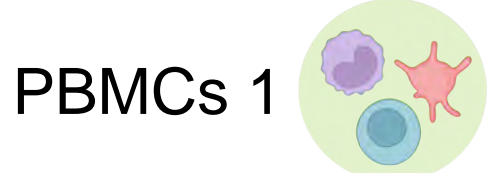
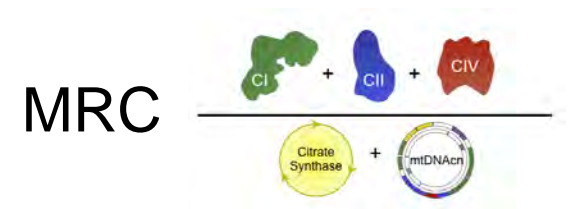
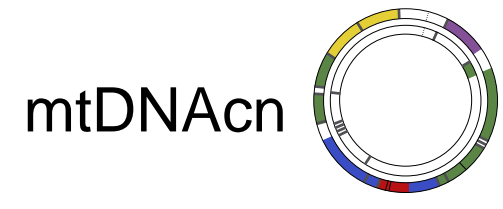
Measurements



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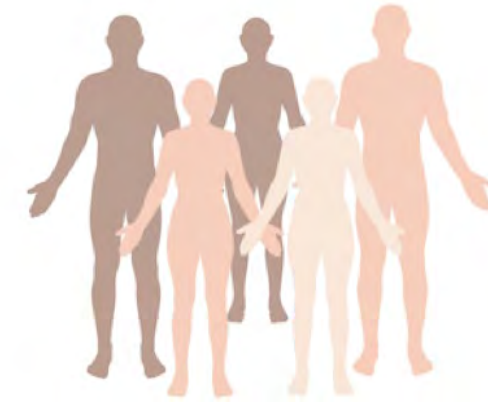
Measurements



Healthy controls
n=68



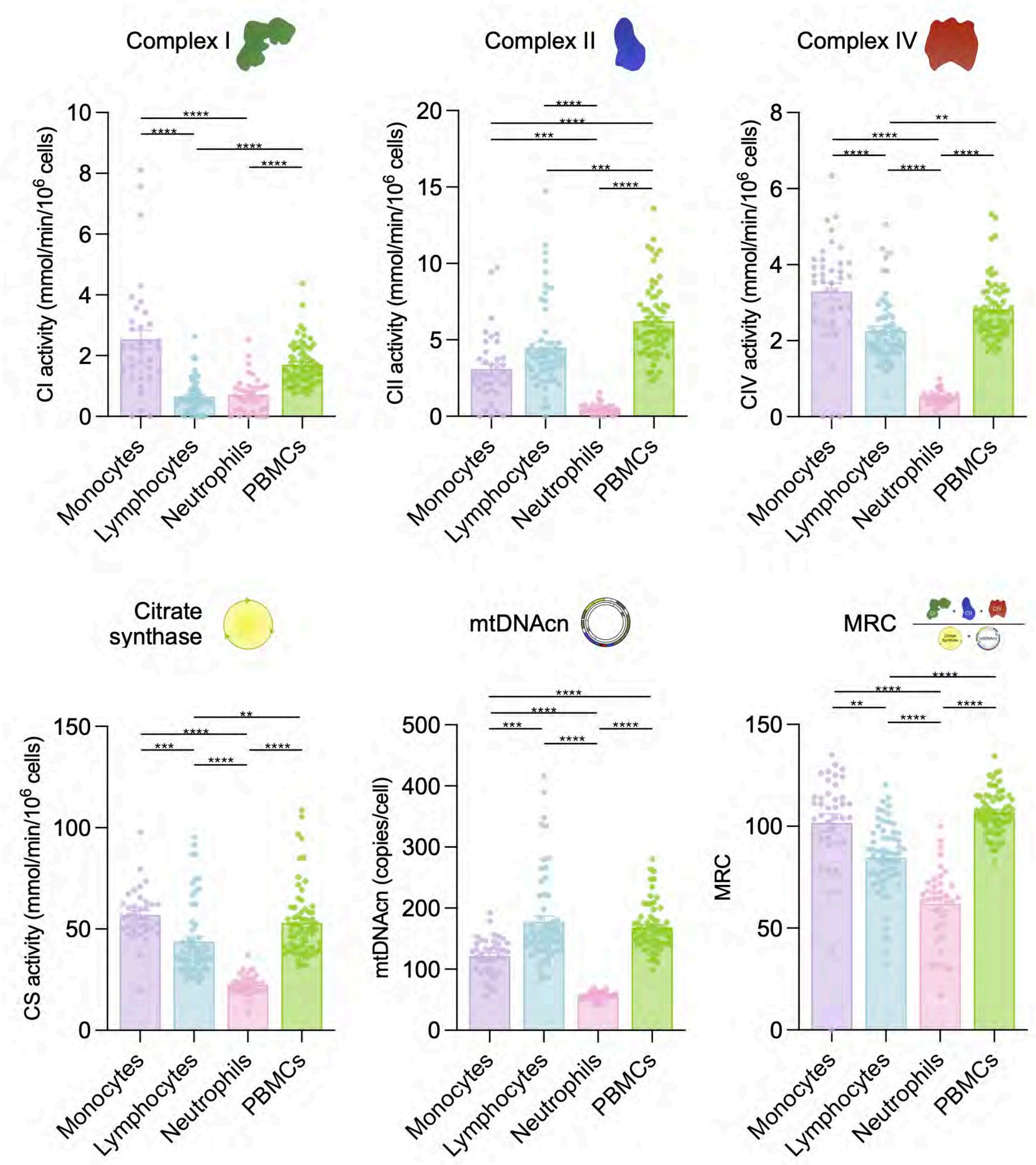
m.3243A>G mutation
n=23



Single large-scale deletion
n=14

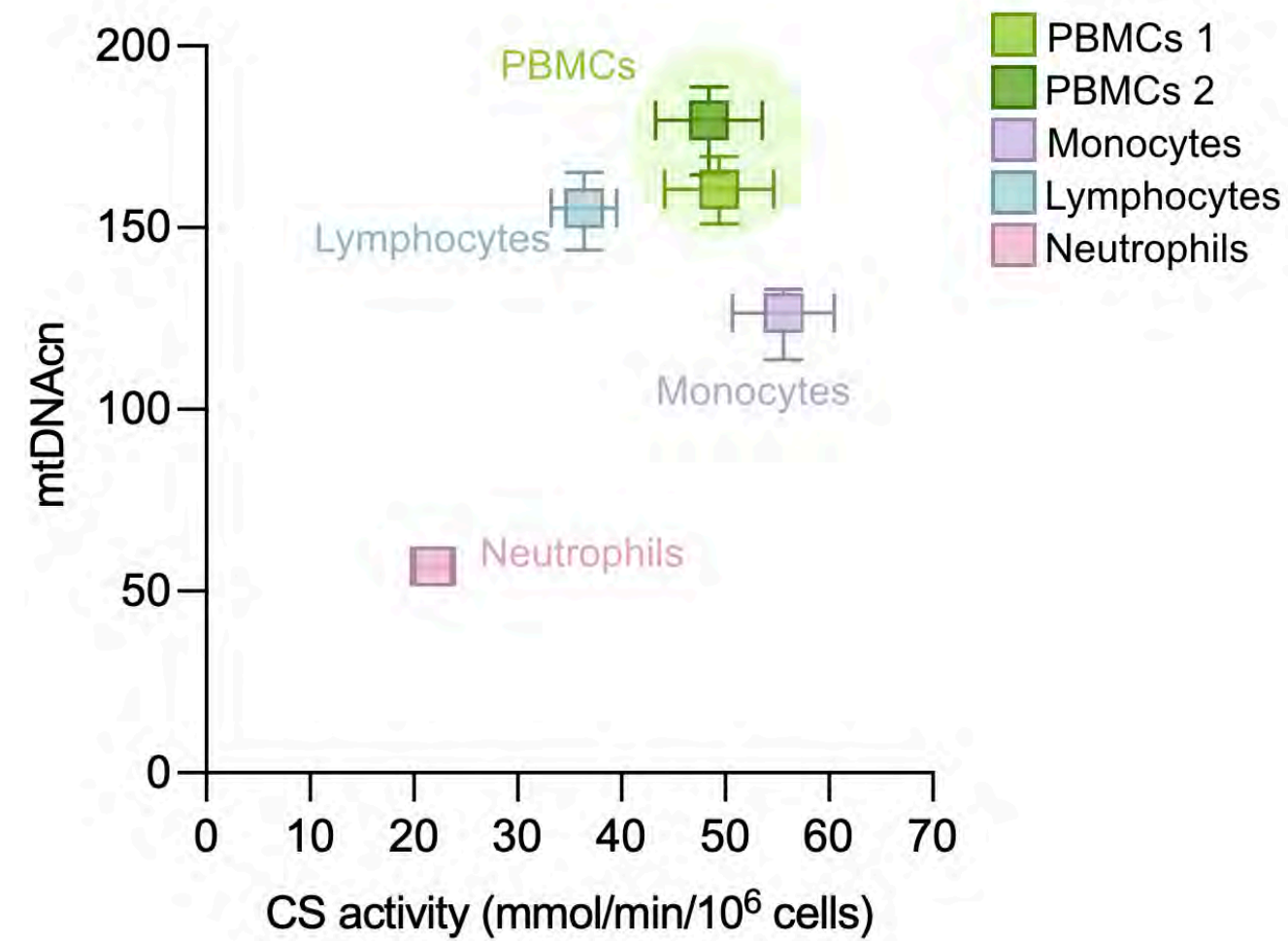
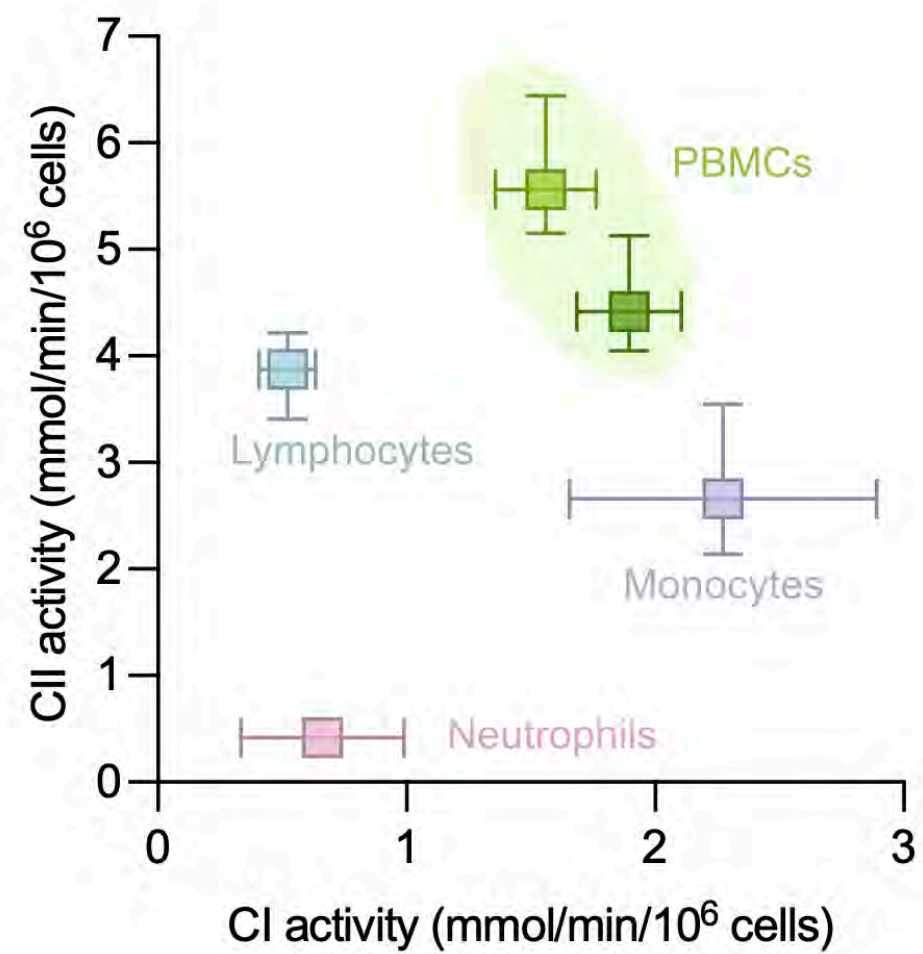
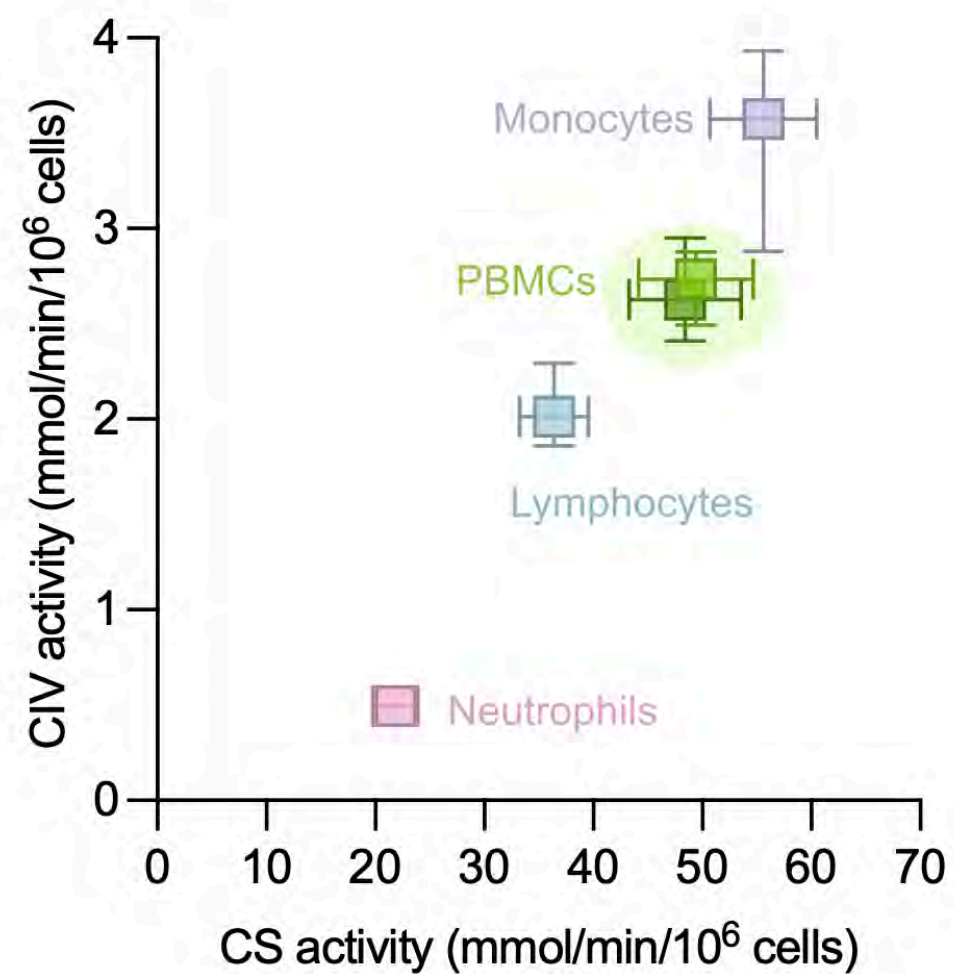
Immune cell subtypes have distinct mitochondrial respiratory capacity measures

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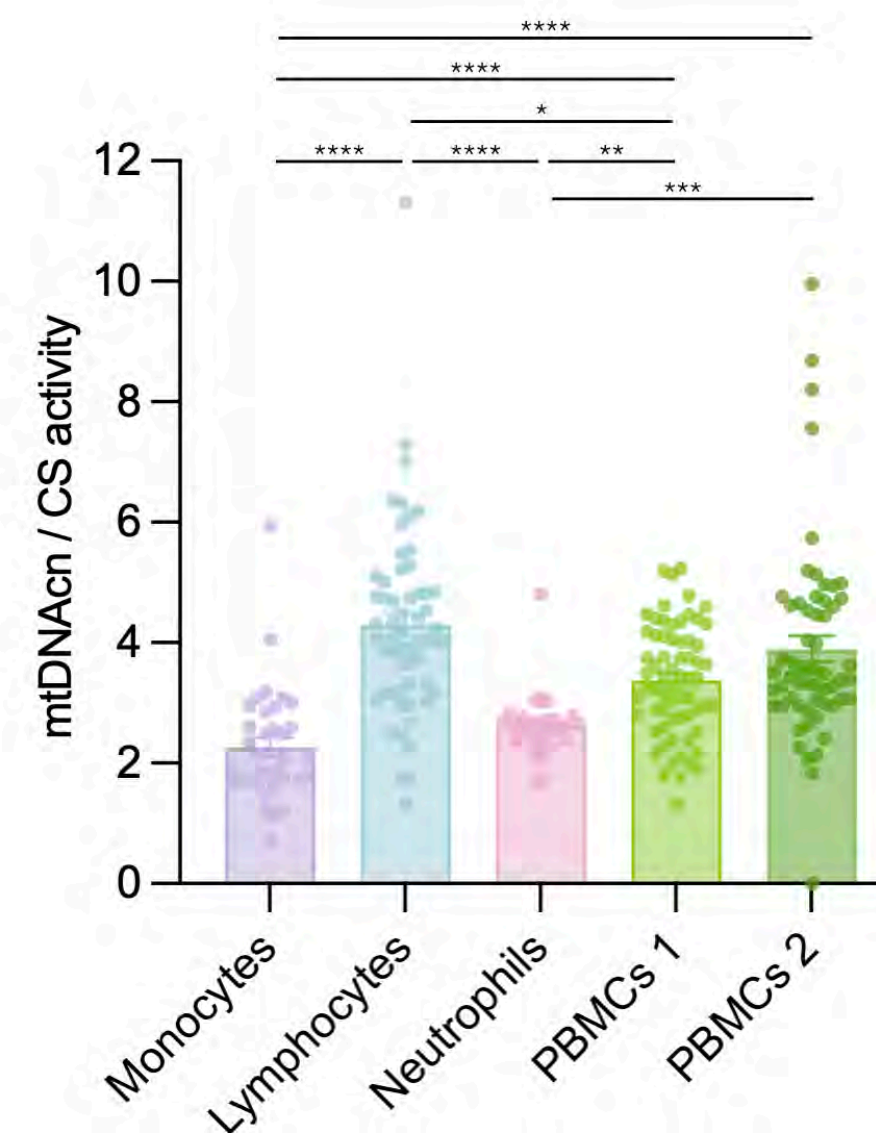
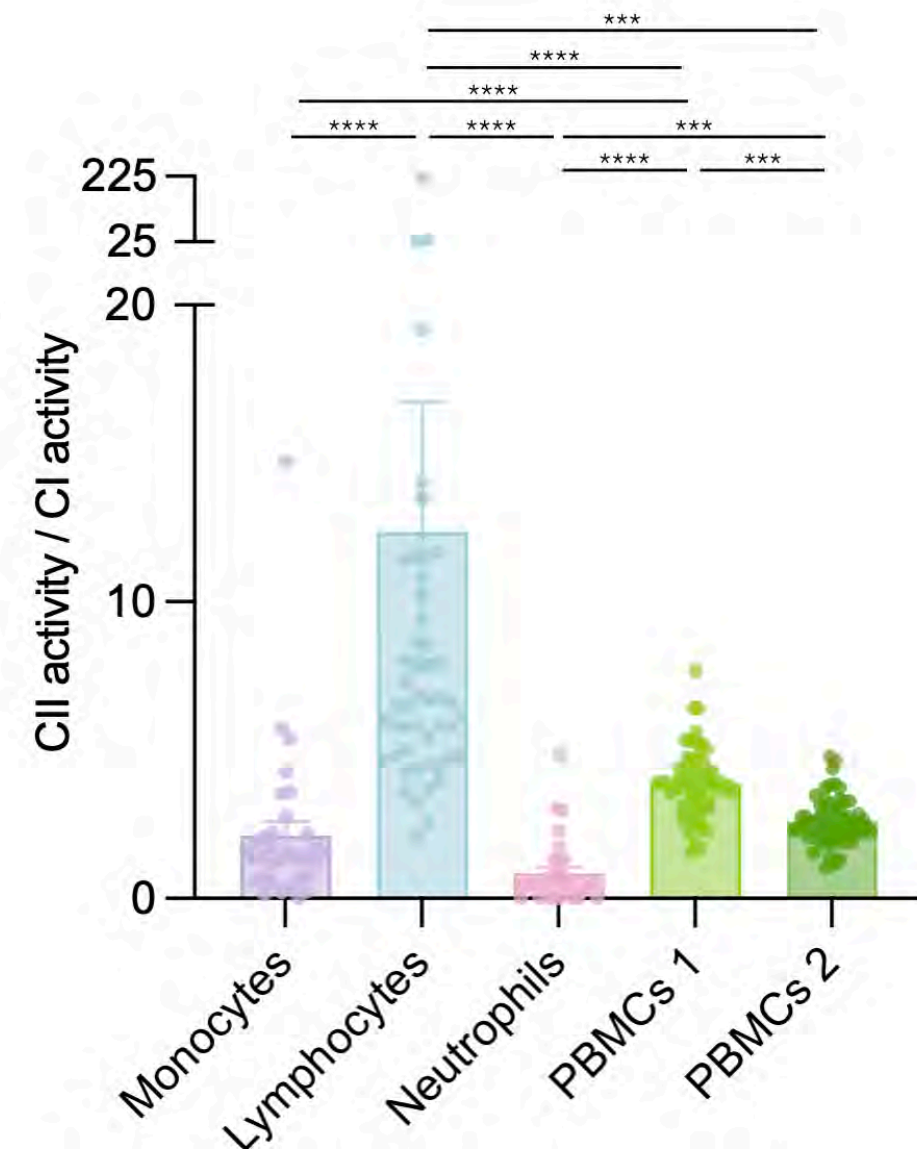
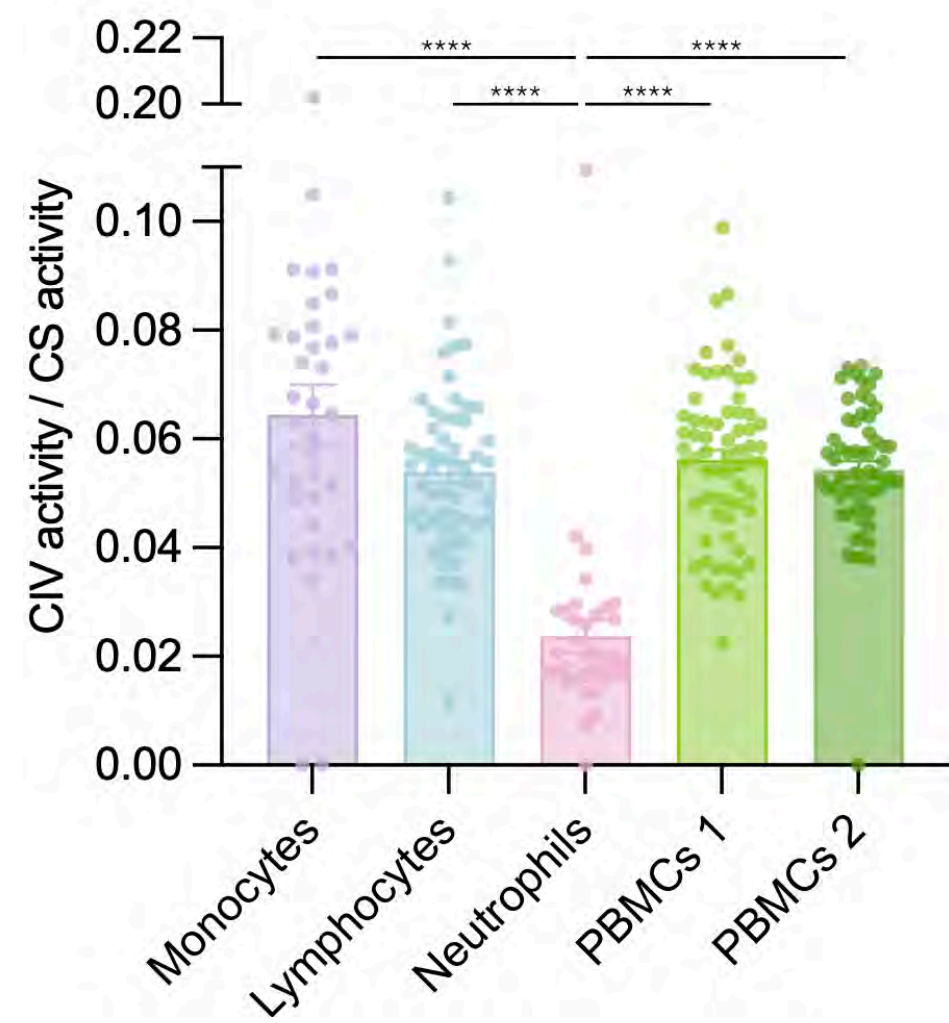
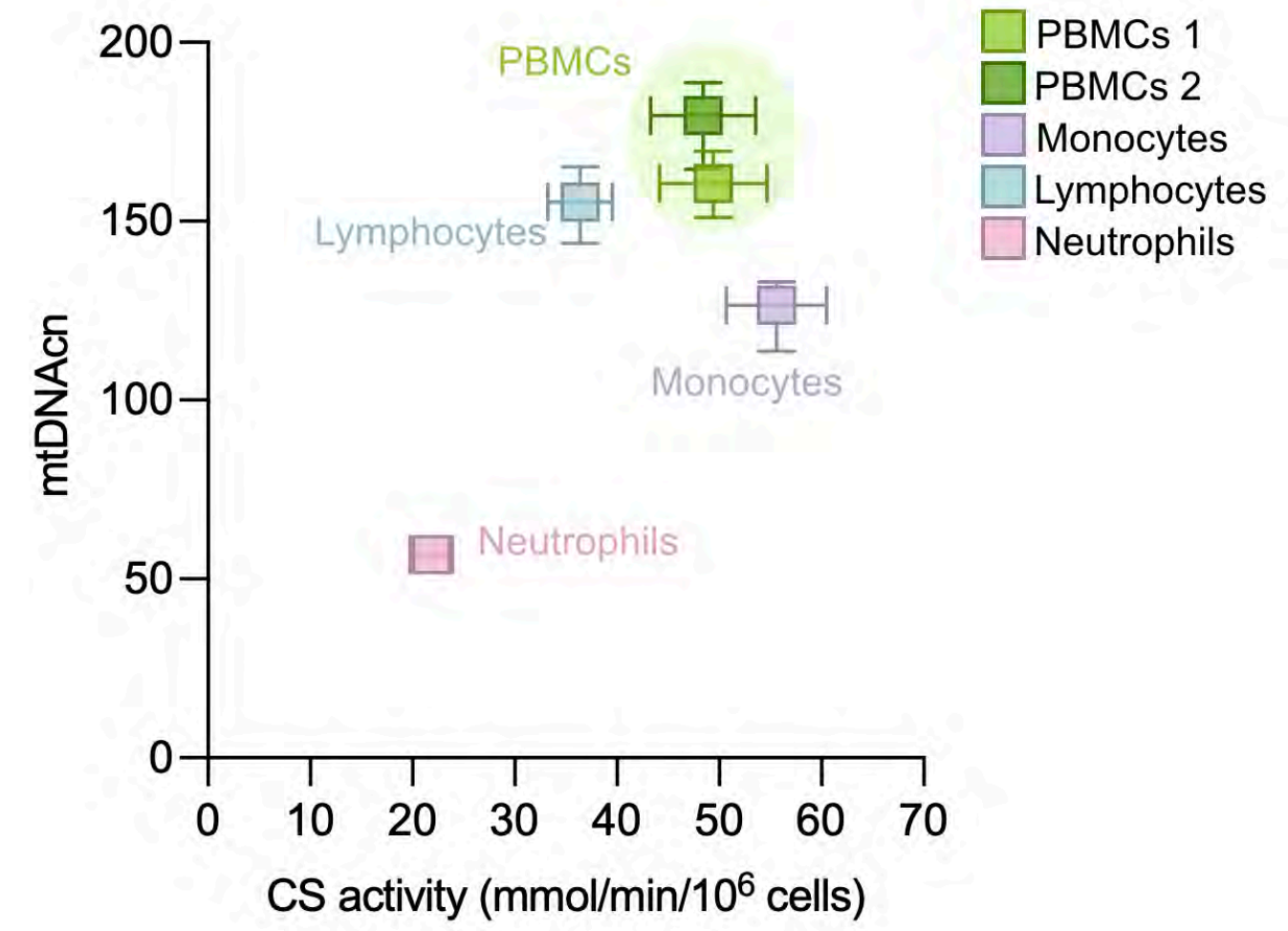
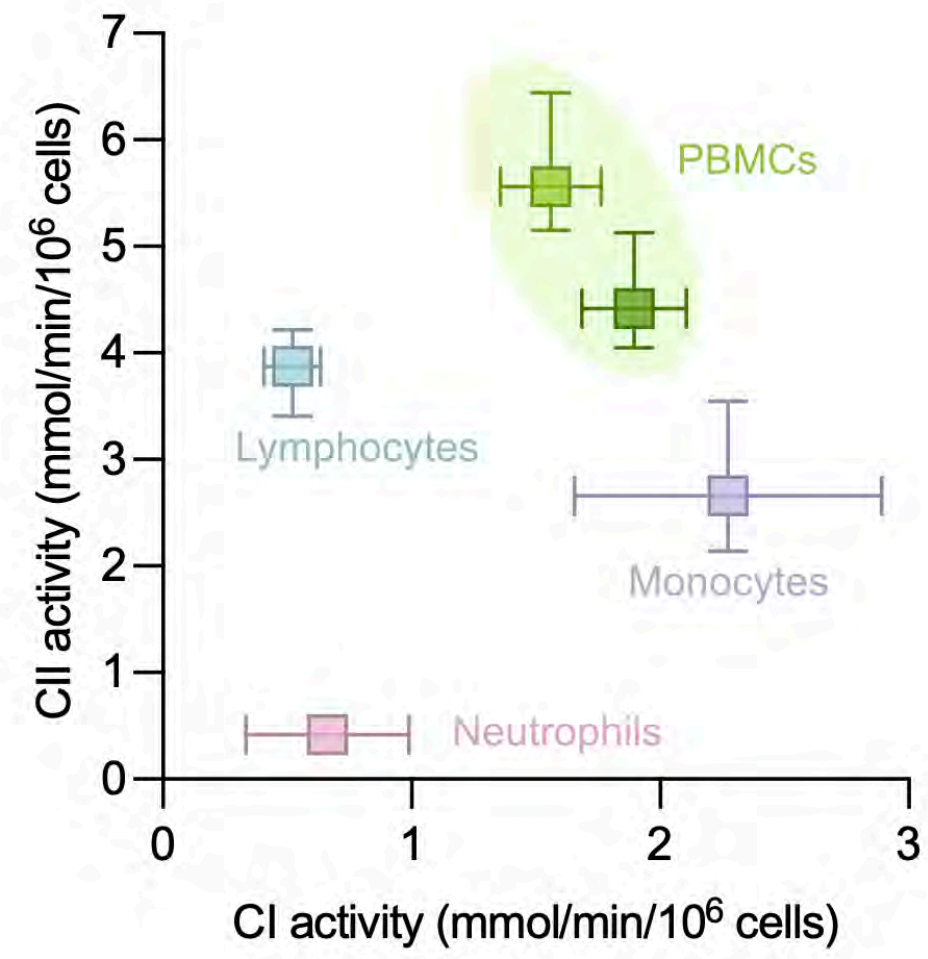
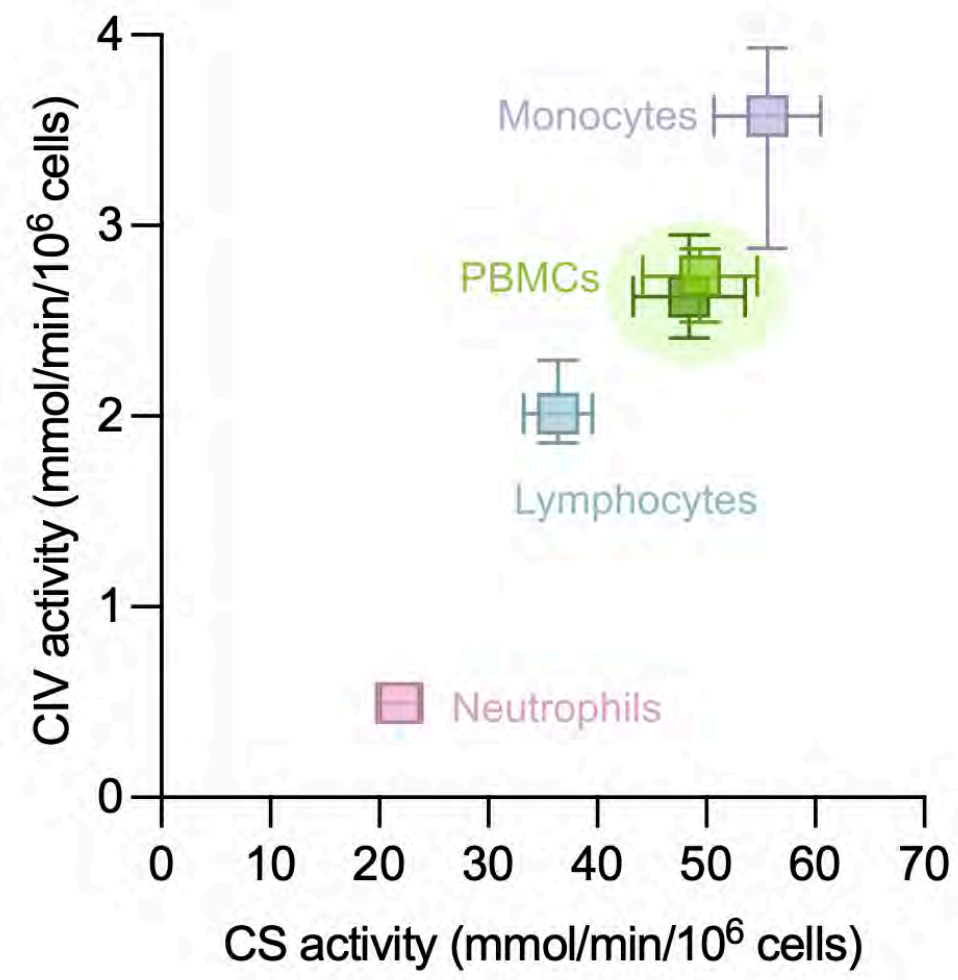


Controls only

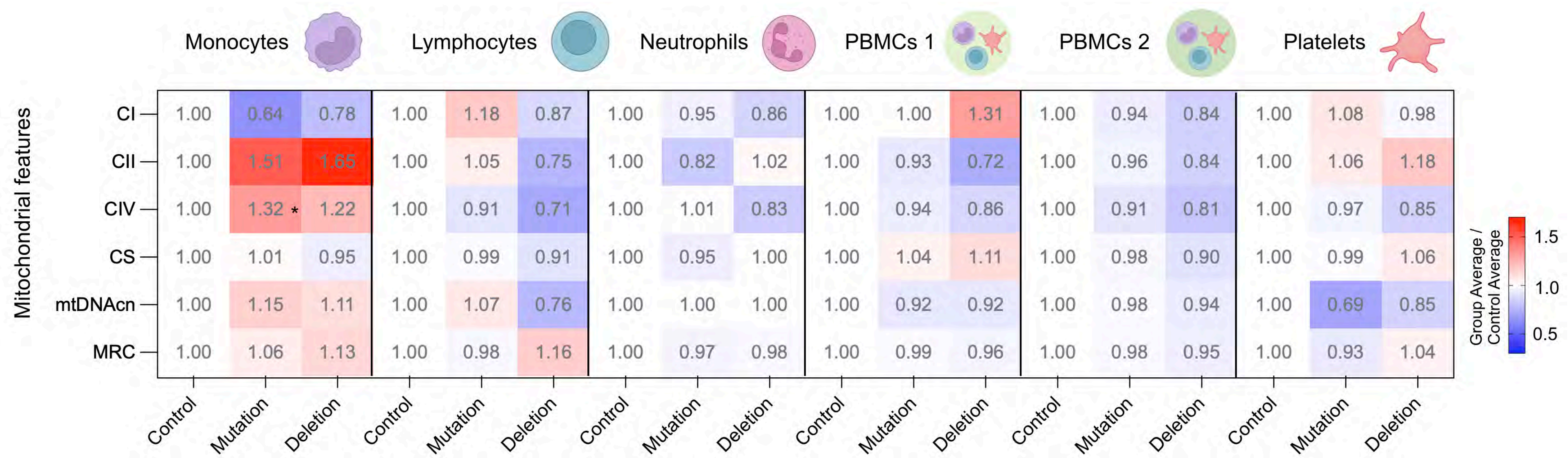
Immune cell subtypes have distinct mitochondrial phenotypes



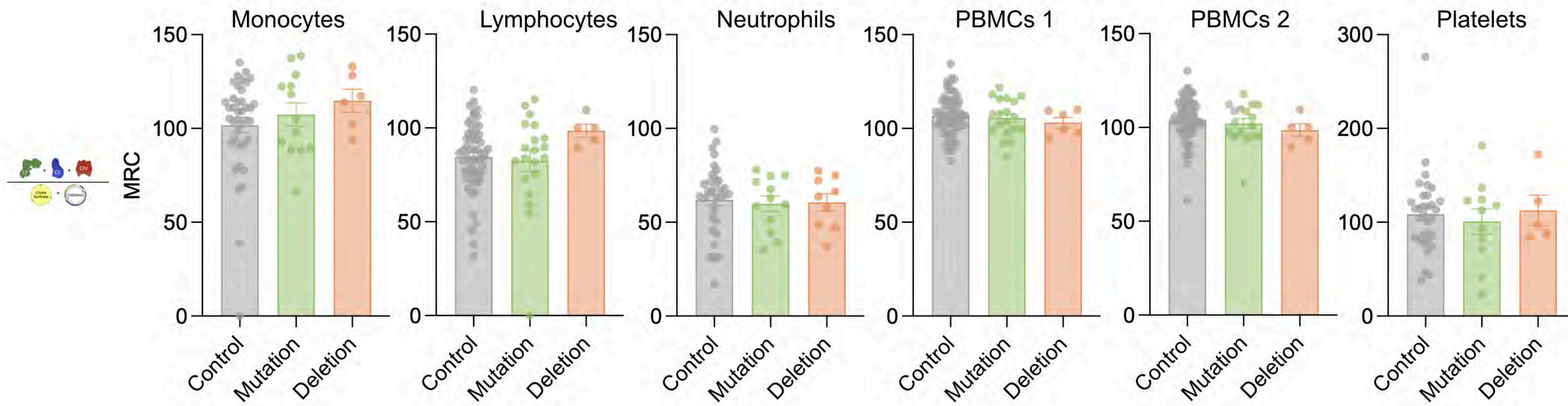
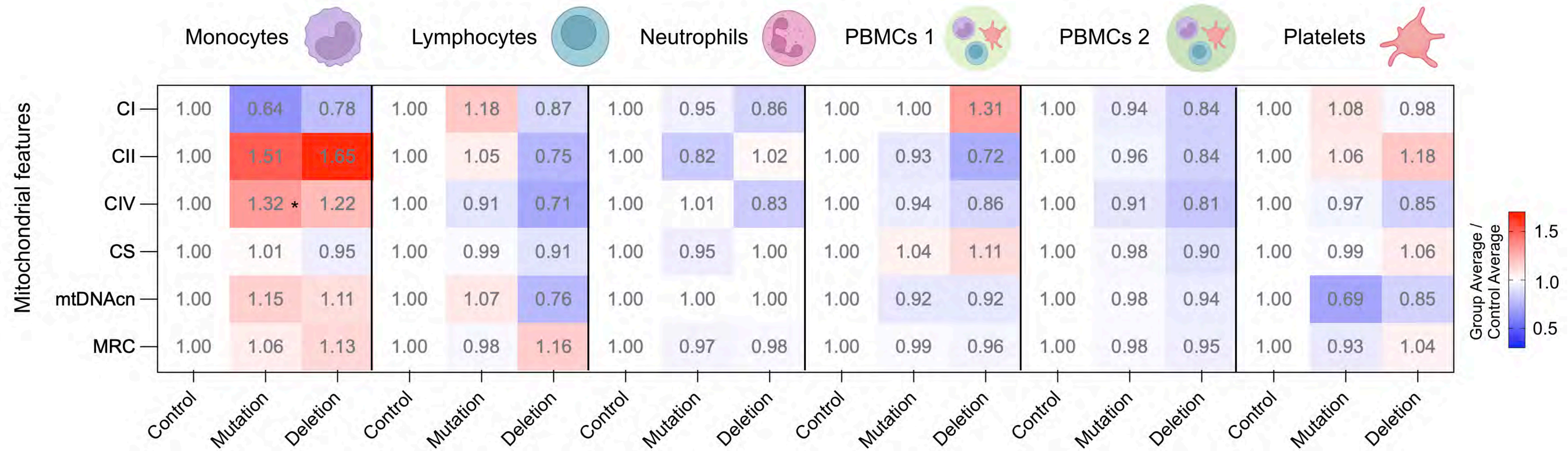
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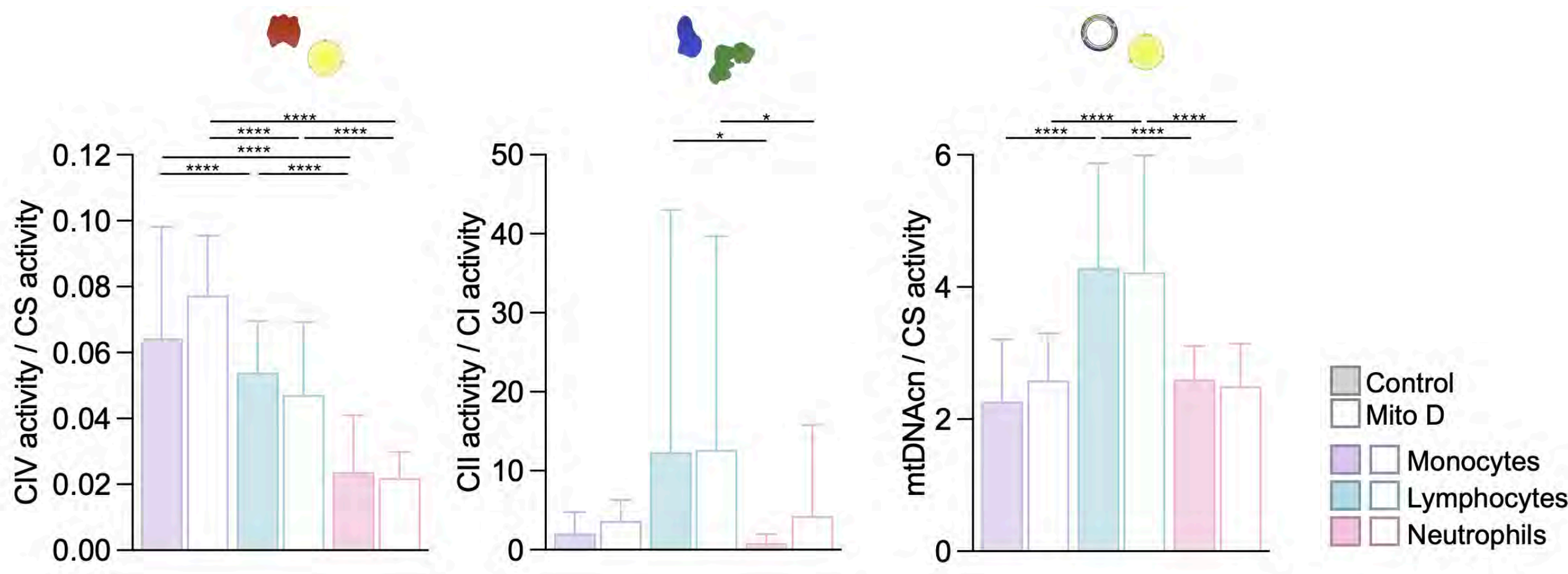
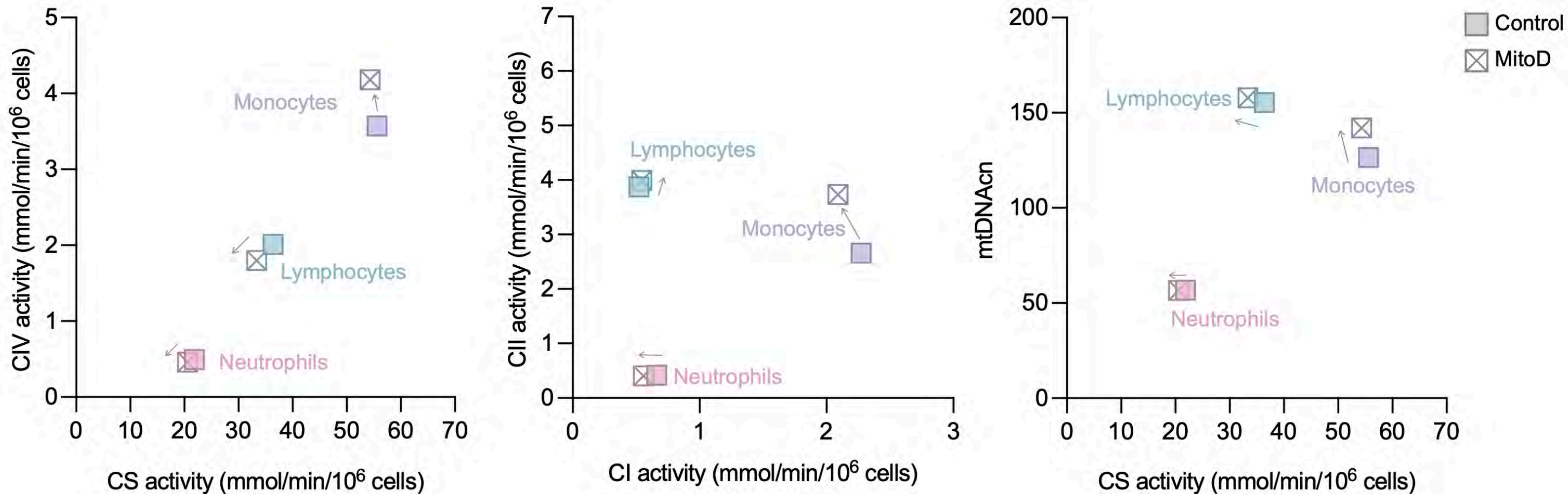
MRC measurements were not significantly affected in Mitochondrial disease



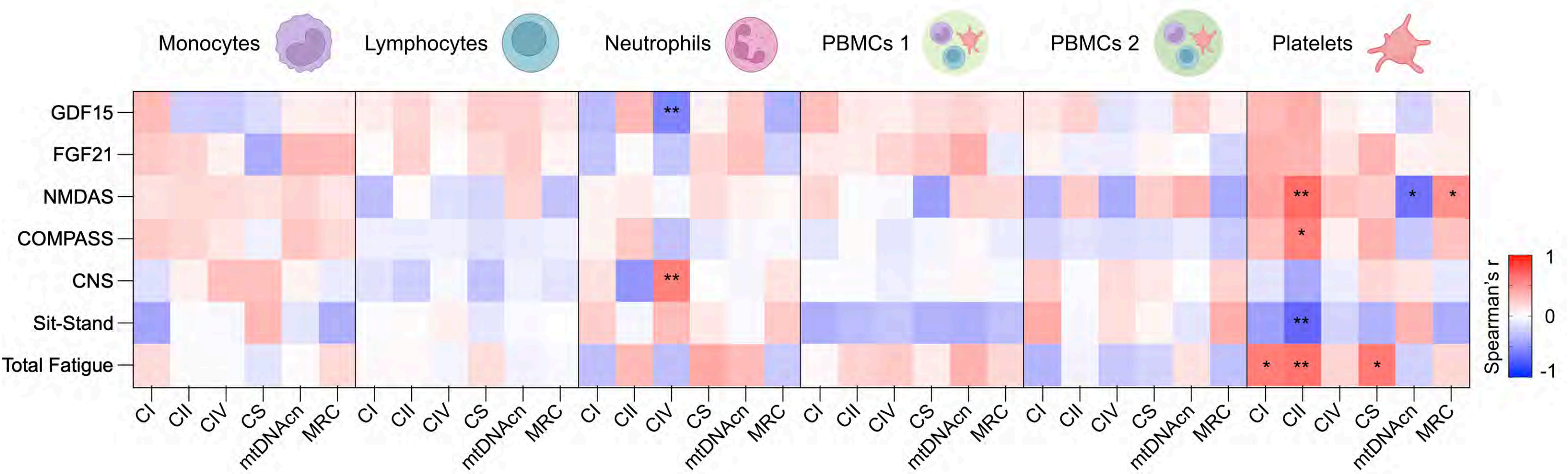
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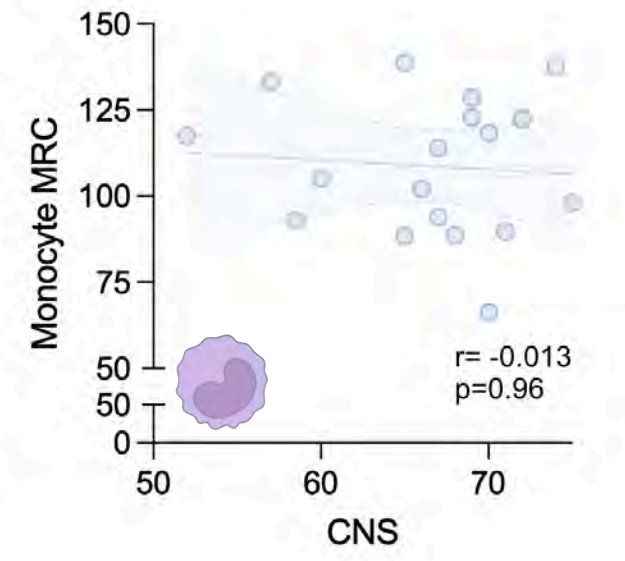
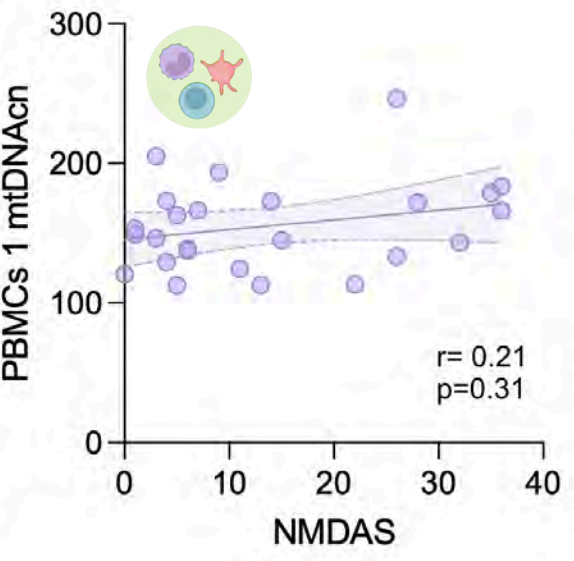
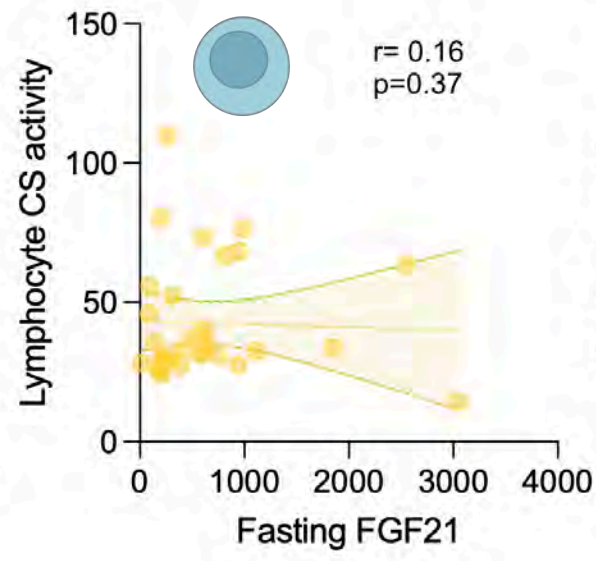
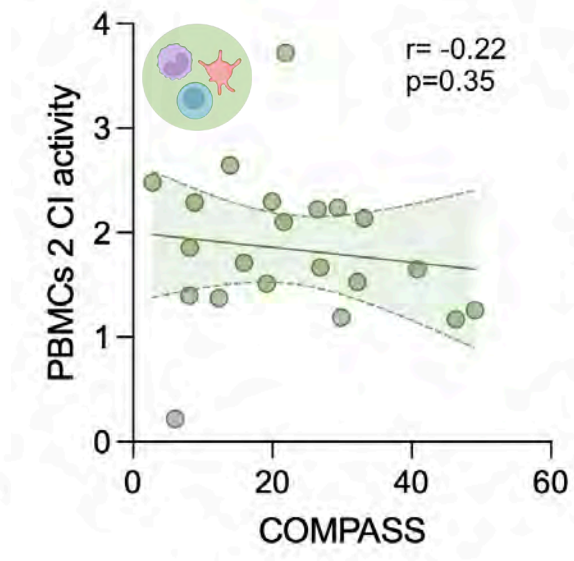
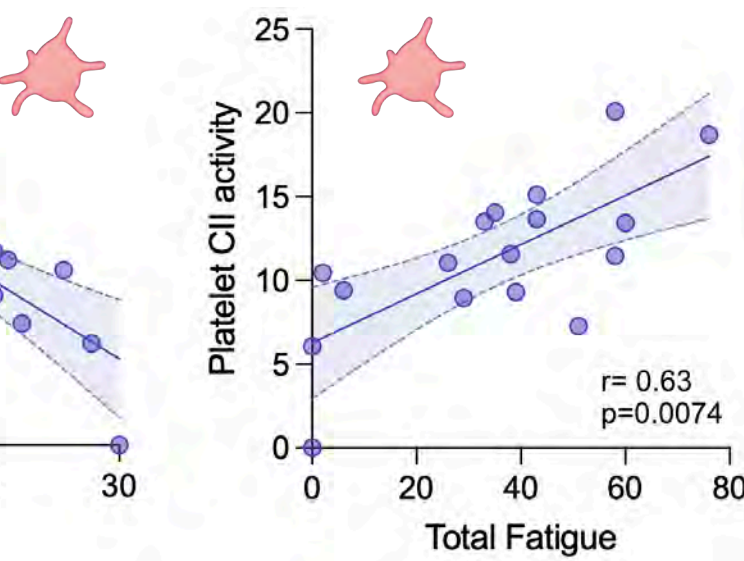
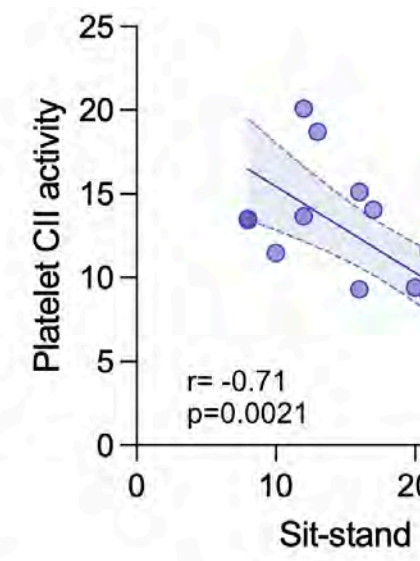
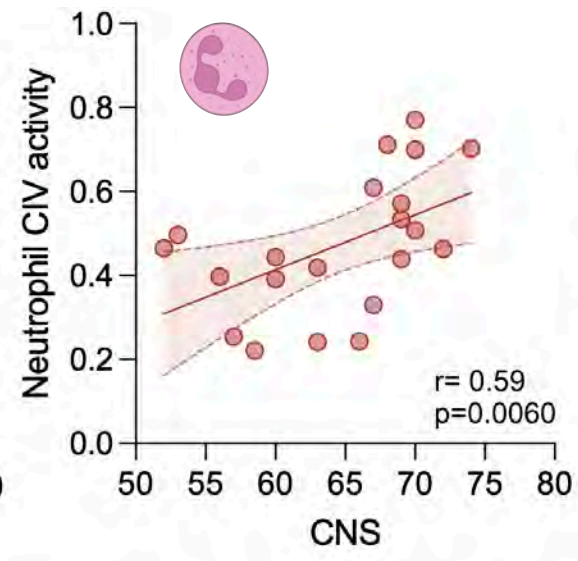
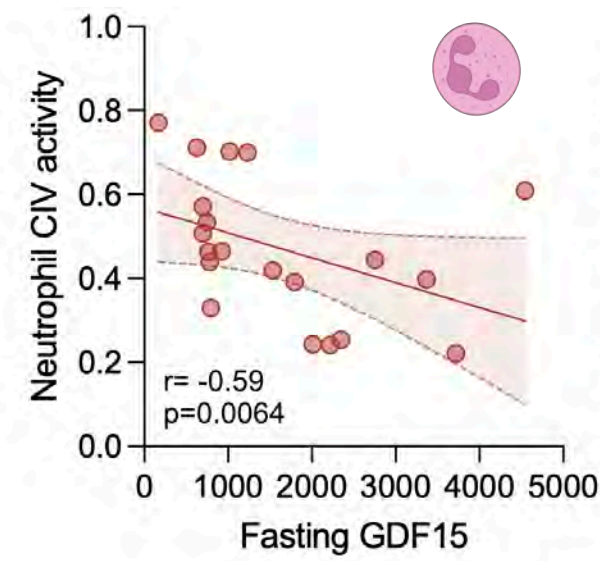
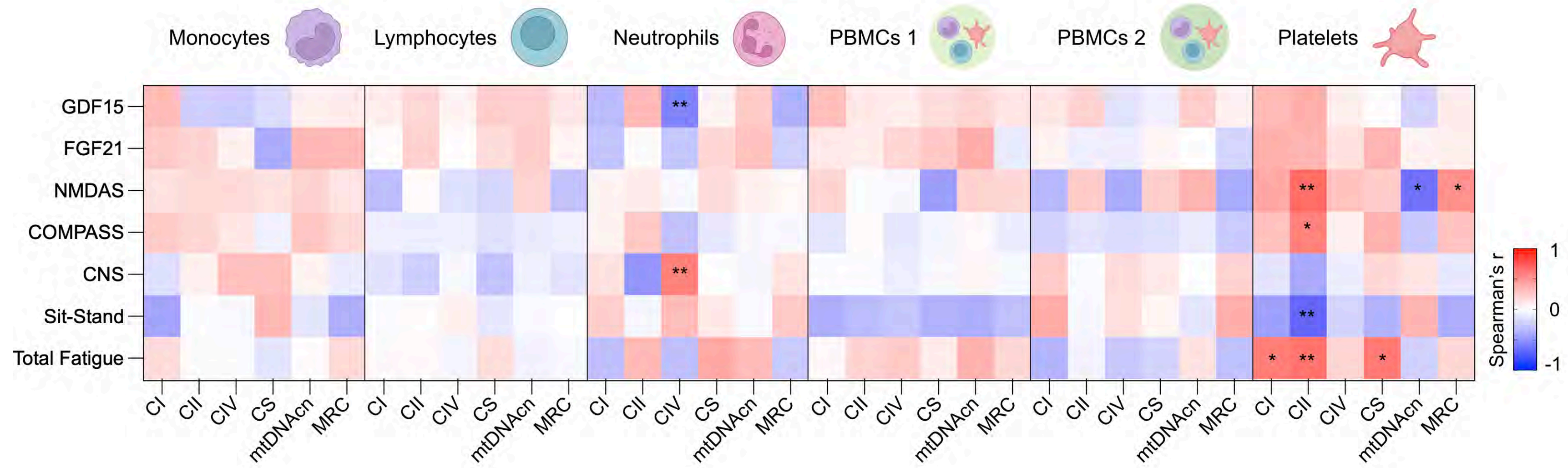
Mitochondrial phenotypes were minimally affected in Mitochondrial disease



Immune cell MRC measurements did not correlate with mitochondrial disease severity

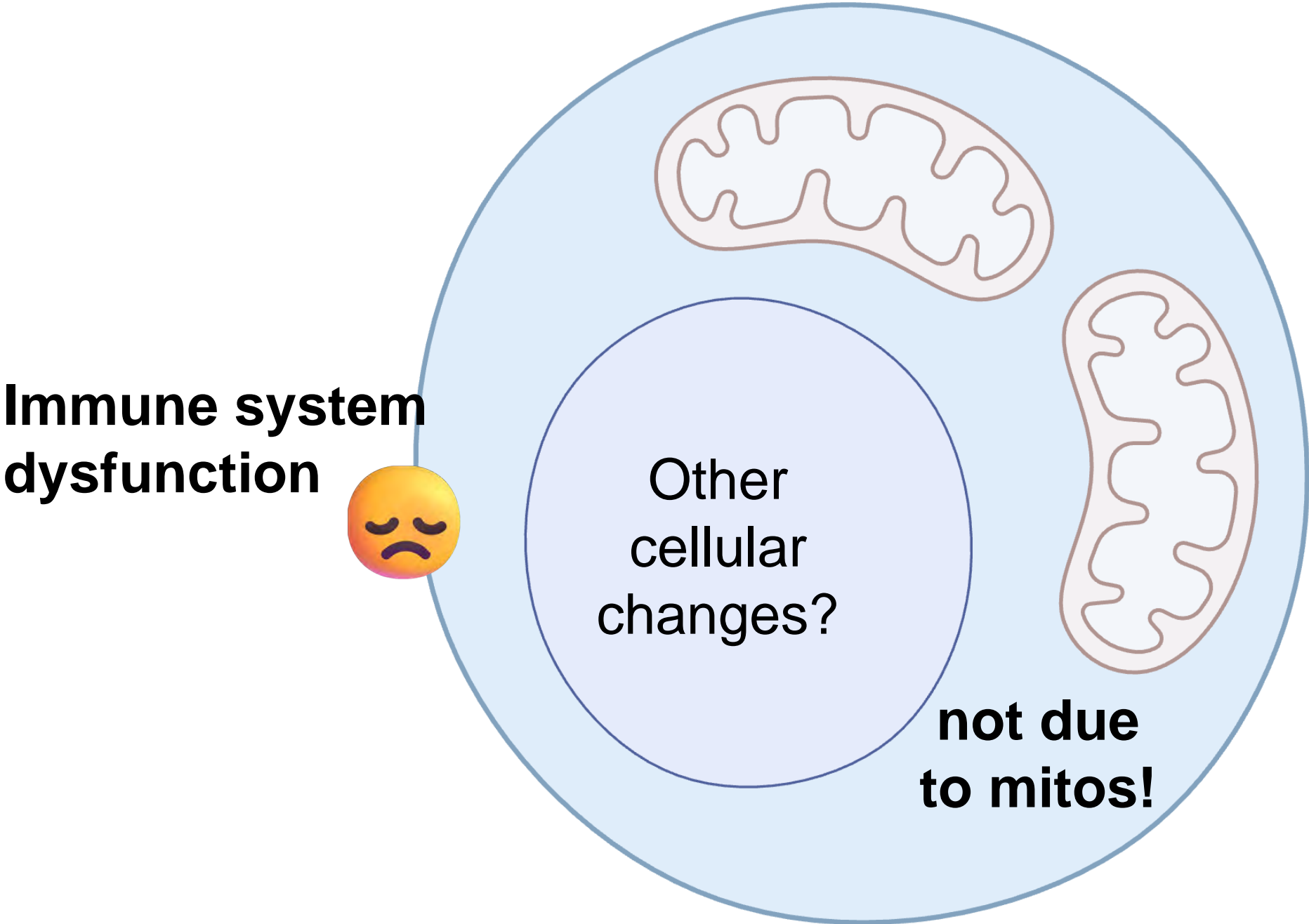


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What could this mean for mitochondrial diseases?

- Immune mitochondrial function is not significantly impaired in MitoD
- Other factors that contribute to immune system dysfunction



Systemic stress response (SNS)

Stress hormones (NE, cortisol)

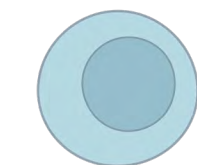
External environment

Psychosocial stress

Relationship to mood disorder symptoms and adversity?

Background

- The mechanisms through which mood disorders develop are not completely understood.
- Adversity and stress are risk factors for developing depression and anxiety:
 - Stress — psychological stress increases risk of depression. (Richter-Levin and Xu 2018)
 - Adversity — early life adversity (ELA) increases risk as well. (Young et al. 1997, Hassel et al. 2011, Liu et al 2017)
- Changes in the immune system have been linked to adversity and stress exposure:
 - changes in immune cell counts & proportion with adversity, but directionality of changes is mixed (Elwenspoek, Luen et al. 2017, Etzel et al. 2022, Apsley et al. 2023)
 - changes in inflammatory immune markers with stress (Malhi & Mann, 2018; Kuhlman et al 2020, Chiang et al. 2022)
 - particular impact on monocytes (Kuhlman et al., 2024; Kuhlman et al., 2025)
- Changes in the immune system have also been linked to mood disorders:
 - changes in immune cell counts & proportion, but directionality of changes is mixed (Stein, Miller, and Trestman 1991; Maes et al. 1992; Irwin et al. 1990)
 - changes in immune cell gene expression. (Cole et al 2012, Schwaiger et al. 2016)

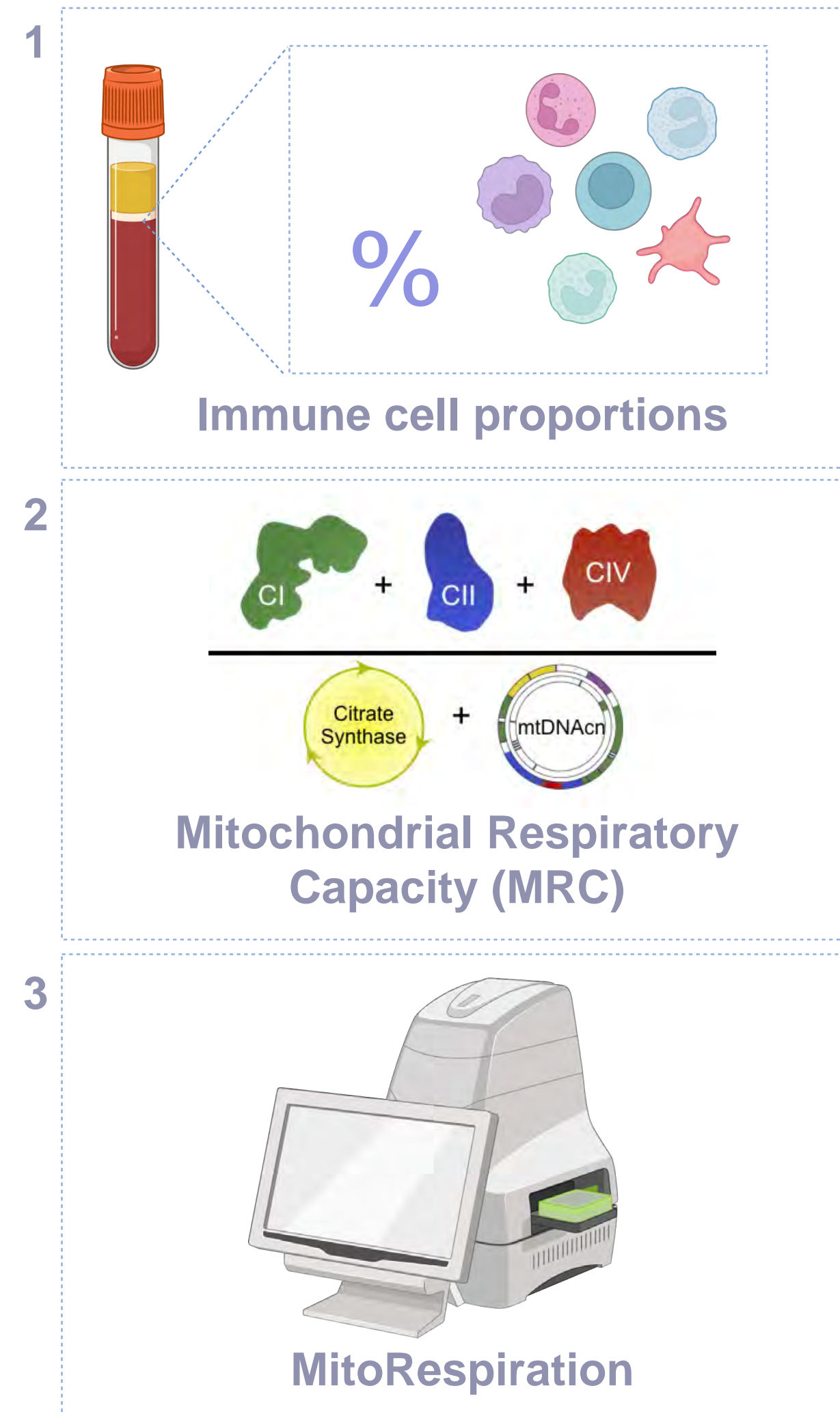
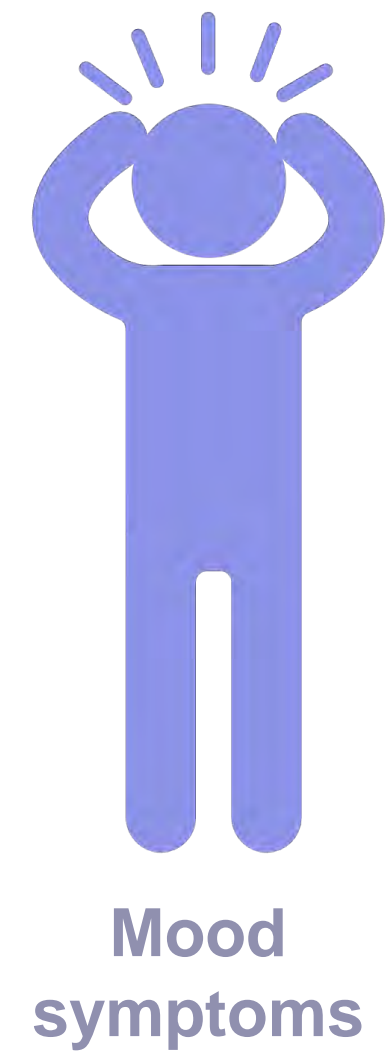


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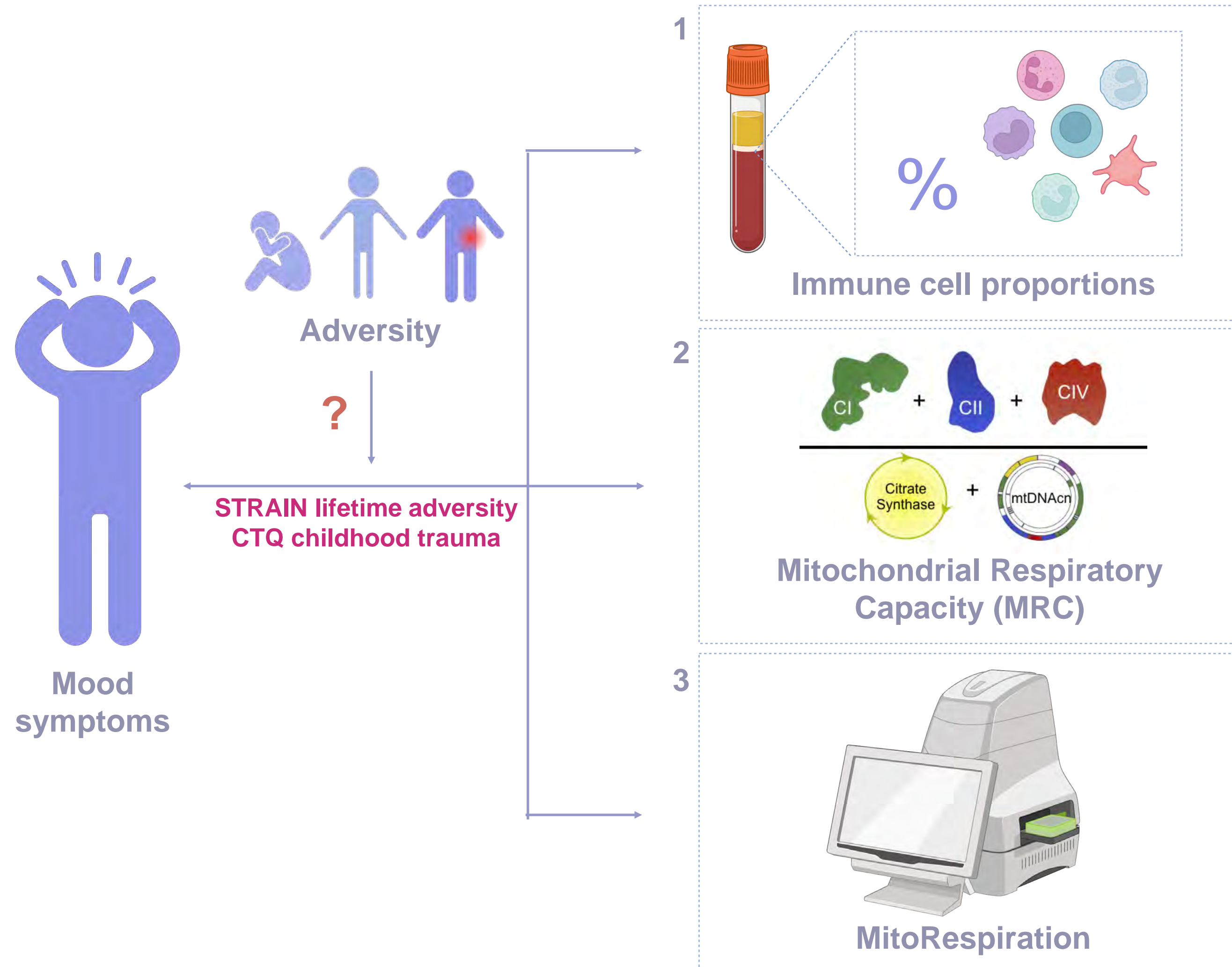


- Changes in mitochondria with stress/adversity exposure:
 - decreased OxPhos activity with stress in rodents (Rezin et al. 2008; Weger et al. 2020; Hunter et al. 2016)
 - decreased respiratory chain protein content in humans. (Trumpff et al. 2024)
 - changes in PBMC respiration in humans (Picard et al., 2018; Wu-Chung et al., 2024, (Boeck et al., 2016; Boeck, Salinas-Manrique, et al., 2018; Gump et al., 2020; Kurkinen et al., 2023)
- Changes in mitochondria with mood disorders:
 - associations with anxiety and depressive link behavior (rodents). (Filiou et al., 2011; Gebara et al., 2021; Rosenberg et al., 2023)
 - decreased brain mitochondrial respiratory complex activity, gene and protein levels in mood disorders (humans). (Andreazza et al., 2010; Ben-Shachar & Karry, 2008; Holper et al., 2019; Konradi et al., 2004; Sun et al., 2006; Whatley et al., 1996)
 - mixed changes in immune cell mitochondrial biology (de Sousa et al., 2015; Fernström et al., 2021; Fisar et al., 2019; Gamradt et al., 2021; Akarsu et al., 2015)
- Interactions between mood disorders and adversity on mitochondrial biology in PBMCs and whole blood. (Boeck, Salinas-Manrique, et al., 2018)
- Cell-type specificity?

Objectives

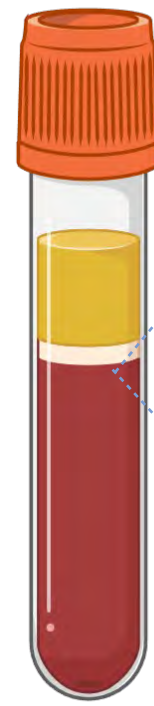
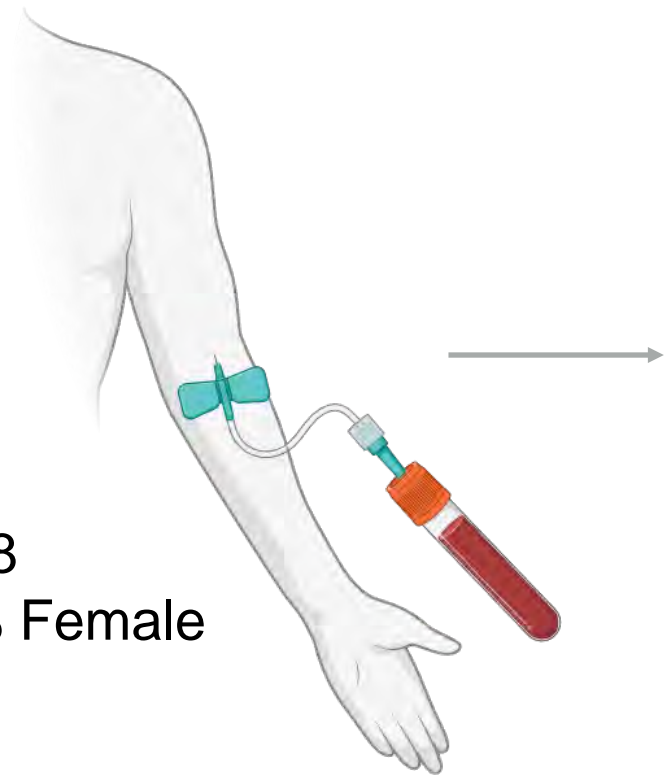


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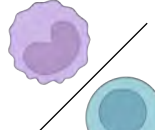

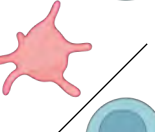
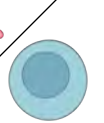






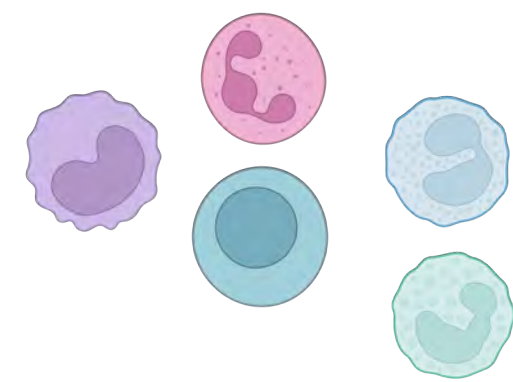
n=68
68% Female



Immune cell proportions

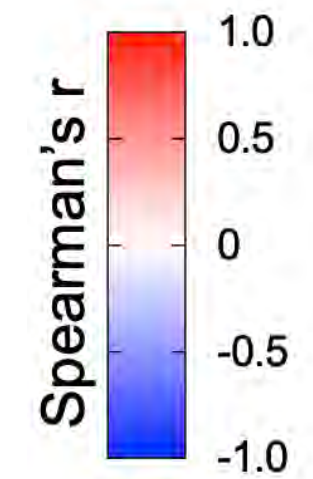
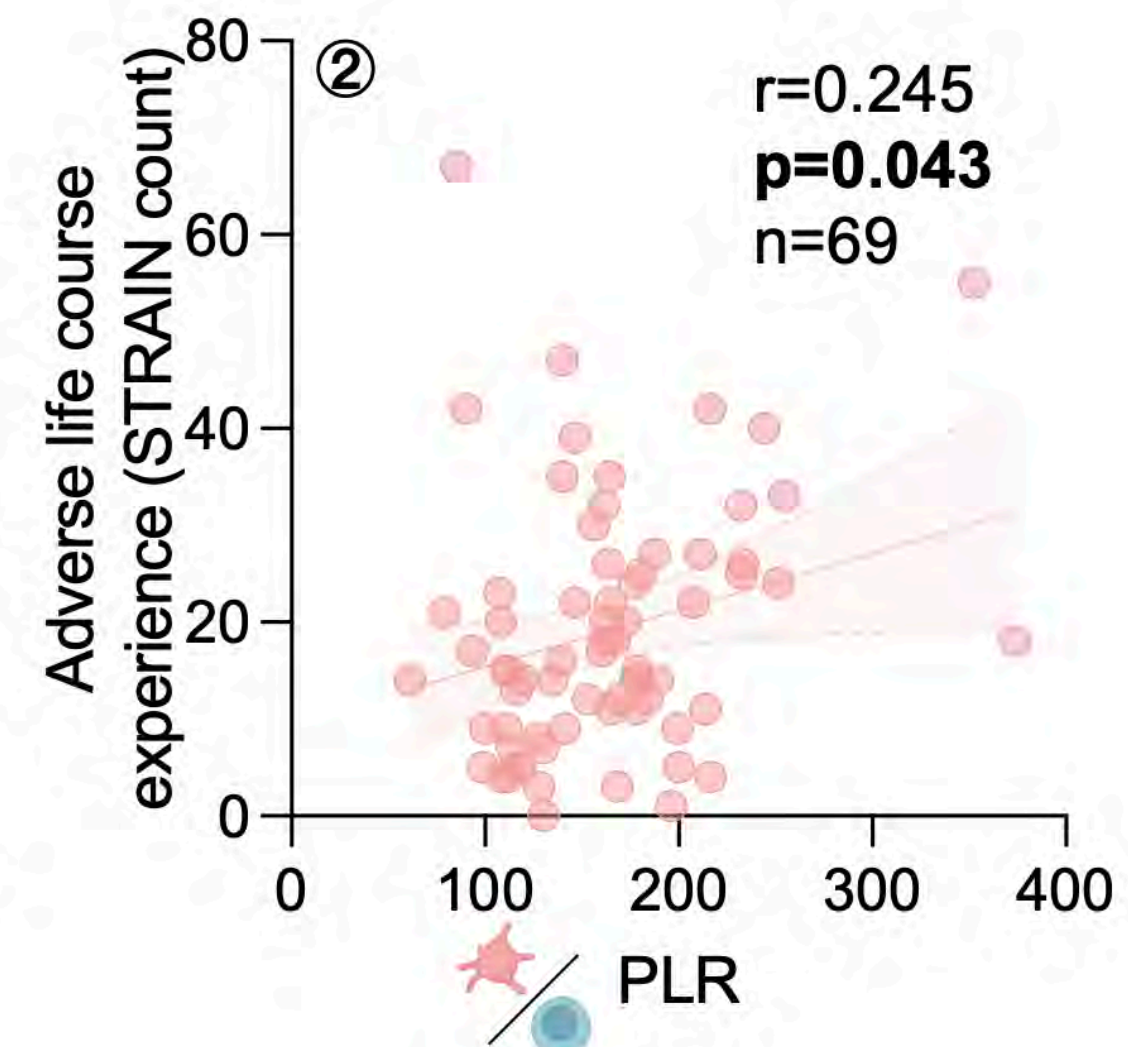
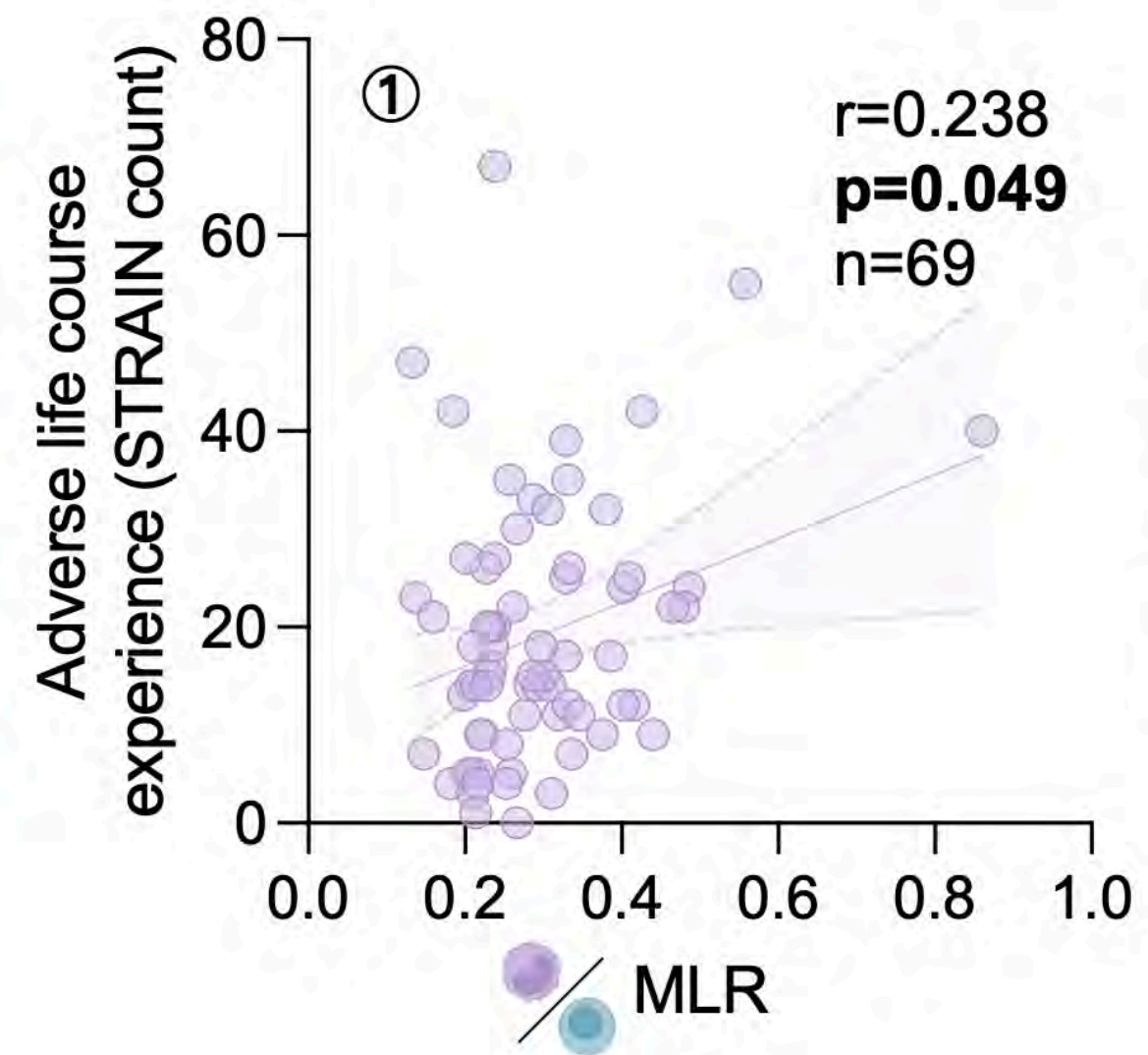
-  % Neutrophils
-  % Lymphocytes
-  % Monocytes
-  /  Neutrophil to Lymphocyte Ratio (NLR)
-  /  Monocyte to Lymphocyte Ratio (MLR)
-  /  Platelet to Lymphocyte Ratio (PLR)
-  % Eosinophils
-  % Basophils

WBC composition and adversity

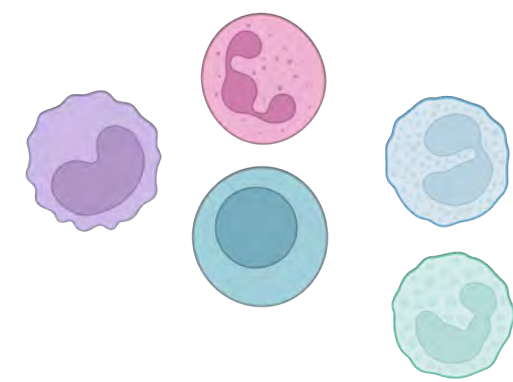


WBC composition and adversity

	Adverse childhood experience (CTQ Sum)	Adverse life course experience (STRAIN count)	Adverse life course experience (STRAIN severity)
% Neutrophils	0.098	0.189	0.127
% Lymphocytes	-0.123	-0.226	-0.162
% Monocytes	-0.040	0.055	0.056
% Eosinophils	0.007	-0.233	-0.237
% Basophils	-0.025	-0.078	-0.102
MLR	0.053	① 0.238*	0.216
NLR	0.120	0.220	0.154
PLR	0.236	② 0.245*	0.226

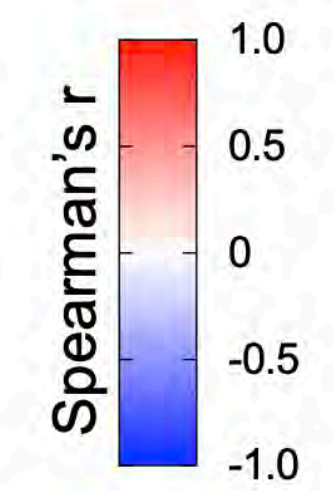
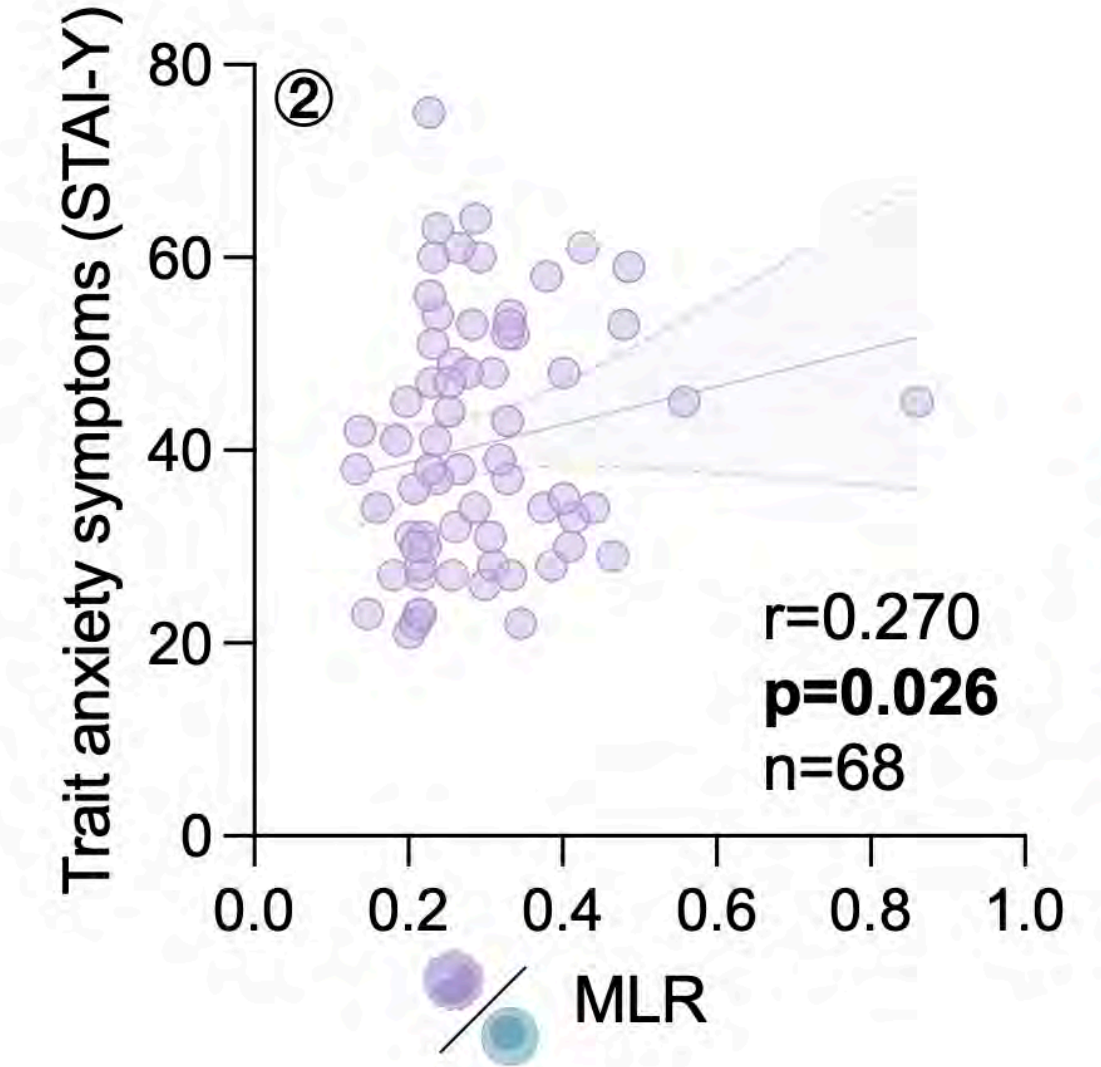
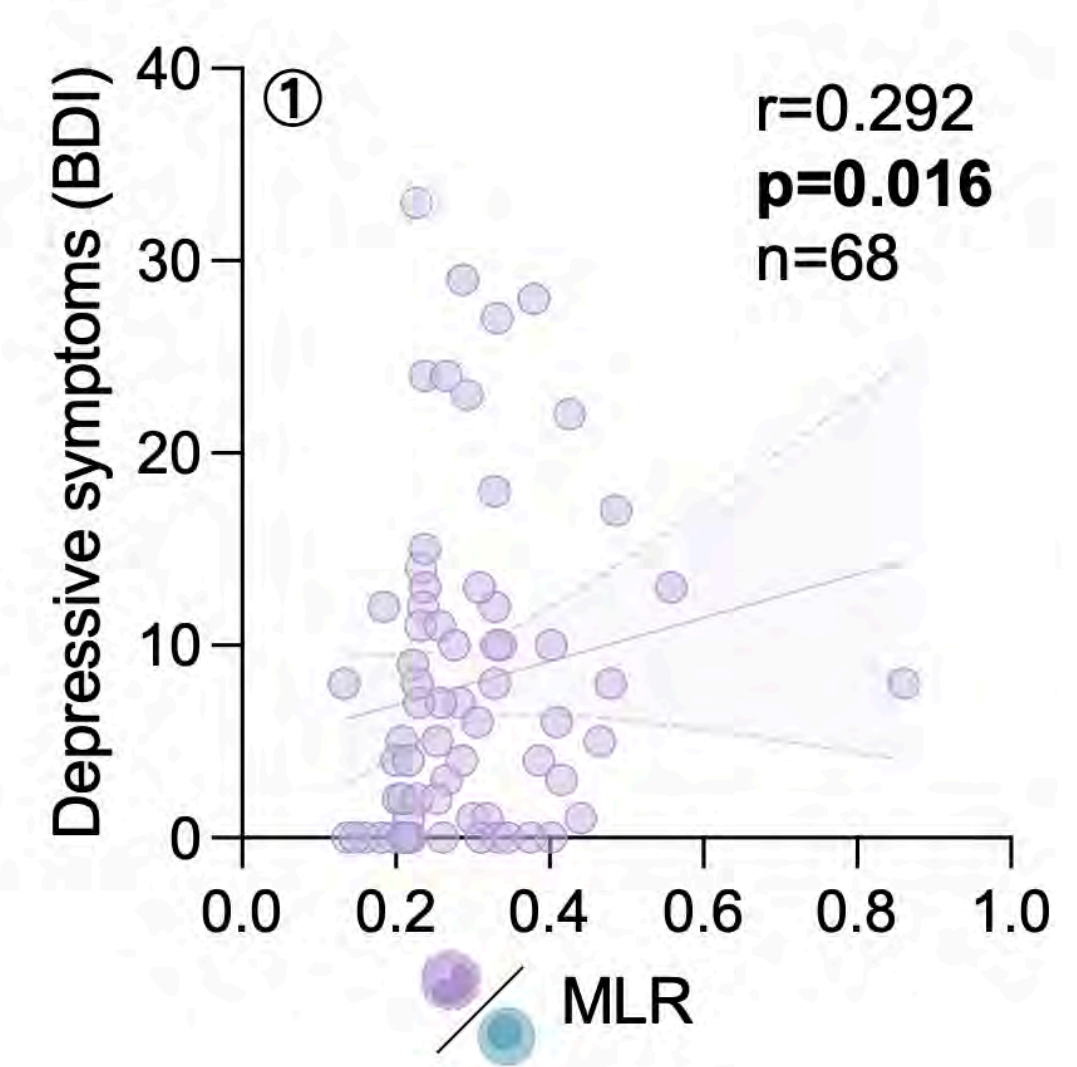


WBC composition and mood symptoms

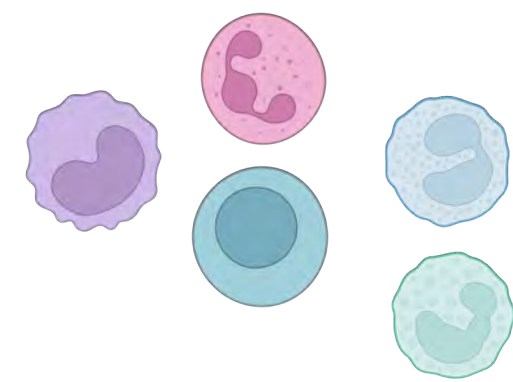


WBC composition and mood symptoms

	Depressive symptoms (BDI)	Trait anxiety (STAI-Y)	State anxiety (STAI-Y)
% Neutrophils	0.097	0.045	-0.132
% Lymphocytes	-0.183	-0.139	0.078
% Monocytes	0.151	0.116	0.166
% Eosinophils	-0.020	-0.006	0.010
% Basophils	0.057	0.002	-0.009
MLR ^①	0.292 * ^②	0.270 *	0.147
NLR	0.149	0.094	-0.114
PLR	0.155	0.147	0.048



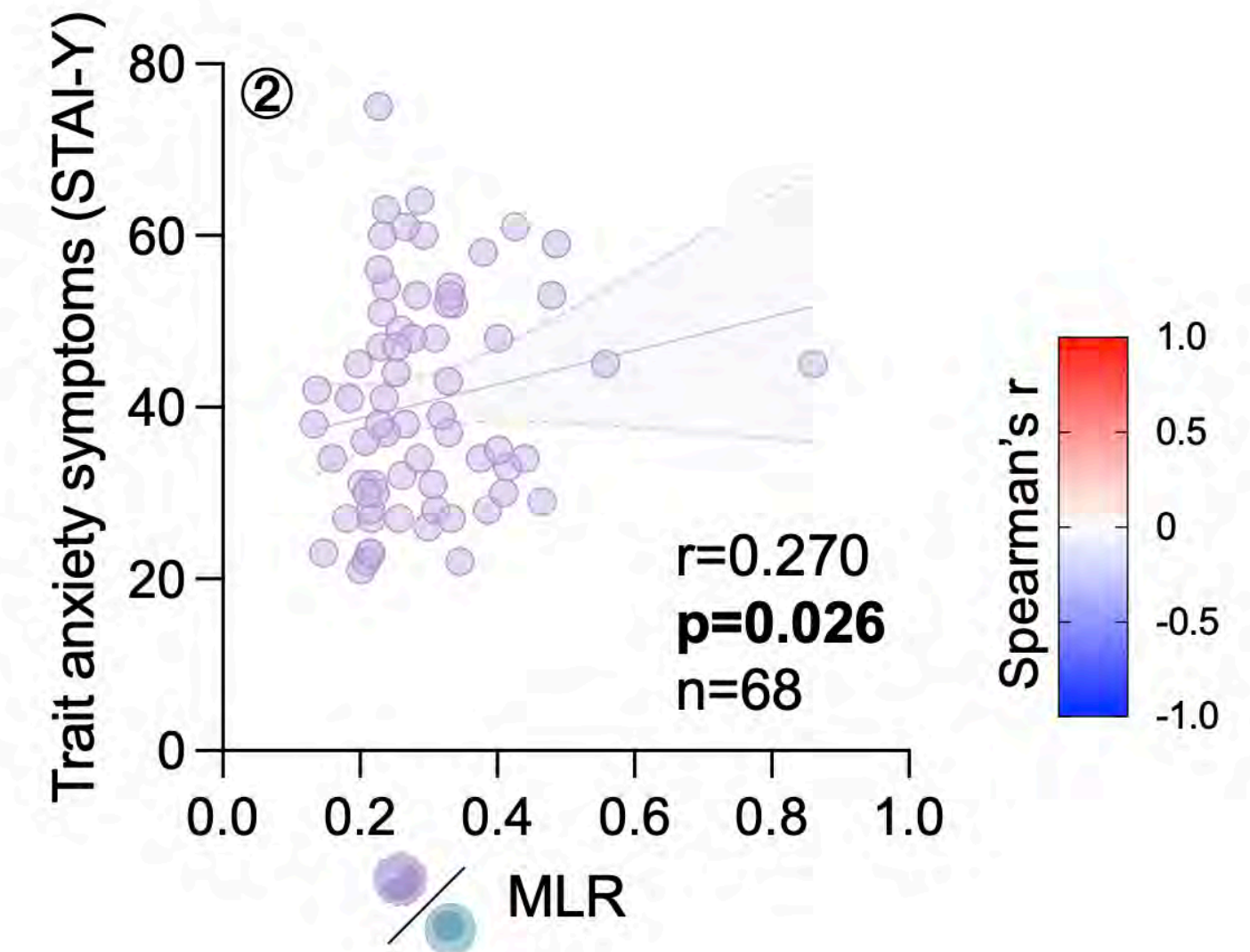
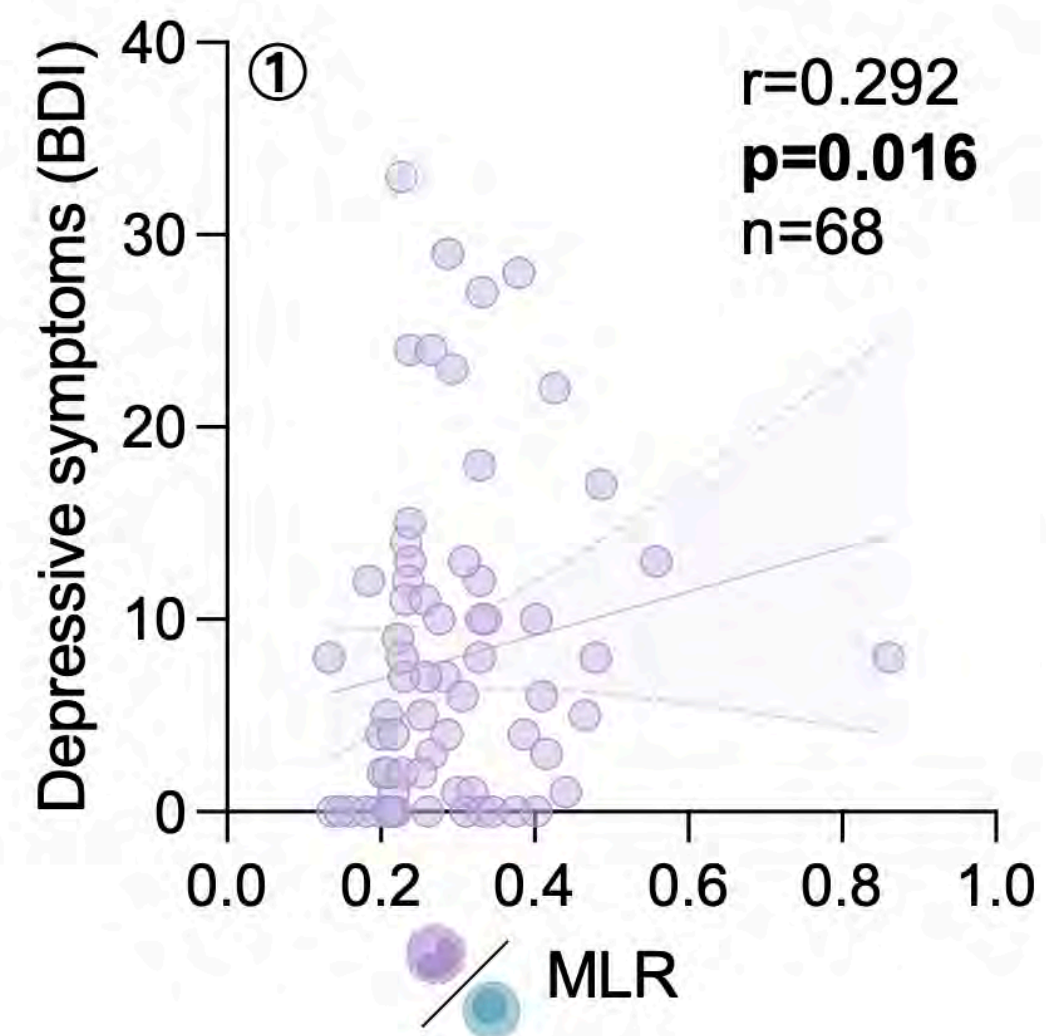
WBC composition and mood symptoms



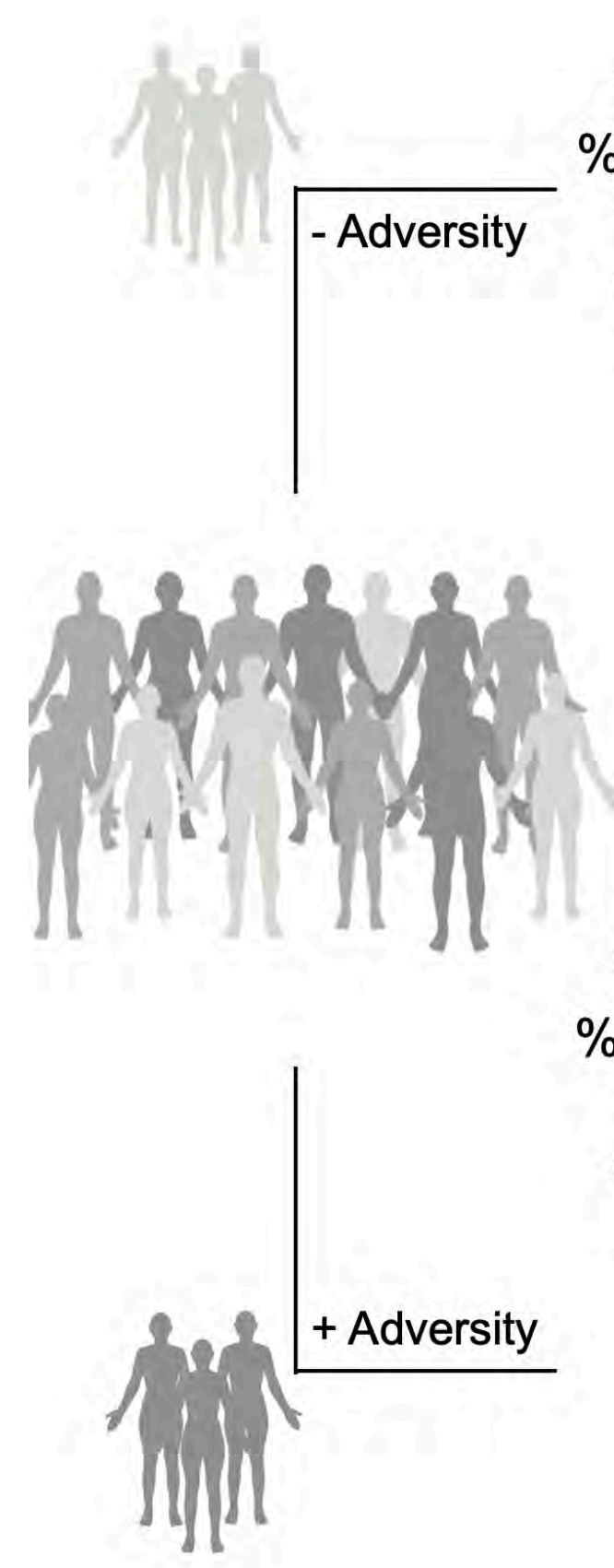
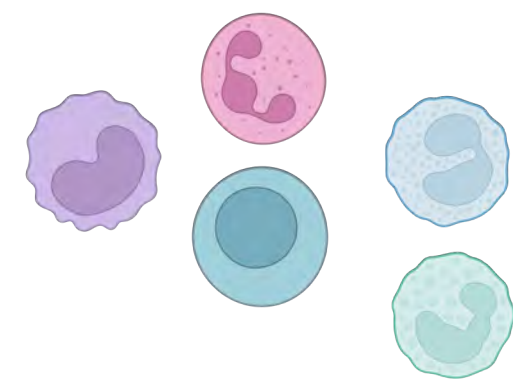
★ significant impact of childhood adversity ★ no significant impacts of lifetime adversity

WBC composition and mood symptoms

	Depressive symptoms (BDI)	Trait anxiety (STAI-Y)	State anxiety (STAI-Y)
% Neutrophils	0.097	0.045	★ -0.132
% Lymphocytes	-0.183	-0.139	★ 0.078
% Monocytes	0.151	0.116	0.166
% Eosinophils	-0.020	-0.006	0.010
% Basophils	0.057	0.002	-0.009
MLR ^①	0.292 *	0.270 *	0.147
NLR	0.149	0.094	-0.114
PLR	★ 0.155	0.147	★ 0.048



WBC composition and mood symptoms, stratified by adversity



Lifetime Adversity (STRAIN)

A Low lifetime adversity

	Depressive symptoms (BDI)	Trait anxiety (STAI-Y)	State anxiety (STAI-Y)
% Neutrophils	0.077	0.033	-0.189
% Lymphocytes	-0.139	-0.106	0.170
% Monocytes	0.094	0.127	0.197
% Eosinophils	0.067	4.365×10^{-5}	0.006
% Basophils	0.001	-0.108	-0.122
MLR	0.260	0.291	0.132
NLR	0.122	0.082	-0.167
PLR	-0.023	0.126	0.027

B High lifetime adversity

	Depressive symptoms (BDI)	Trait anxiety (STAI-Y)	State anxiety (STAI-Y)
% Neutrophils	0.121	0.139	0.008
% Lymphocytes	-0.142	-0.208	-0.072
% Monocytes	0.232	0.107	0.131
% Eosinophils	-0.041	0.058	0.004
% Basophils	0.303	0.251	0.198
MLR	0.201	0.209	0.124
NLR	0.139	0.178	0.056
PLR	0.188	0.141	0.064

Childhood Trauma (CTQ)

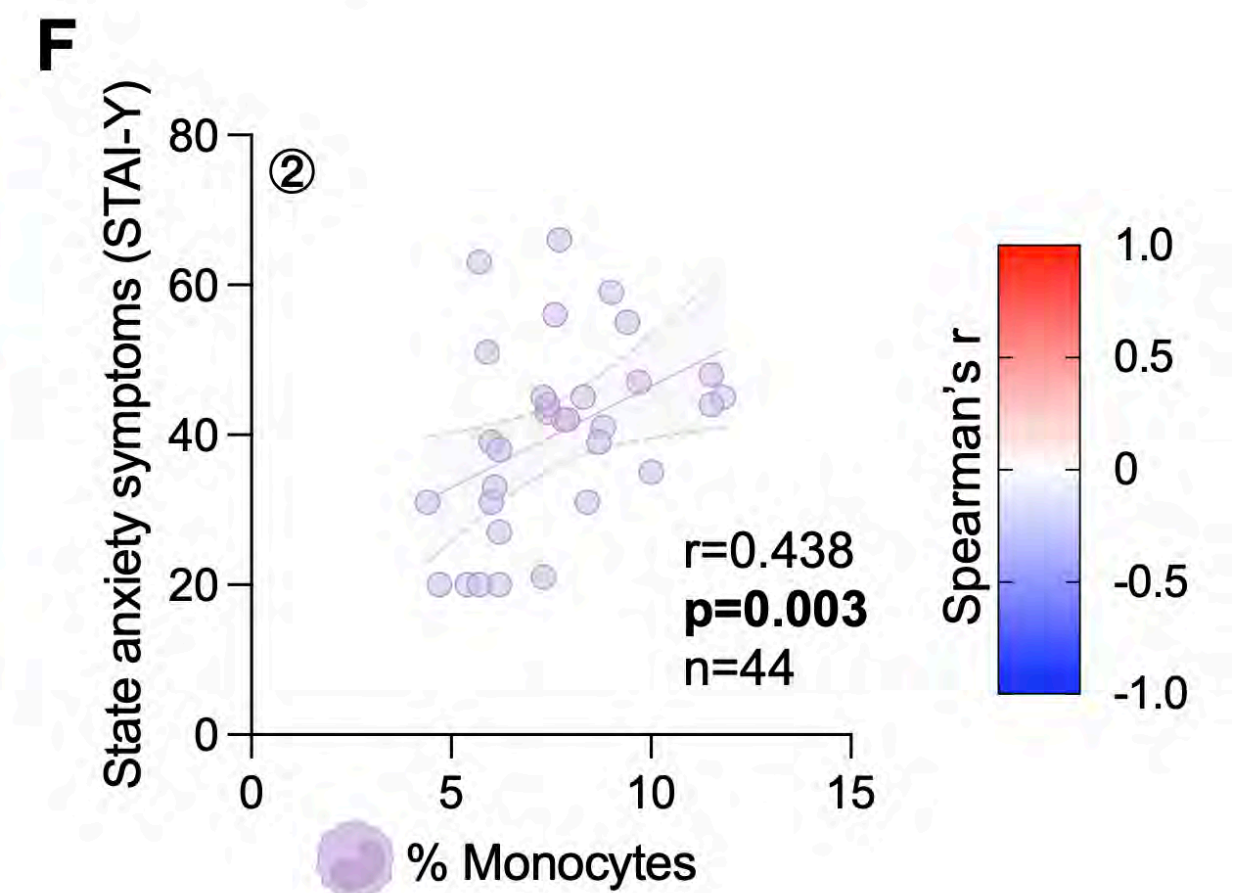
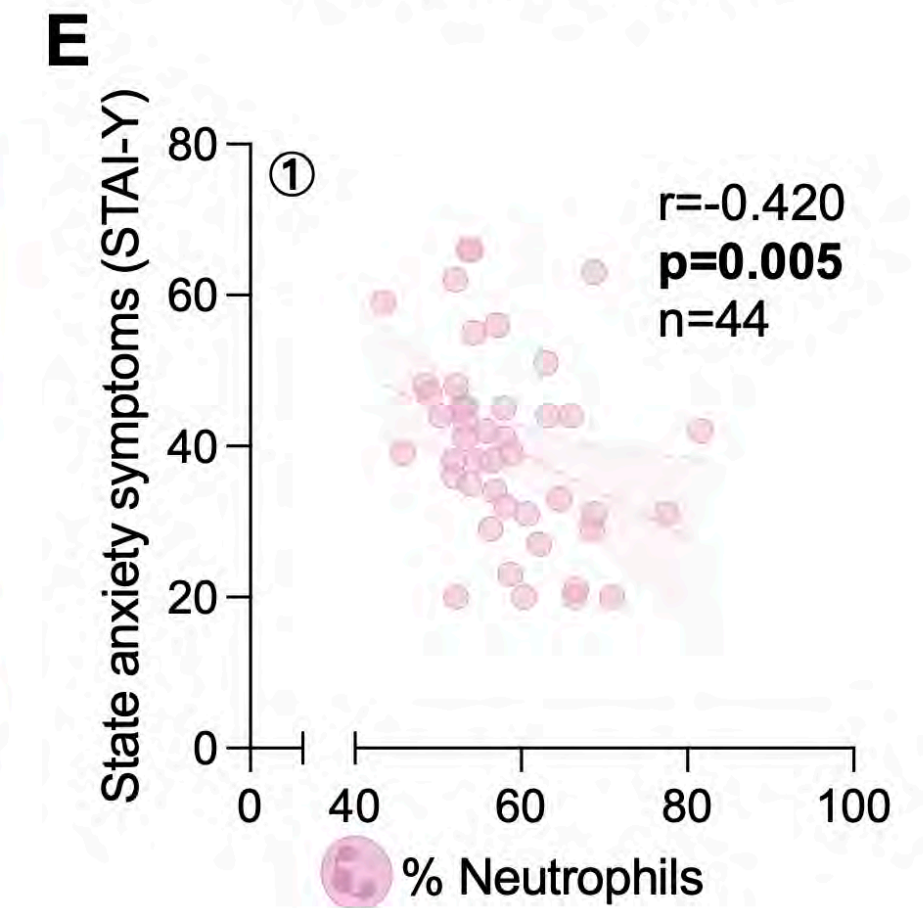
C No Childhood Trauma

	Depressive symptoms (BDI)	Trait anxiety (STAI-Y)	State anxiety (STAI-Y)
% Neutrophils	0.197	0.277	0.169
% Lymphocytes	-0.312	-0.398	-0.224
% Monocytes	-0.035	-0.152	-0.205
% Eosinophils	-0.001	0.120	0.181
% Basophils	-0.177	-0.226	-0.170
MLR	0.243	0.215	0.035
NLR	0.262	0.343	0.212
PLR	0.051	-0.056	-0.031

D Experienced Childhood Trauma

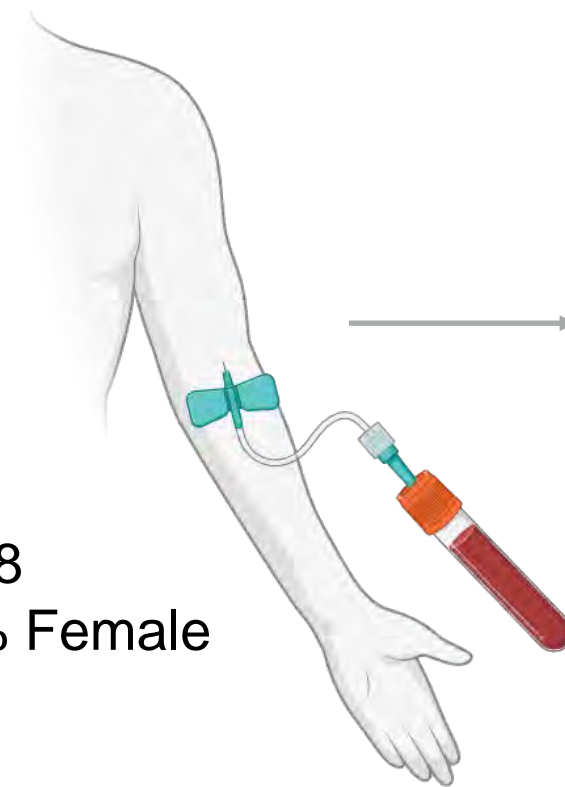
	Depressive symptoms (BDI)	Trait anxiety (STAI-Y)	State anxiety (STAI-Y)
% Neutrophils	-0.045	-0.137	-0.420 **
% Lymphocytes	-0.043	0.009	0.343
% Monocytes	0.356 *	0.367 * ②	0.439 **
% Eosinophils	-0.069	0.001	-0.022
% Basophils	0.184	0.168	0.160
MLR	0.315 *	0.346 *	0.144
NLR	0.029	-0.050	① -0.384 *
PLR	0.144	0.130	-0.018

Selected scatterplots

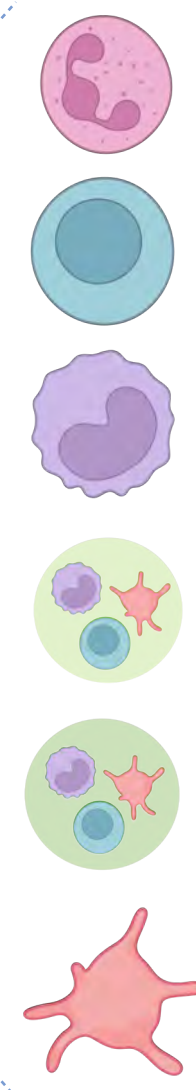
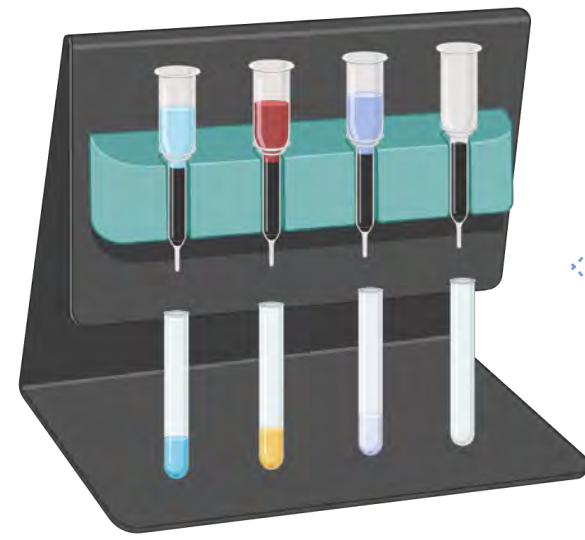




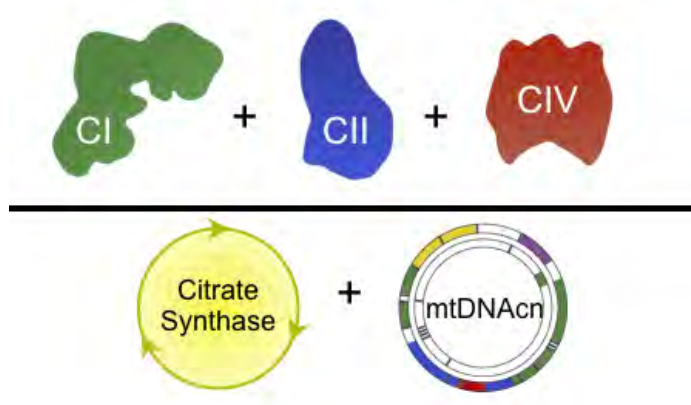
n=68
68% Female



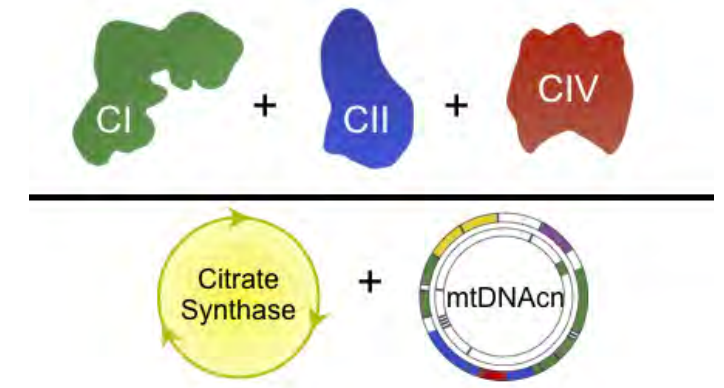
Immune cell sorting



Mitochondrial Respiratory Capacity (MRC)

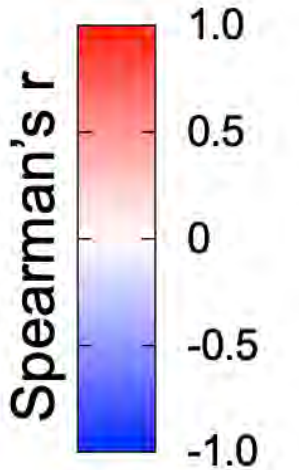
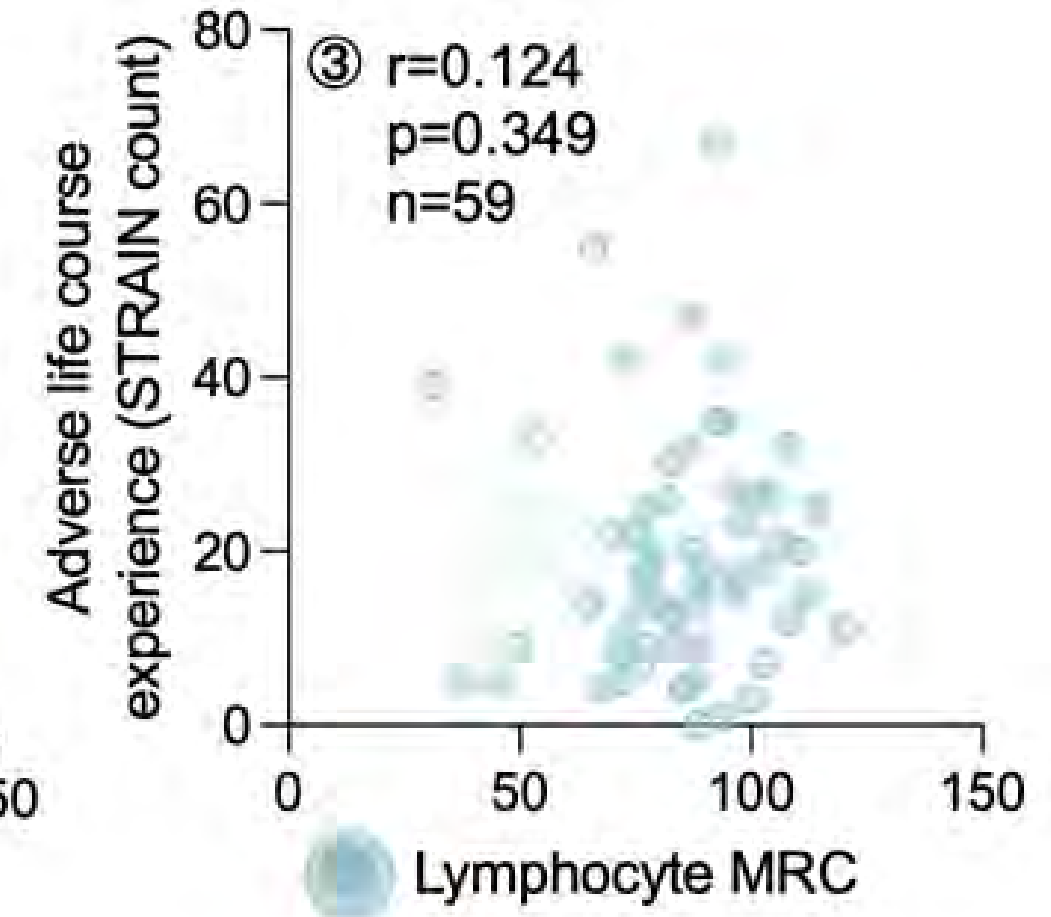
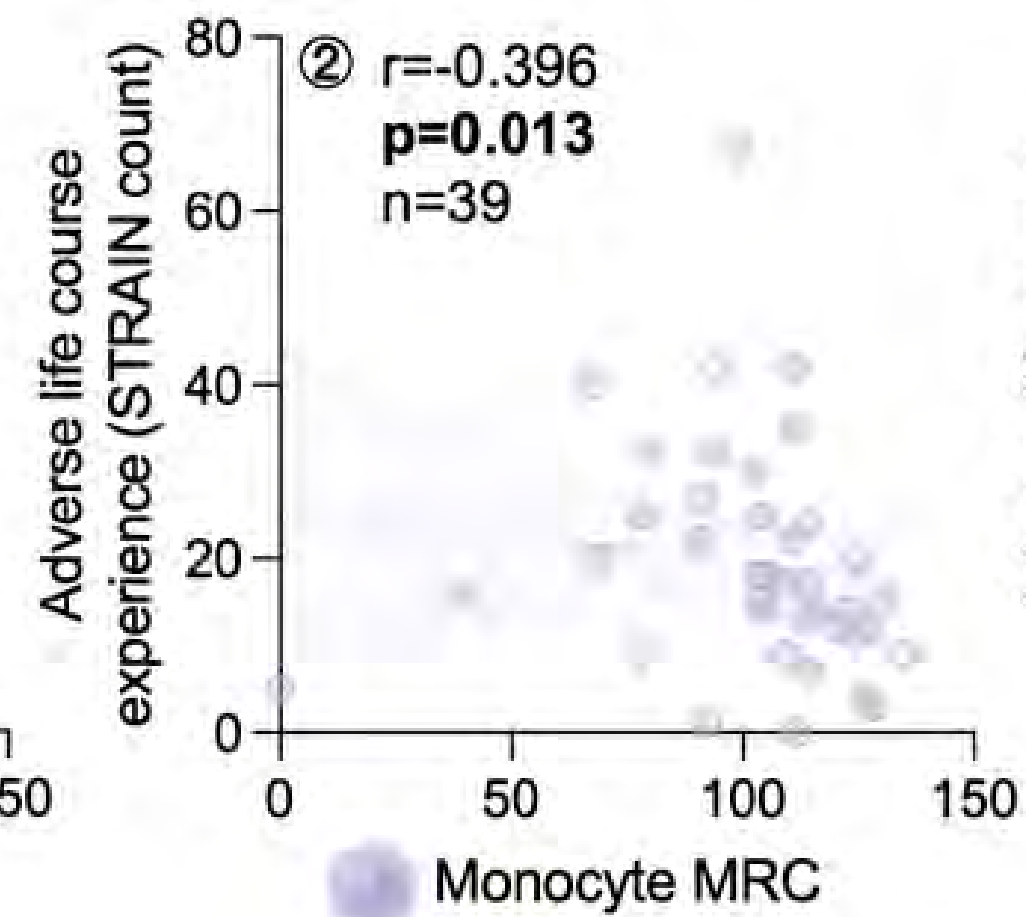
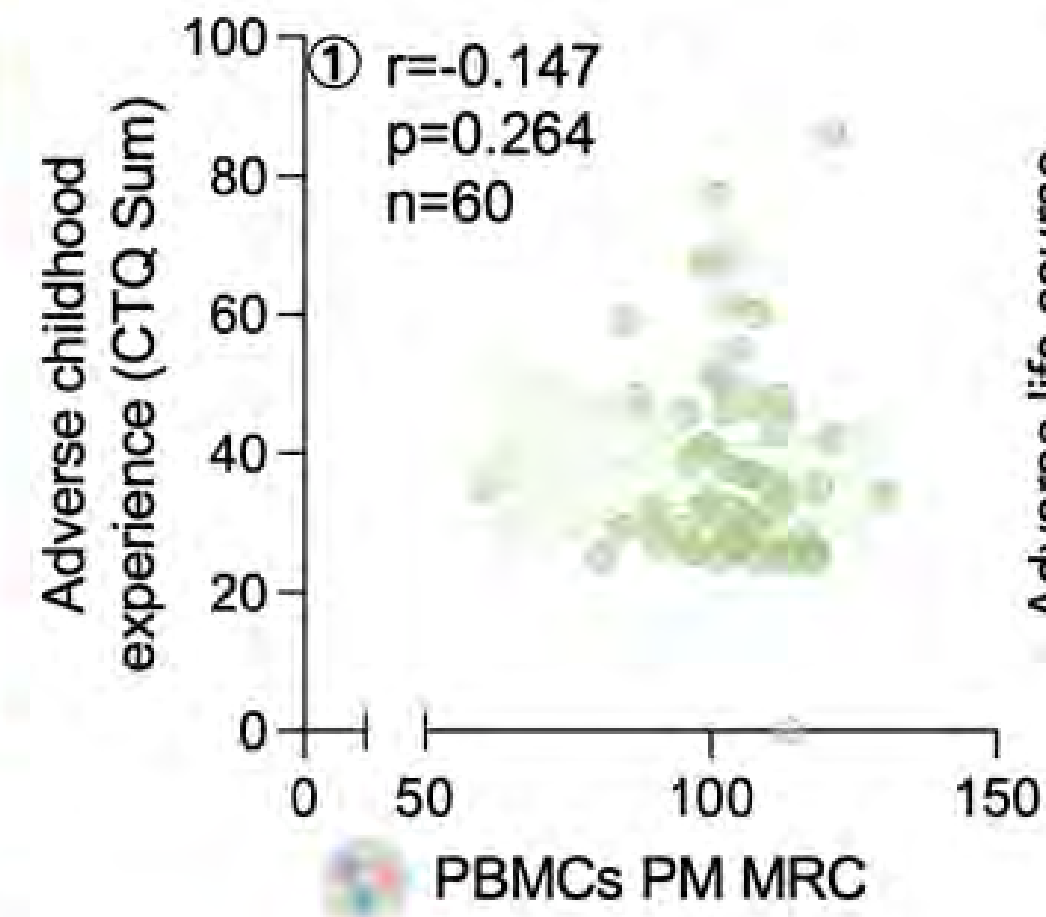


MRC and adversity

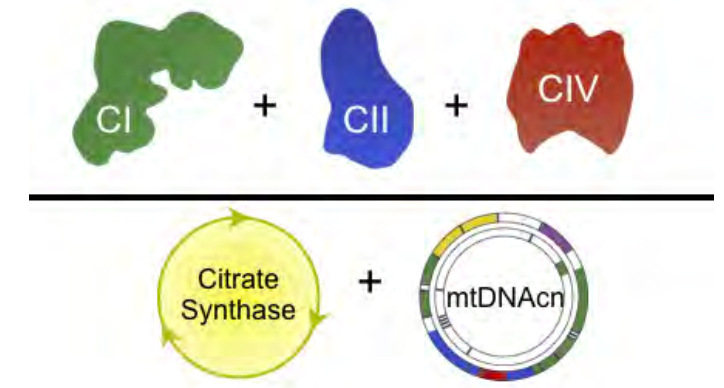


MRC and adversity

	Adverse childhood experience (CTQ Sum)	Adverse life course experience (STRAIN count)	Adverse life course experience (STRAIN severity)
Monocytes	-0.122	^② -0.396 *	-0.367 *
Lymphocytes	-0.156	^③ 0.124	0.119
Neutrophils	-0.135	-0.218	-0.148
PBMCs AM	-0.104	-0.059	-0.114
PBMCs PM ^①	-0.147	-0.032	-0.106
Platelets	0.164	0.184	0.294

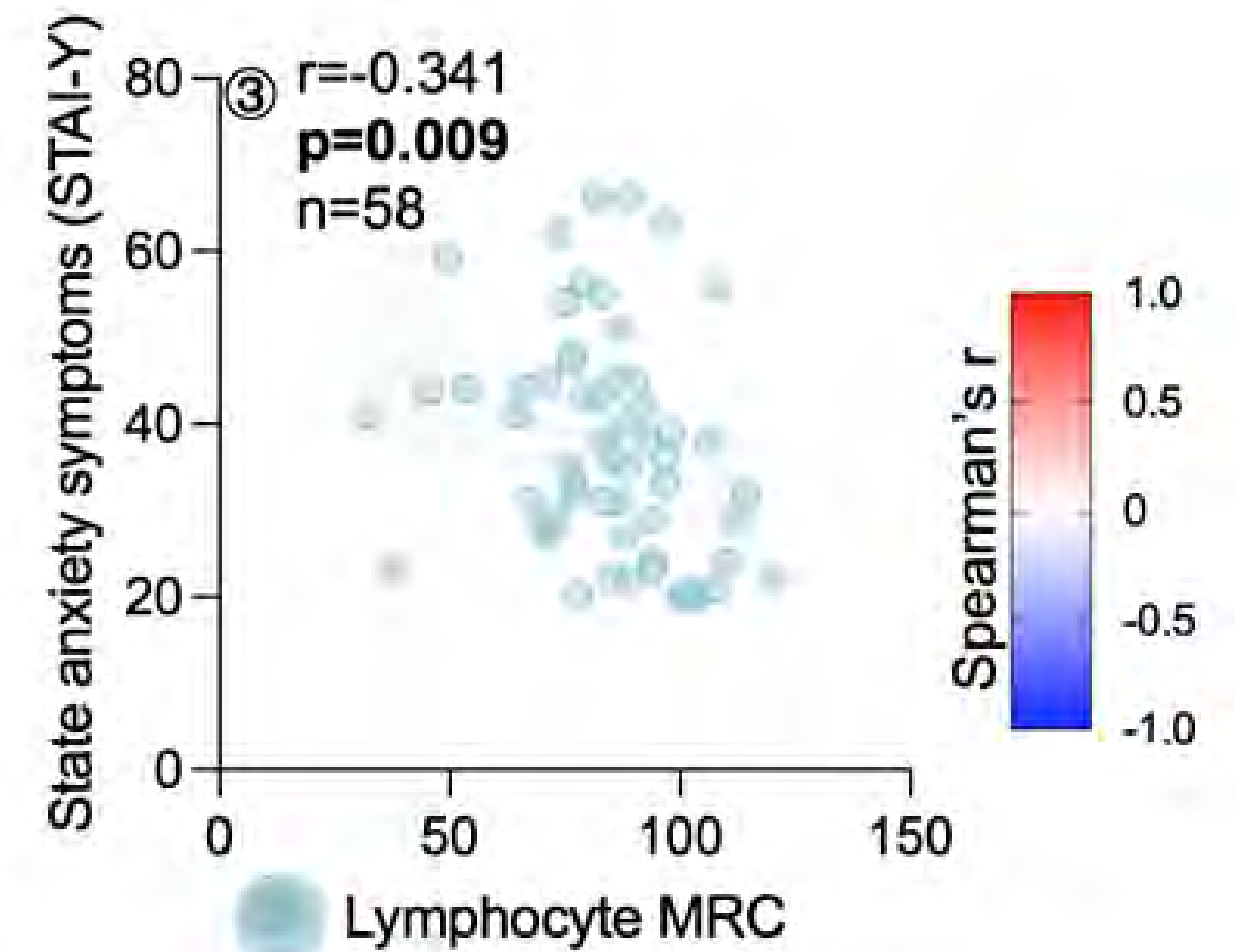
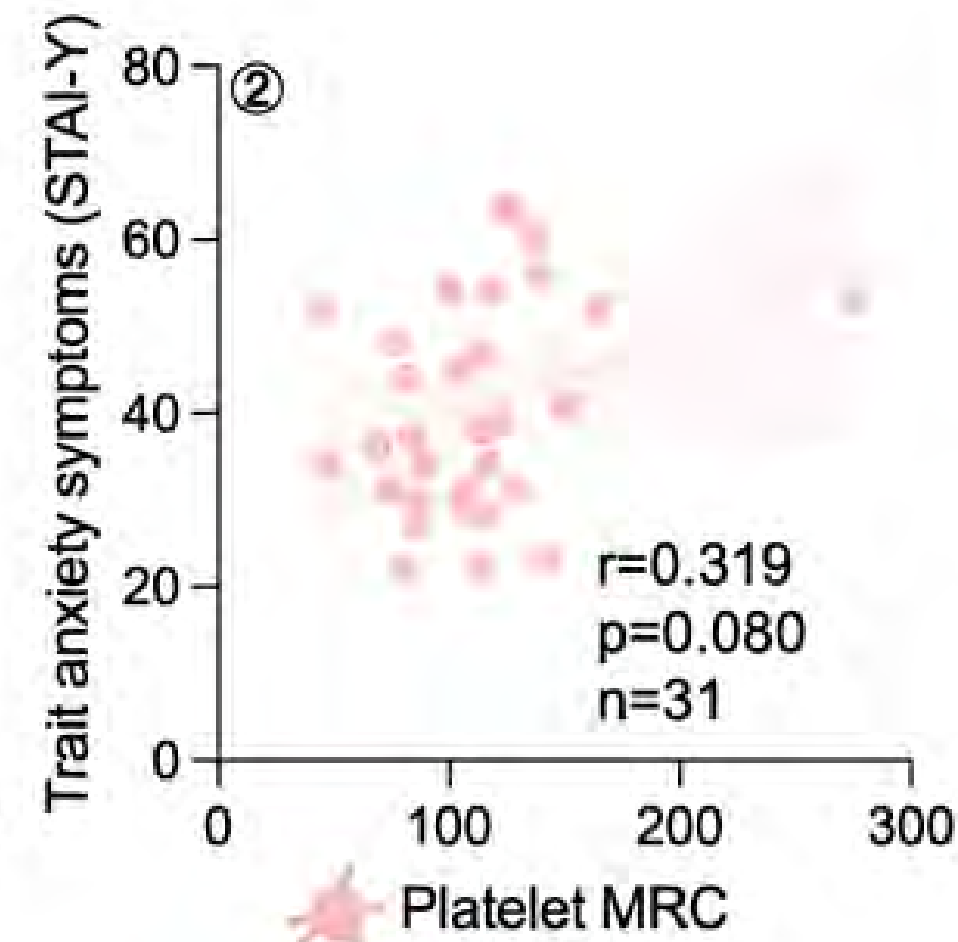
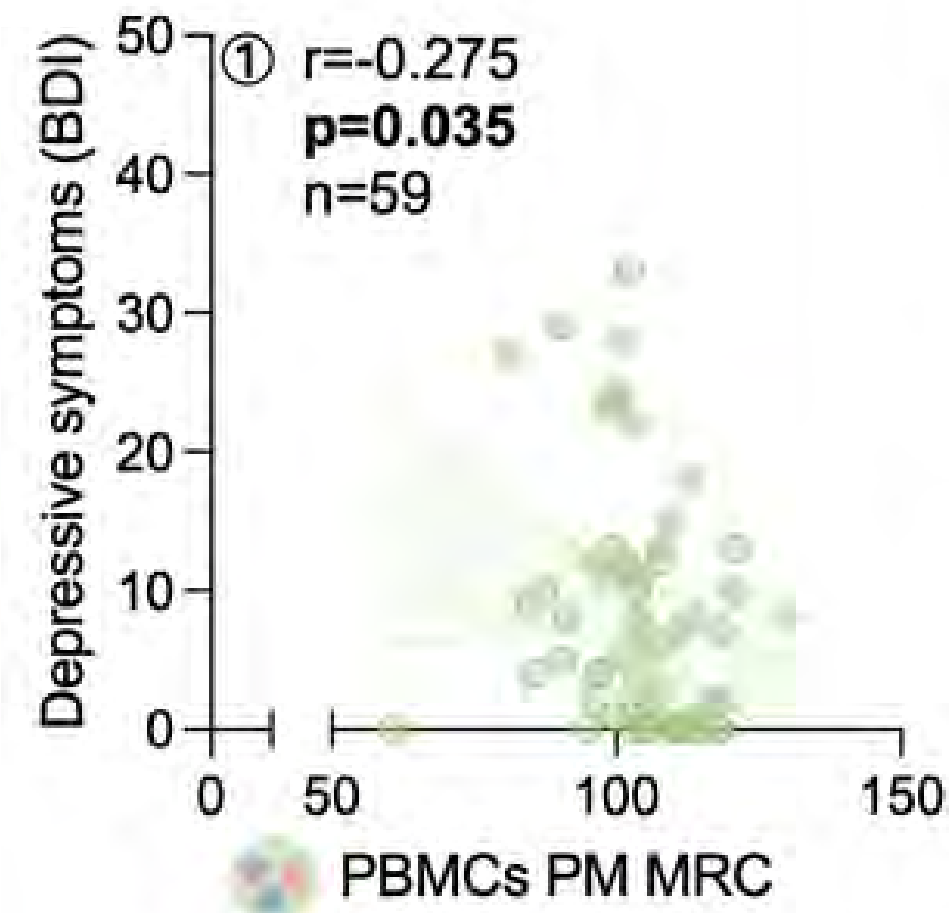


MRC and mood symptoms

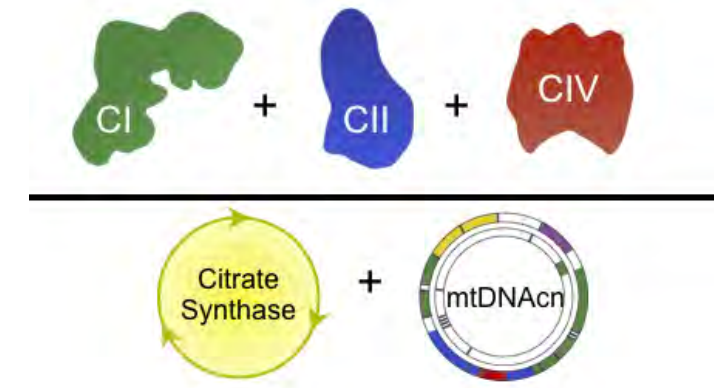


MRC and mood symptoms

	Depressive symptoms (BDI)	Trait anxiety (STAI-Y)	State anxiety (STAI-Y)
Monocytes	-0.228	-0.161	-0.176
Lymphocytes	-0.188	-0.261 *	-0.341**
Neutrophils	-0.130	0.025	-0.151
PBMCs AM	-0.098	-0.126	-0.083
PBMCs PM	-0.275 *	-0.143	-0.138
Platelets	0.250	0.319	0.263



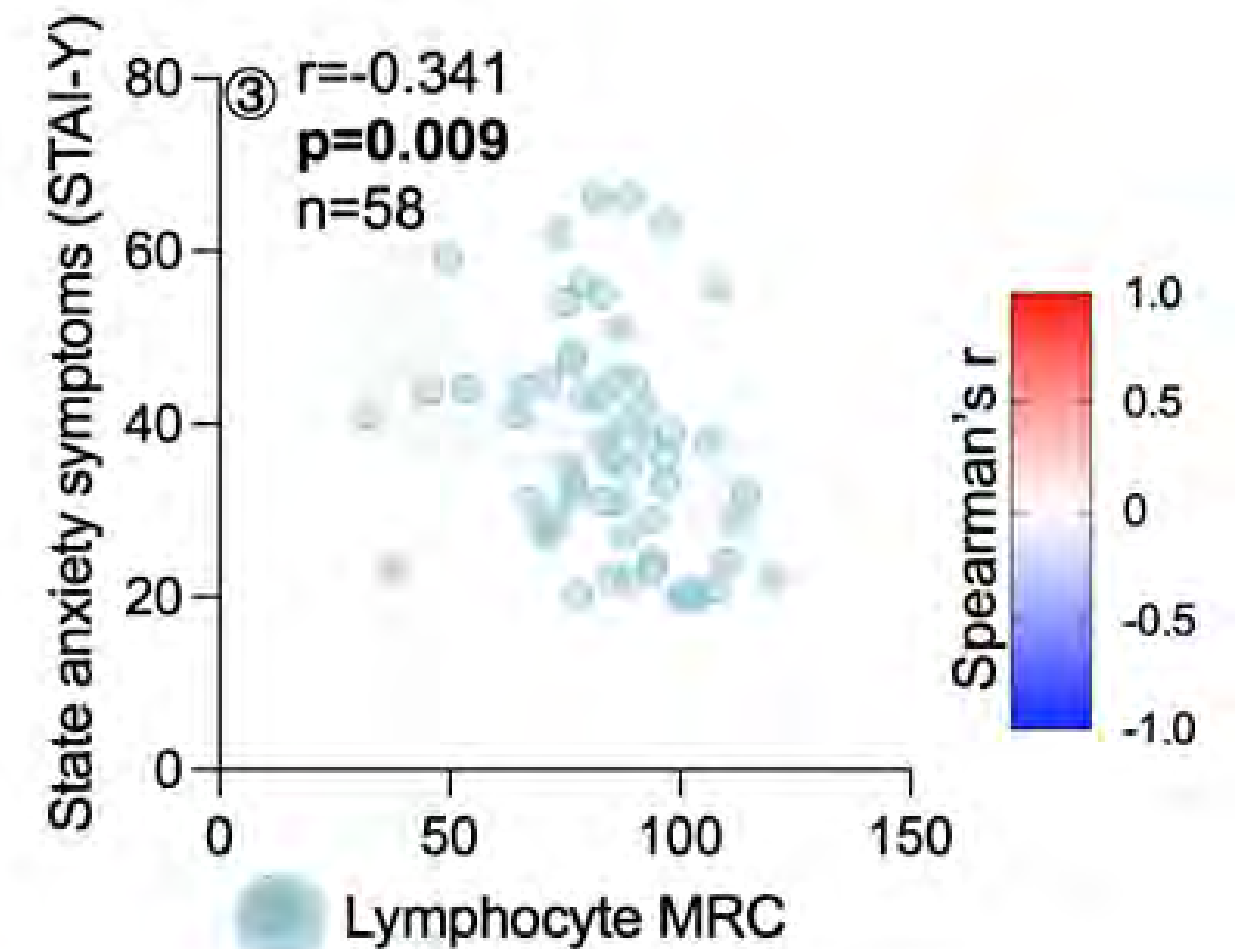
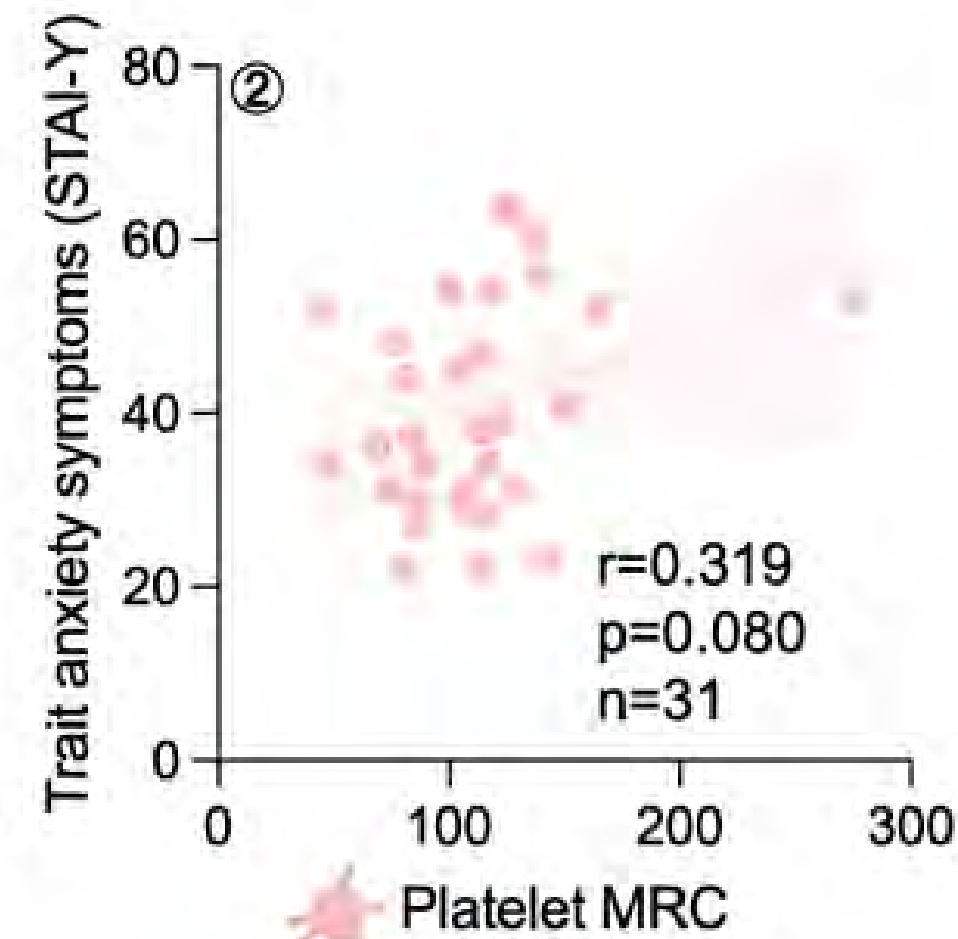
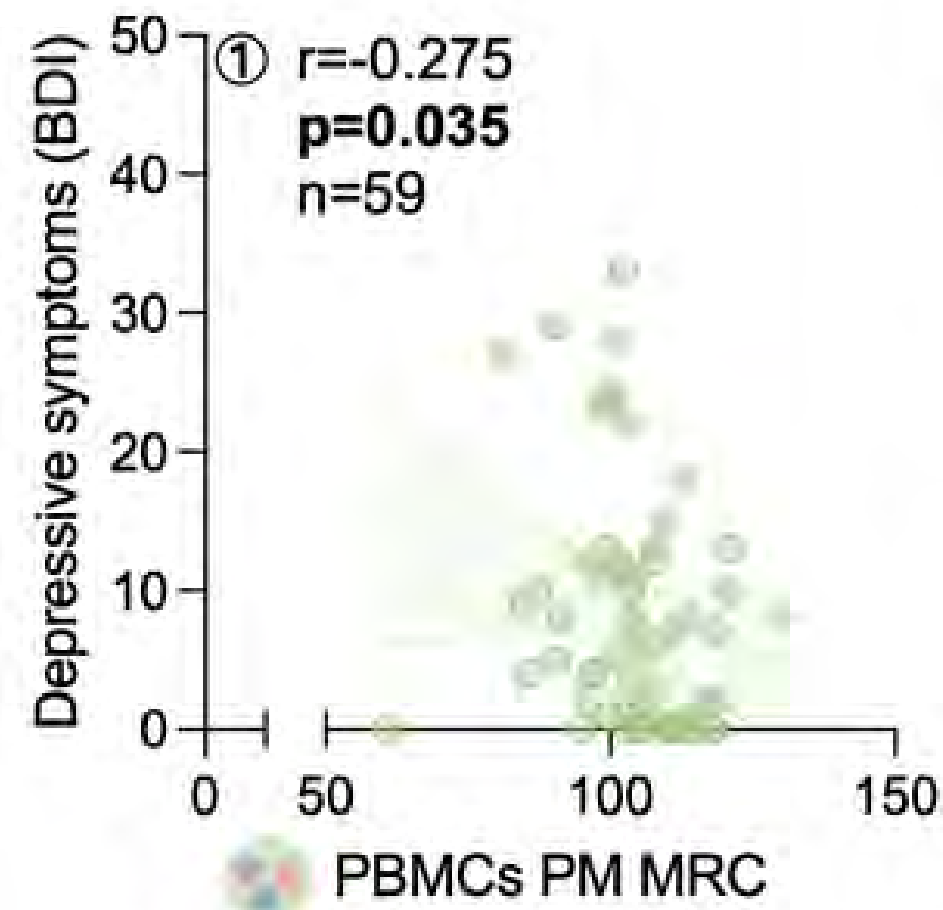
MRC and mood symptoms



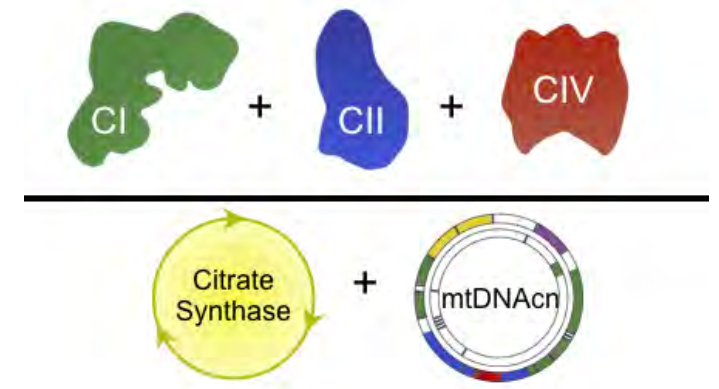
★ significant impact of childhood adversity ★ significant impacts of lifetime adversity

MRC and mood symptoms

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Monocytes	-0.228	-0.161	-0.176
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Neutrophils	-0.130	0.025	-0.151
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Platelets	0.250	② 0.319	0.263

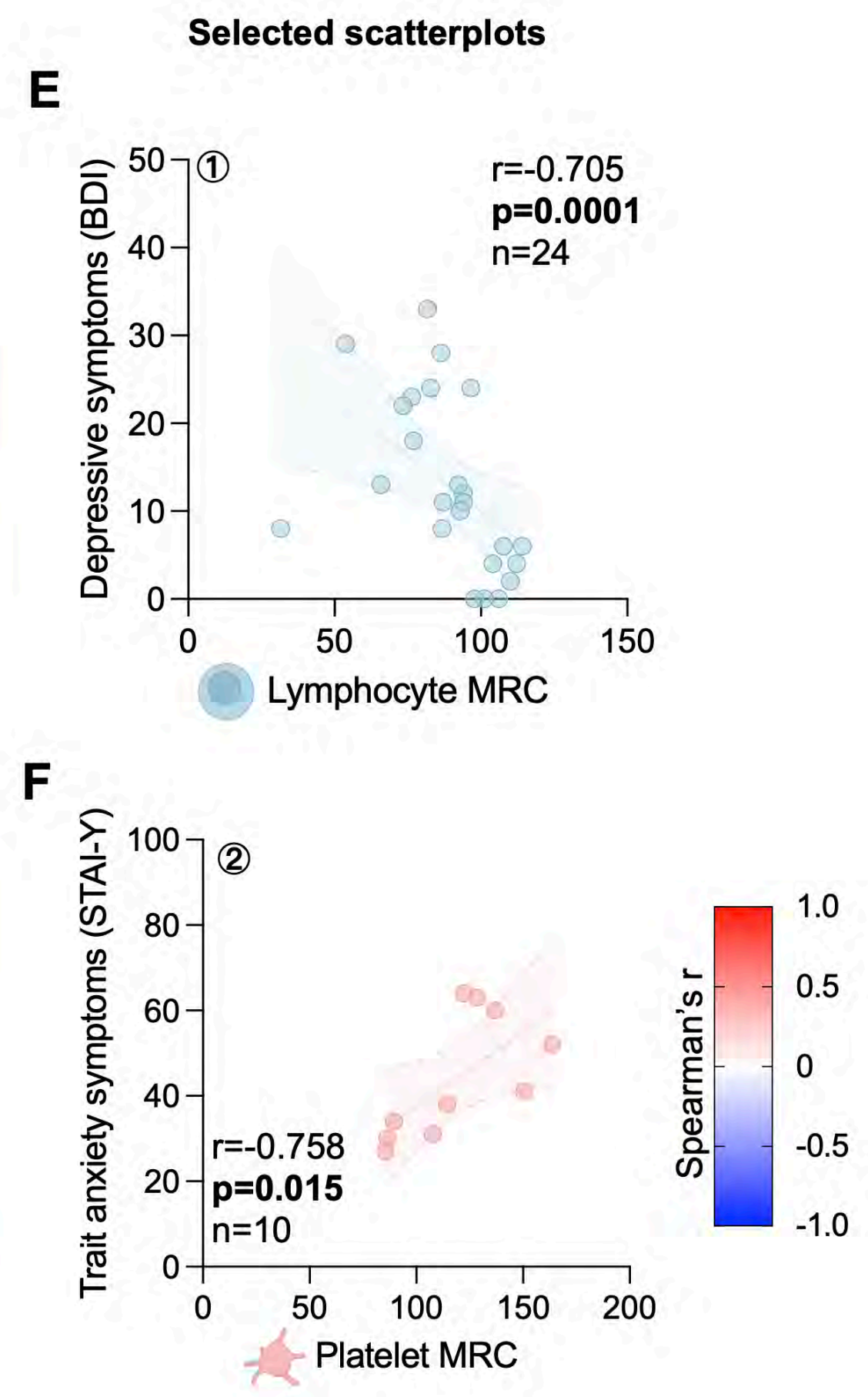


MRC and mood symptoms, stratified by adversity



Lifetime Adversity (STRAIN)				Childhood Trauma (CTQ)			
	Low lifetime adversity			No Childhood Trauma			
Monocytes	-0.179	-0.149	-0.238	0.034	-0.256	-0.126	
Lymphocytes	-0.078	-0.066	-0.186	-0.005	0.014	-0.161	
Neutrophils	0.010	0.072	-0.070	-0.061	0.333	-0.116	
PBMCs AM	-0.073	-0.078	-0.083	-0.228	-0.214	-0.132	
PBMCs PM	-0.315	-0.102	-0.163	-0.638**	-0.298	-0.247	
Platelets	-0.022	0.070	0.150	-0.224	-0.059	-0.161	
	Depressive symptoms (BDI)	Trait anxiety (STAI-Y)	State anxiety (STAI-Y)	Depressive symptoms (BDI)	Trait anxiety (STAI-Y)	State anxiety (STAI-Y)	

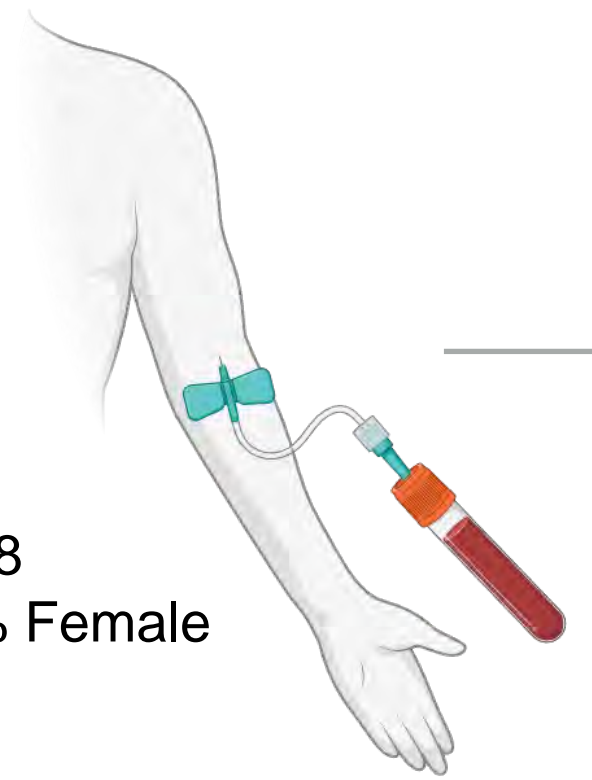
Lifetime Adversity (STRAIN)				Childhood Trauma (CTQ)			
	High lifetime adversity			Experienced Childhood Trauma			
Monocytes	0.181	0.132	0.242	-0.281	-0.024	-0.242	
Lymphocytes	① -0.705***	-0.700***	-0.653**	-0.189	-0.258	-0.269	
Neutrophils	-0.211	-0.053	-0.181	-0.087	0.062	-0.040	
PBMCs AM	-0.174	-0.242	-0.074	-0.016	-0.086	-0.020	
PBMCs PM	-0.226	-0.223	-0.035	-0.155	-0.056	-0.063	
Platelets	0.553	② 0.758*	0.591	0.489	0.476	0.499	
	Depressive symptoms (BDI)	Trait anxiety (STAI-Y)	State anxiety (STAI-Y)	Depressive symptoms (BDI)	Trait anxiety (STAI-Y)	State anxiety (STAI-Y)	



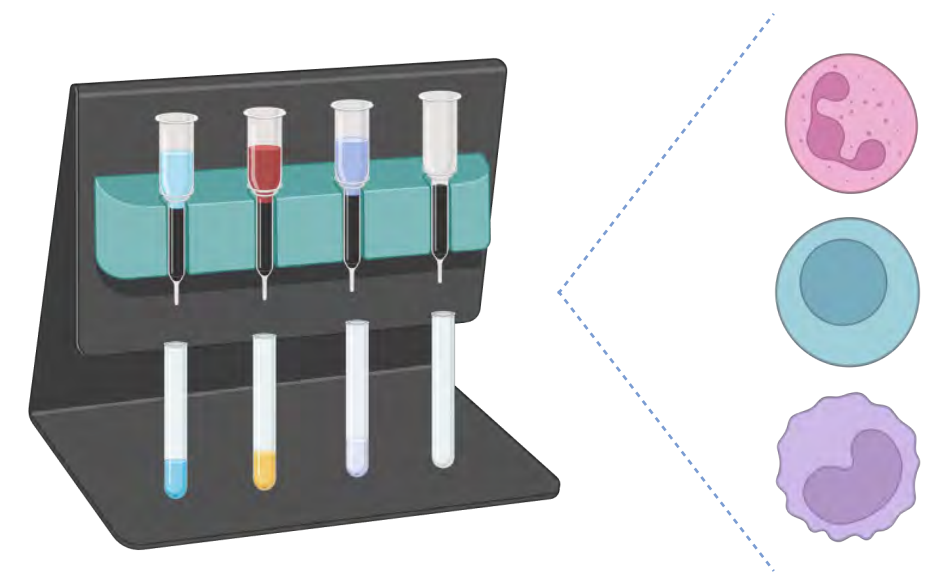
Controls only



n=68
68% Female



Immune cell sorting



MitoRespiration

(ATP-linked baseline respiration)
*preliminary data

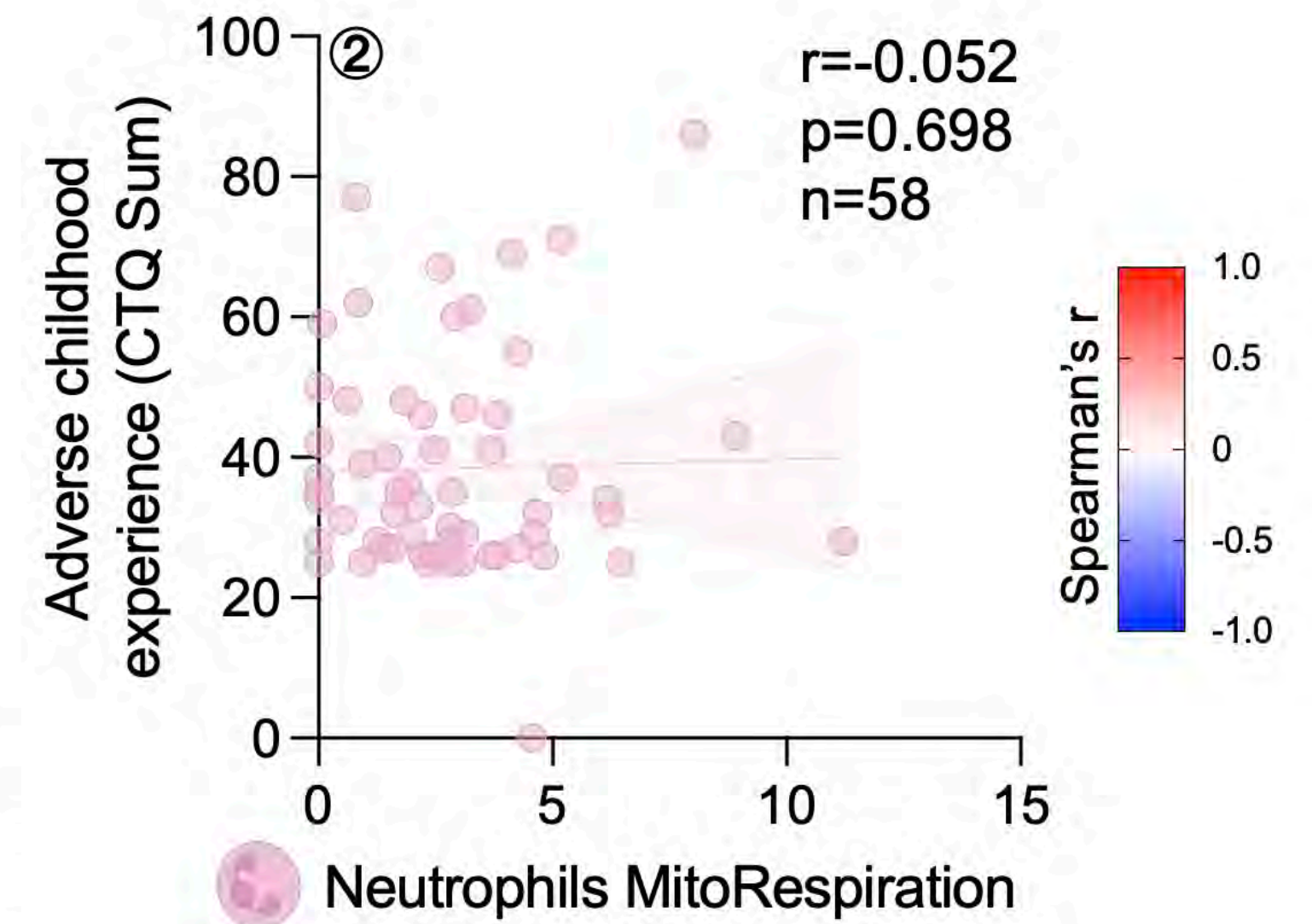
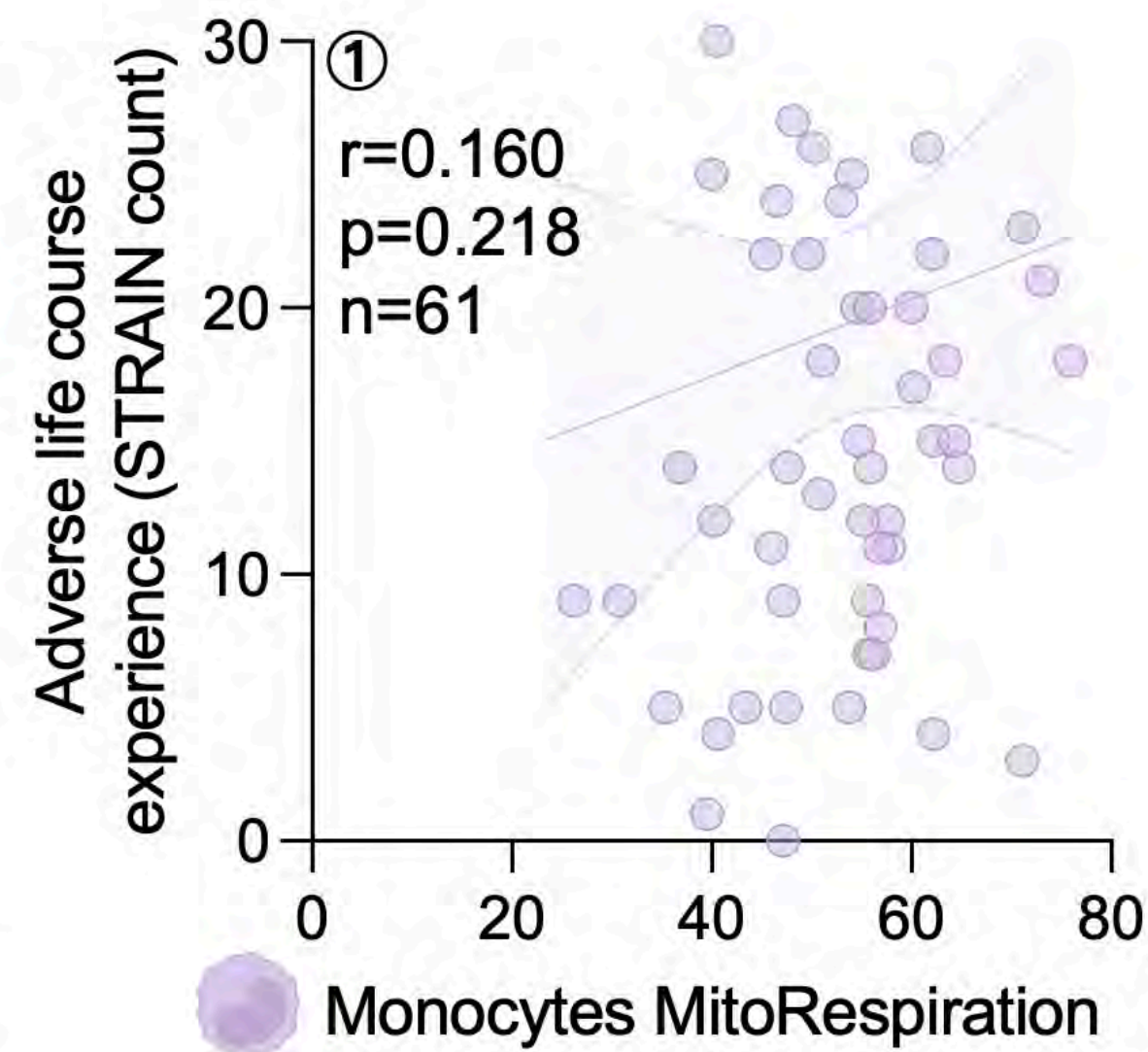


MitoRespiration and adversity



MitoRespiration and adversity

Monocytes	0.085	0.160 ^①	0.137
Lymphocytes	-0.093	0.025	0.005
Neutrophils	-0.052 ^②	0.080	0.052
	Adverse childhood experience (CTQ Sum)	Adverse life course experience (STRAIN count)	Adverse life course experience (STRAIN severity)

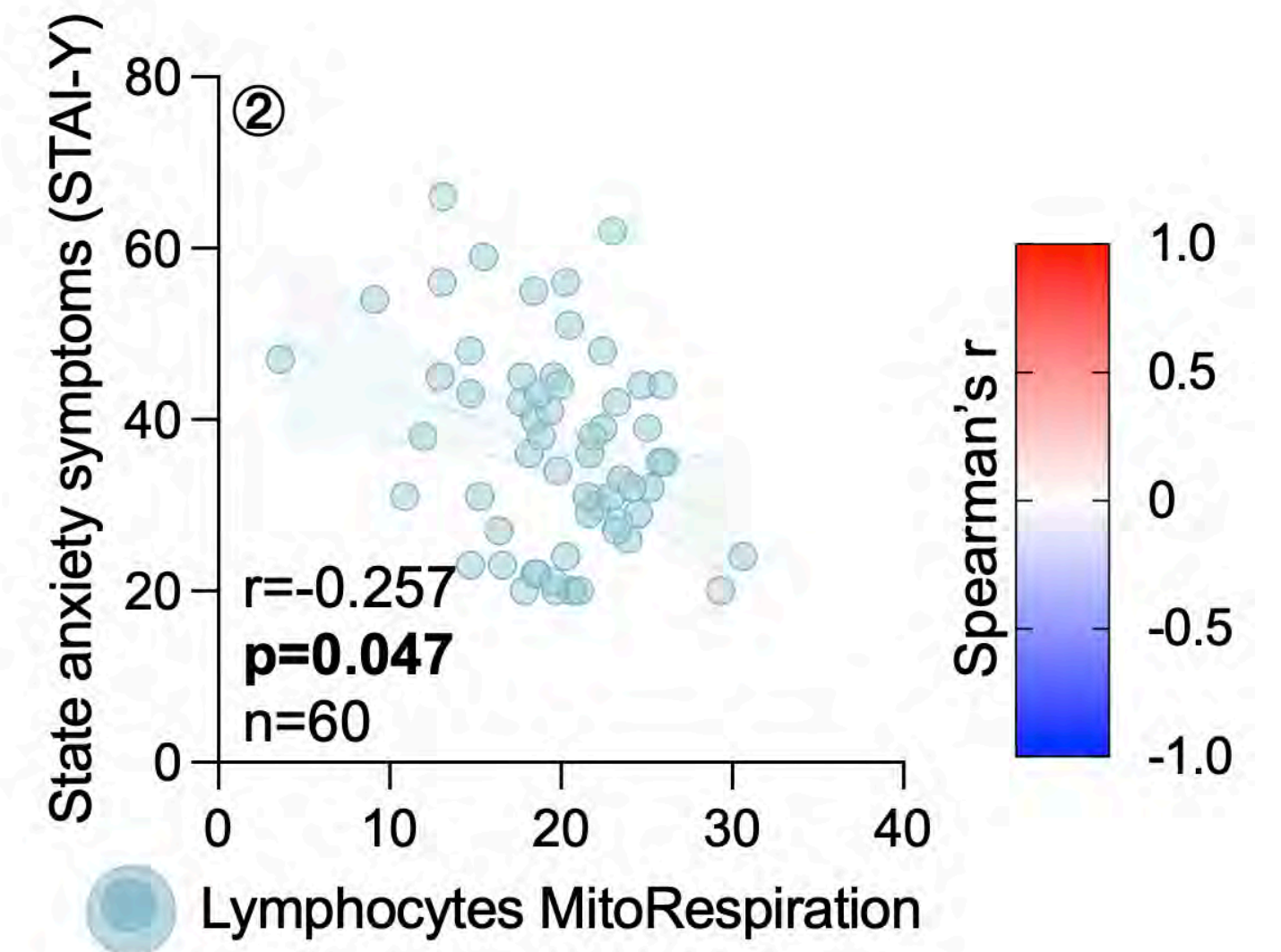
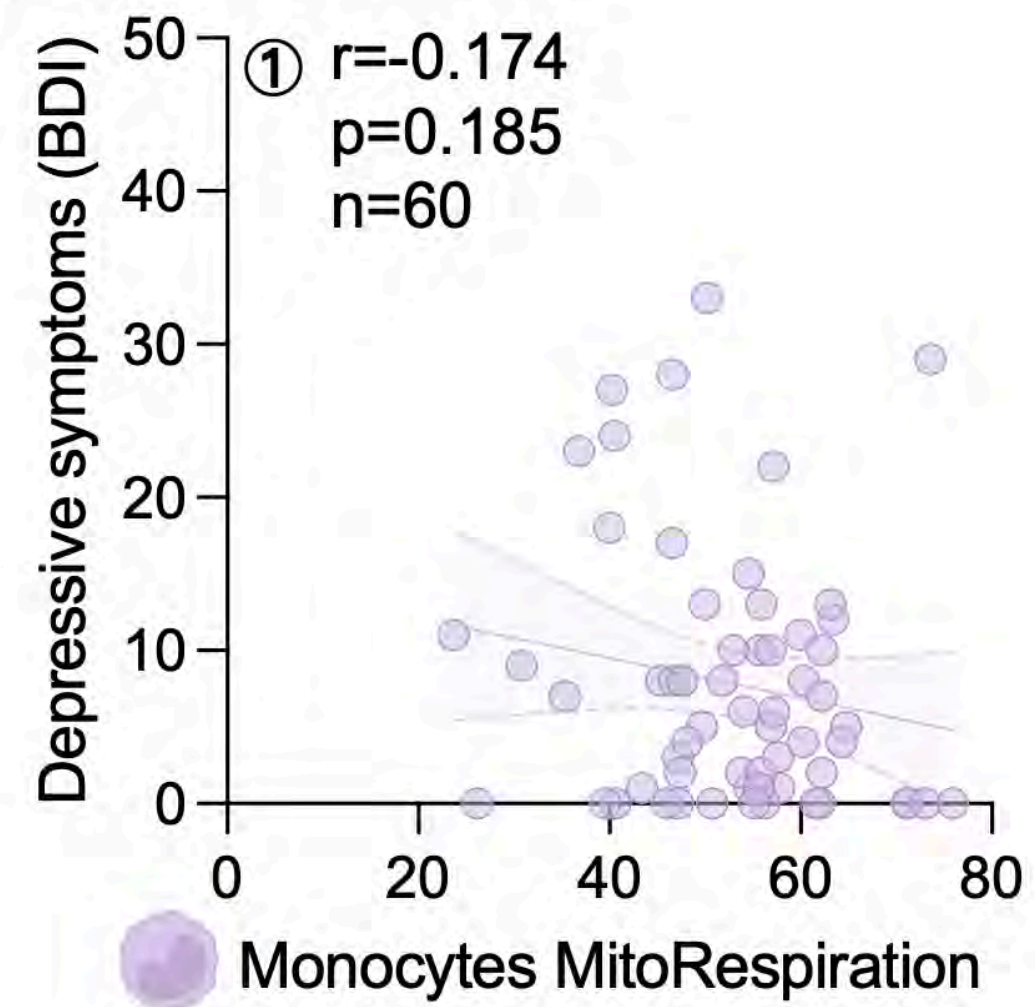


MitoRespiration and mood symptoms



MitoRespiration and mood symptoms

	Depressive symptoms (BDI)	Trait anxiety (STAI-Y)	State anxiety (STAI-Y)
Monocytes	① -0.173	-0.018	-0.135
Lymphocytes	-0.149	-0.114	② -0.257 *
Neutrophils	0.002	0.067	-0.019



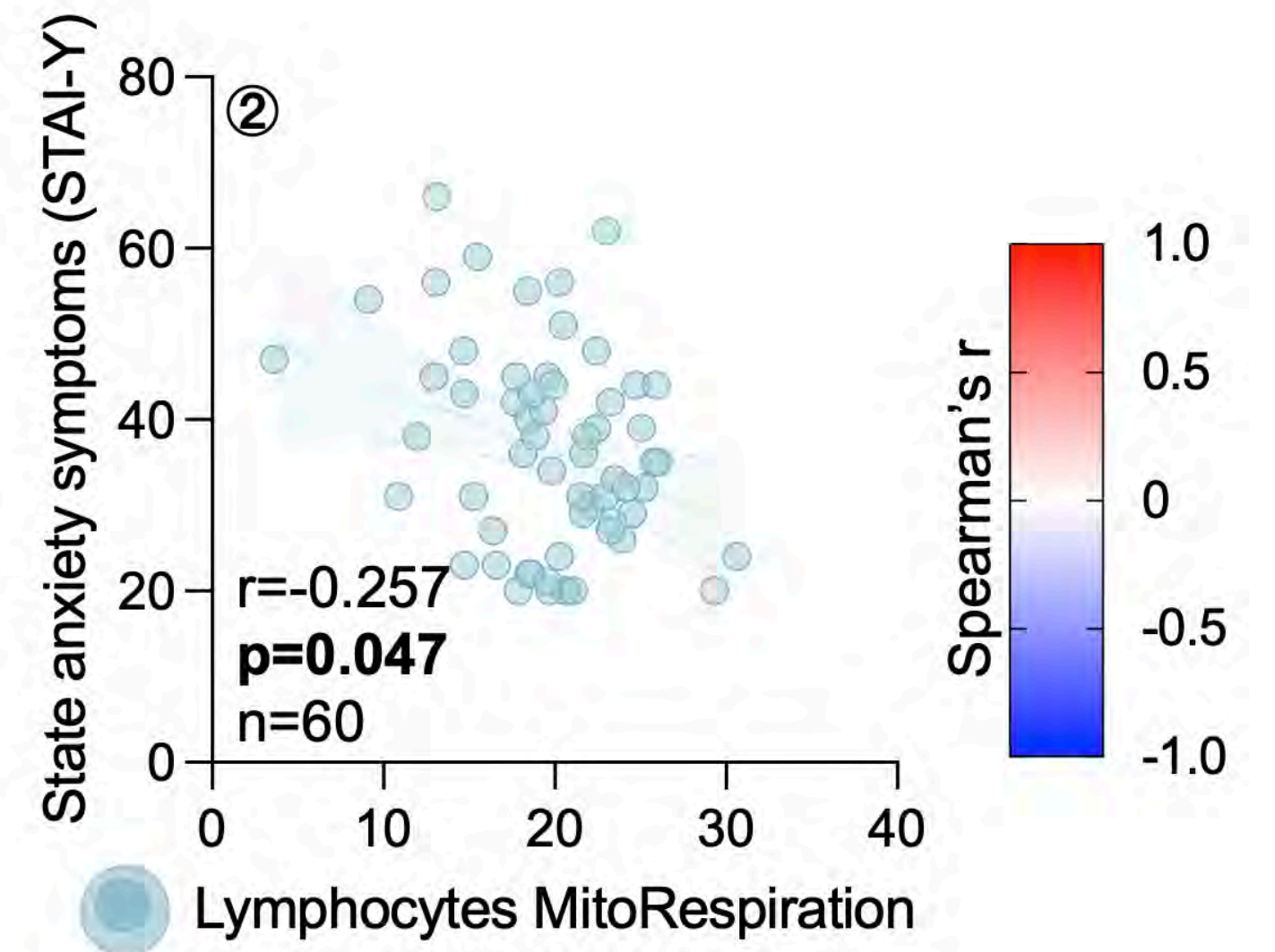
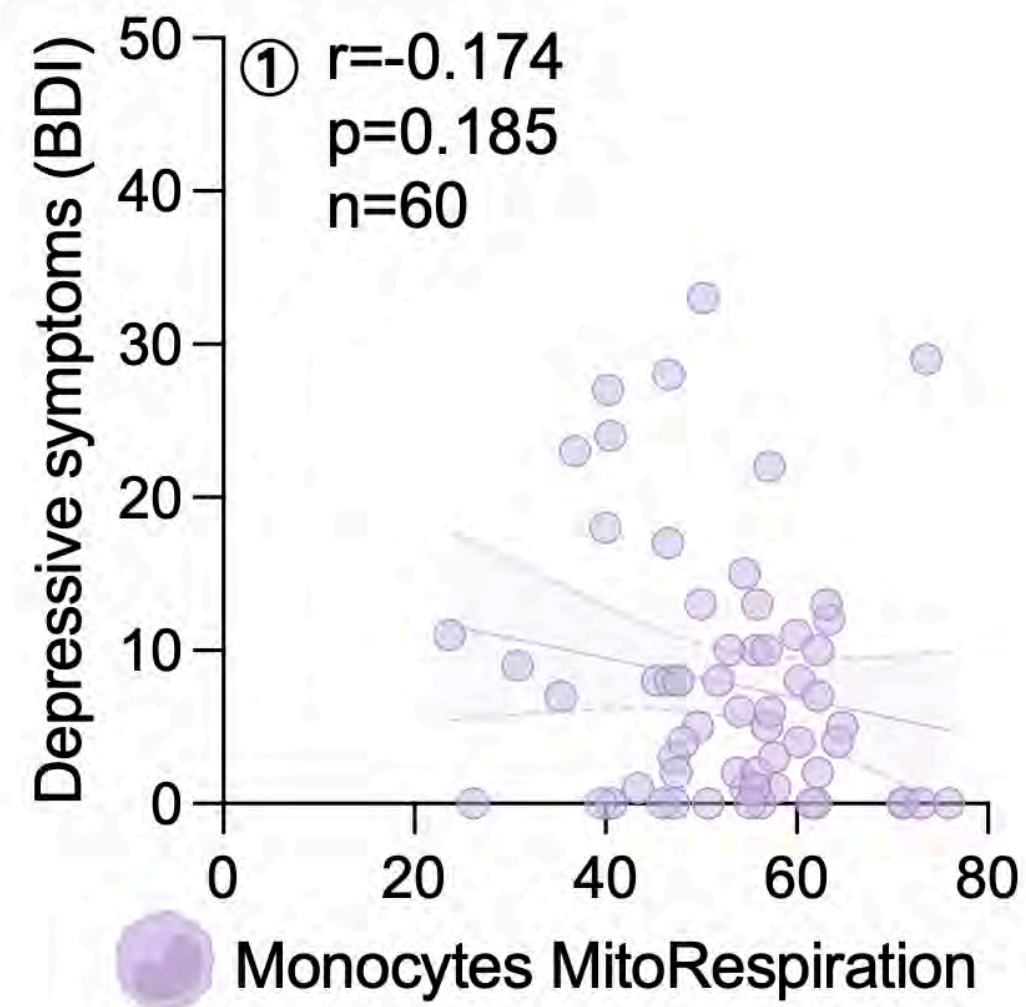
MitoRespiration and mood symptoms



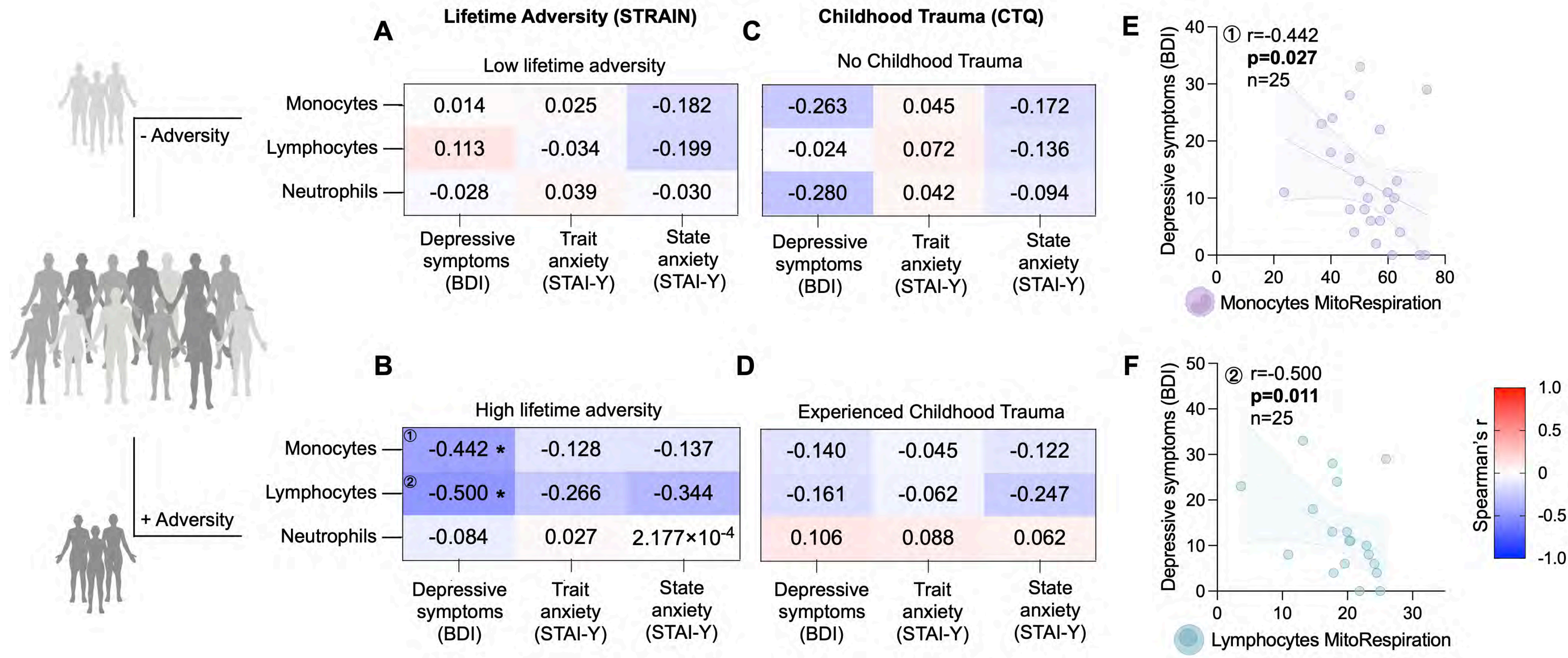
no significant impact of childhood adversity significant impacts of lifetime adversity ☆

MitoRespiration and mood symptoms

	Depressive symptoms (BDI)	Trait anxiety (STAI-Y)	State anxiety (STAI-Y)
Monocytes	① -0.173	-0.018	-0.135
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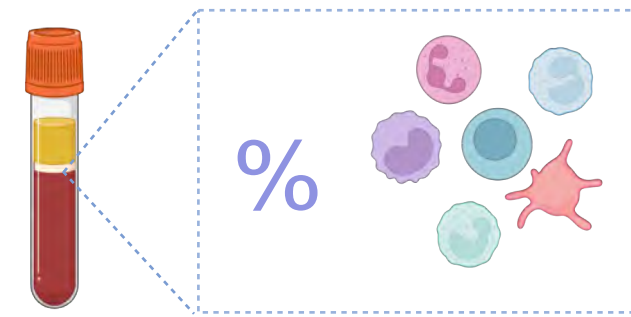


MitoRespiration and mood symptoms, stratified by adversity

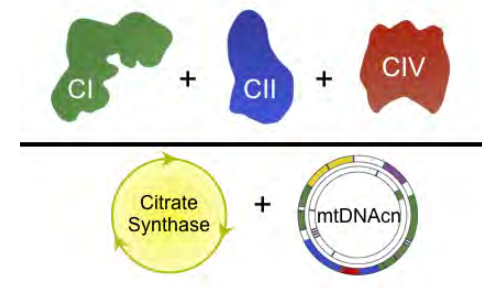


Summary

Laboratory methods



Immune cell proportions



Mitochondrial Respiratory Capacity (MRC)

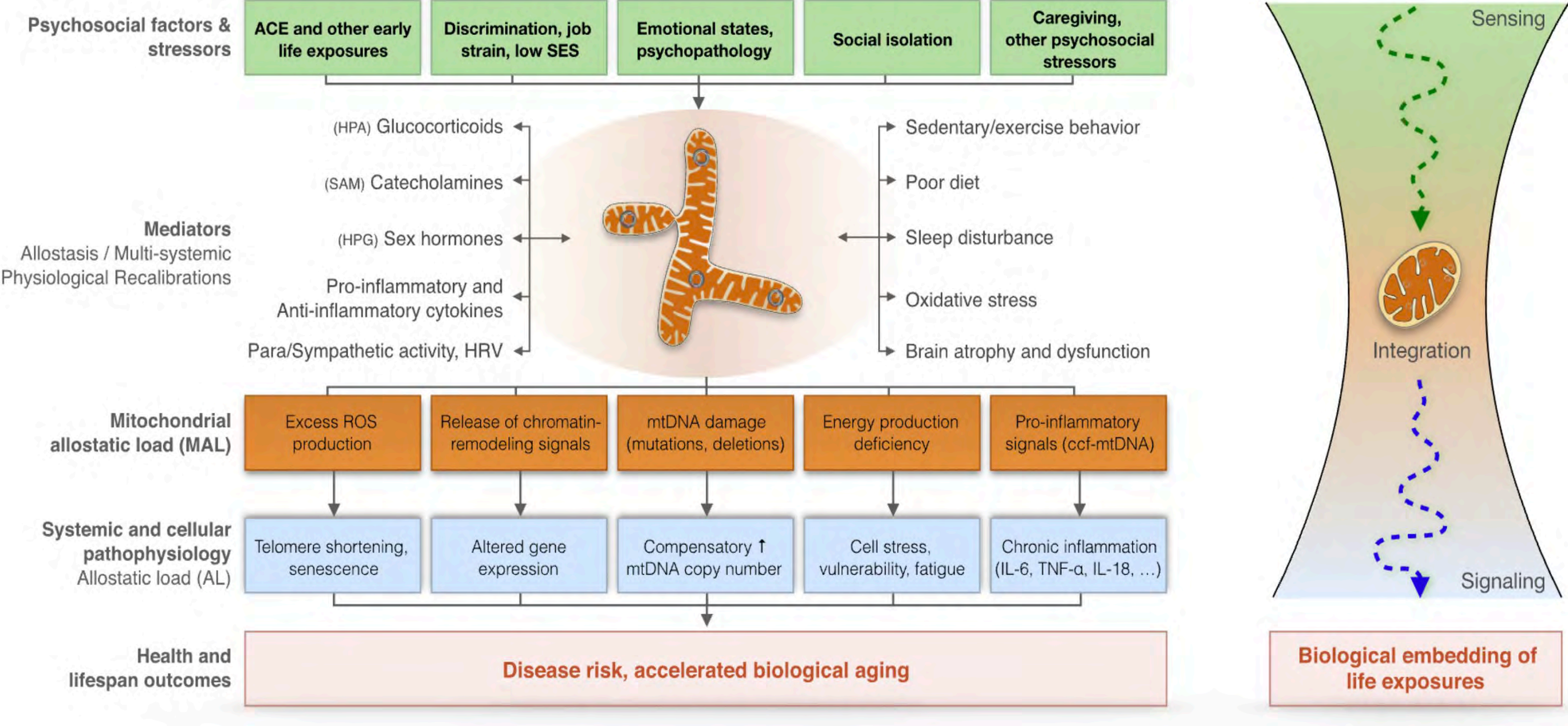


MitoRespiration

<p>Adversity</p>	<p>MLR PLR</p>	<p>Monocytes</p>	<p>✗ No significant association</p>
<p>Mood symptoms</p>	<p>MLR</p>	<p>Lymphocytes</p>	<p>Lymphocytes</p>
<p>+ Adversity</p>	<p>Neutrophils NLR</p> <p>*Childhood trauma</p>	<p>Lymphocytes</p> <p>*Life adversity Childhood trauma</p>	<p>Lymphocytes</p> <p>*Life adversity</p>
<p>- Adversity</p>	<p>✗ No significant association</p>	<p>✗ No significant association</p>	<p>✗ No significant association</p>

What could this mean for human health?

- stress, disease & mitochondria



Picard and McEwen 2018

- Here, we suggest the relevance of mitochondrial biology to adversity and the development mood symptoms



Thank you!
Questions?

BASZUCKI
BRAIN RESEARCH FUND

NIH National Institute
of Mental Health

The Nathaniel
Wharton Fund *nwf*



Thank you!
Questions?

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