The World Journal of Biological Psychiatry

ISSN: 1562-2975 (Print) 1814-1412 (Online) Journal homepage: www.tandfonline.com/journals/iwbp20

Whole blood mitochondrial DNA copy number in depressed patients with and without a history of adverse childhood experiences: the role of blood cell composition

Karin de Punder, Sonja Entringer, Dries S. Martens, Alexander Karabatsiakis, Bilbo Kipka, Christine Heim, Christian E. Deuter, Christian Otte, Katja Wingenfeld & Linn K. Kuehl

To cite this article: Karin de Punder, Sonja Entringer, Dries S. Martens, Alexander Karabatsiakis, Bilbo Kipka, Christine Heim, Christian E. Deuter, Christian Otte, Katja Wingenfeld & Linn K. Kuehl (05 Jan 2026): Whole blood mitochondrial DNA copy number in depressed patients with and without a history of adverse childhood experiences: the role of blood cell composition, The World Journal of Biological Psychiatry, DOI: 10.1080/15622975.2025.2601134

To link to this article: https://doi.org/10.1080/15622975.2025.2601134

THE WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY
https://doi.org/10.1080/15622975.2025.2601134

BRIEF REPORT

OPEN ACCESS Check for updates

Whole blood mitochondrial DNA copy number in depressed patients with and without a history of adverse childhood experiences: the role of blood cell composition

Karin de Punder[a,b], Sonja Entringer[a,c,d,e], Dries S. Martens[f], Alexander Karabatsiakis[a], Bilbo Kipka[i], Christine Heim[a,e,h], Christian E. Deuter[g,i], Christian Otte[g,e], Katja Wingenfeld[g,e] and Linn K. Kuehl[i]

[a]Institute of Medical Psychology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt Universität zu Berlin, and Berlin Institute of Health (BIH), Berlin, Germany; [b]Department of Psychology, Clinical Psychology II, University of Innsbruck, Innsbruck, Austria; [c]Department of Pediatrics, University of California, Irvine, Irvine, CA, USA; [d]Development, Health and Disease Research Program, University of California, Irvine, Irvine, CA, USA; [e]The German Centre for Mental Health, Mannheim, Germany; [f]Centre for Environmental Sciences, Hasselt University, Diepenbeek, Belgium; [g]Department of Psychiatry and Psychotherapy, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt Universität zu Berlin, and Berlin Institute of Health (BIH), Berlin, Germany; [h]Department of Biobehavioral Health, College of Health and Human Development, Pennsylvania State University, University Park, PA, USA; [i]Department of Psychology, MSB Medical School Berlin, Berlin, Germany

ABSTRACT

Objectives: Adverse childhood experiences (ACE) are a significant risk factor for developing major depressive disorder (MDD) later in life, with mitochondria, key sensors of biological stress signals, emerging as a potential underlying mechanism. In the present study, we investigated the effects of ACE and MDD on whole blood mitochondrial DNA copy number (mtDNAcn), a proposed biomarker of mitochondrial health. In our analyses, we accounted for the platelet-to-leukocyte ratio, recognised as a source of variation in mtDNAcn measurements.

Methods: Whole blood mtDNAcn was measured by qPCR in $n=21$ healthy participants without ACE, $n=25$ MDD patients without ACE, $n=22$ healthy participants with ACE, $n=23$ patients with MDD and ACE. None of the participants was taking psychotropic medication.

Results: We observed a significant effect of ACE on whole blood mtDNAcn, while no effect of MDD or ACE and MDD interaction was seen. After adjustment for the platelet-to-leukocyte ratio, the effect of ACE on mtDNAcn was no longer significant.

Conclusions: Our findings do not support an association between ACE or MDD and whole blood mtDNAcn. Considering blood cell composition may enhance the understanding of whole blood mtDNAcn findings in trauma- and MDD-related research.

ARTICLE HISTORY
Received 8 September 2025
Revised 4 December 2025
Accepted 4 December 2025

KEYWORDS
Adverse childhood experiences; biomarker research; major depressive disorder (MDD); mitochondrial DNA copy number (mtDNAcn); platelet-to-leukocyte ratio

1. Introduction

Major depressive disorder (MDD) is a common mental disorder, affecting approximately 280 million people worldwide (WHO 2024). Despite numerous studies conducted over the past decades, clinical findings regarding the pathological mechanisms contributing to MDD remain inconclusive (Otte et al. 2016). Therefore, it is pivotal to understand the biological processes and pathways that underlie the pathophysiology of depression in order to develop a robust signature for early interventions and personalised treatments. Exposure to adverse childhood experiences (ACEs), such as physical and sexual abuse, is a significant risk factor for the development of MDD (Heim et al. 2010). Childhood adversities can become biologically embedded, leading to long-lasting disruptions in key physiological systems, including the neuroendocrine stress response and immune system (Heim et al. 2010; de Punder et al. 2018; Entringer et al. 2020).

Mitochondria represent a key site for detecting and responding to biological stress signals. The (dys)function of mitochondria, particularly when assessed in immune cells, has been implicated in the pathophysiology of various psychiatric disorders and stress-related conditions, including ACEs (Karabatsiakis et al. 2014; Boeck et al. 2016, 2018; Picard and McEwen 2018;

CONTACT Karin de Punder karin.de-punder@uibk.ac.at Department of Psychology, Clinical Psychology II, University of Innsbruck, Universitätsstraße 15, 6020 Innsbruck, Austria

Supplemental data for this article can be accessed online at https://doi.org/10.1080/15622975.2025.2601134.

Gumpp et al. 2020; Zitkovsky et al. 2021). Mitochondrial DNA (mtDNA), a circular double-stranded macromolecule essential for maintaining mitochondrial function and energy production, has emerged as a promising biomarker for mitochondrial health (Castellani et al. 2020; Filograna et al. 2021).

Various studies examined mtDNAcn levels measured in extracted DNA from peripheral (whole) blood in relation to MDD, however, with inconsistent results (Calarco et al. 2024). Both higher (Tyrka et al. 2016; Chung et al. 2019; Tsujii et al. 2019; Ryan et al. 2023) and lower (Kim et al. 2011) whole blood mtDNAcn have been observed in people with MDD or in the context of depressive symptoms. Also, one study found no significant difference in whole blood mtDNAcn between individuals with MDD and MDD-free controls (He et al. 2014). Similar, whole blood mtDNAcn has been positively associated with childhood adversity in some studies (Tyrka et al. 2016; Ridout et al. 2020), but negatively in others (Kang et al. 2021).

In summary, there is evidence for whole blood mtDNAcn changes in the context of MDD and ACE, although results are not conclusive. A reason for the variability in findings may be attributable to the lack of accounting for blood cell composition. Specifically, the platelet-to-leukocyte ratio represents a significant source of variation in mtDNAcn when DNA is extracted from whole blood (Picard 2021). Since mtDNAcn is calculated by normalising mitochondrial DNA (mtDNA) to nuclear DNA (nDNA) (i.e. mtDNAcn/nuclear single-gene DNAcn), platelets, that also contain mitochondria, contribute to the numerator (mtDNA) but not to the denominator (nDNA), leading to an overestimation of mtDNAcn (Shim et al. 2020; Picard 2021). Importantly, both MDD and ACE are linked with low-grade systemic inflammation and alterations in immune cell subsets (Baumeister et al. 2016; de Punder et al. 2018; Behnke et al. 2023; Chin Fatt et al. 2025), which as a consequence, could alter the platelet-to-leukocyte ratio. This underscores the importance of accounting for this variable to ensure accurate and reliable findings.

Thus, the goal of the present study was to study the effects of ACE and MDD on mtDNAcn using a full factorial design (ACE±and MDD±) including four carefully diagnosed groups of healthy participants and MDD patients, both with and without a history of ACE, while accounting for the platelet-to-leukocyte ratio in our analyses. None of the patients and participants was taking psychotropic medication.

2. Material and methods

2.1. Participants

Both male and female healthy participants with and without ACE and patients diagnosed with MDD were recruited from the Affective Disorder-unit at the Department of Psychiatry and Psychotherapy, Campus Benjamin Franklin, Charité -Universitätsmedizin Berlin and by public postings. MDD as an inclusion criterion for patients was validated using the Structured Clinical Interview for DSM-IV axis I (SCID-I) (Wittchen et al. 1997). The severity of depressive symptoms was assessed in an interview with the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979; Williams and Kobak 2008) as well by self-report using the Beck Depression Inventory (BDI) II (Beck et al. 1996). ACE was defined as repeated physical or sexual abuse at least once a month over one year or more before the age of 18 and measured by a semi-structured interview, the Early trauma Interview (ETI) (Bremner et al. 2000; Wingenfeld et al. 2011) and by self-report with the Childhood Trauma Questionnaire (CTQ) (Bernstein et al. 2003; Wingenfeld et al. 2010). Using both assessments enabled clear group assignment as well as a quantification of ACE severity, which facilitates comparability with other studies.

In the MDD group, schizophrenia, schizoaffective disorder, bipolar disorder, depressive disorder with psychotic features, dementia, eating disorders, panic disorder and substance dependence were rated as exclusion criteria. Healthy participants (with and without experiences of ACE) did not have any current or lifetime mental health diagnosis and had never experienced depression, either currently or in the past. Further exclusion criteria for all were neurological diseases, severe somatic diseases, diabetes type 1 and 2, steroid diseases, hypertonia, current infections, pregnancy and the intake of psychotropic medication at study inclusion. Physical health was checked by a comprehensive medical examination, which included an assessment of vital functions, organ functions, neurological status, physical appearance, weight and a clinical interview covering the current health condition and medical history. Additionally, a complete blood count was performed.

All participants provided written informed consent prior to study participation. Healthy participants and outpatients received monetary compensation for participation. The study was approved by the Charité's Ethics Committee with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

The study sample comprised $n = 21$ individuals with no current or lifetime MDD and no ACE (MDD–/ACE–), $n = 25$ individuals with MDD without ACE (MDD+/ACE–), $n = 22$ individuals with ACE but no current, or lifetime MDD (MDD–/ACE+) and $n = 23$ individuals with MDD and ACE (MDD+/ACE+). Table 1 summarises group demographics and clinical characteristics.

Table 1. Demographic and clinical characteristics of MDD patients and healthy participants with and without ACE.

	MDD−/ACE− ($n=21$)	MDD+/ACE− ($n=25$)	MDD−/ACE+ ($n=22$)	MDD+/ACE+ ($n=23$)	Statistics (ANOVA, Kruskal–Wallis test, Chi^2)
Age (years), *M* (*SD*)	36.1 (10.2)	33.2 (11.6)	34.7 (10.7)	38.1 (11.4)	$p = .48$
BMI, *M* (*SD*)	23.5 (3.6)[a, b]	21.9 (3.5)[a]	23.9 (3.1)[a, b]	25.1 (2.9)[b]	**$p = .01$**
Sex (m/f)	9/12	7/18	7/15	9/14	$p = .71$
Current smoking (y/n)	6/15	7/18	8/14	14/9	$p = .07$
School education (years) *M* (*SD*)	12.3 (1.2)	12.1 (1.4)	11.8 (1.4)	11.2 (1.7)	$p = .06$
Depressive symptoms					
BDI-II sum score, *M* (*SD*)	1.3 (1.6)[a]	25.3 (8.7)[b]	4.5 (4.7)[a]	26.8 (8.6)[b]	**$p < .001$**
MADRS score, *M* (*SD*)	0.8 (1.4)[a]	28 (5.7)[b]	1.6 (1.8)[a]	27.4 (8.0)[b]	**$p < .001$**
Adverse childhood experiences					
CTQ sum score, *M* (*SD*)	31.3 (4.7)[a]	40.7 (10.5)[a]	60.7 (17.2)[b]	71.8 (16.3)[c]	**$p < .001$**
ETI score, *M* (*SD*)	14.8 (21.7)[a]	192.8 (197.3)[a]	612.3 (364.4)[b]	732.7 (431.4)[b]	**$p < .001$**
Biological markers					
Relative mtDNAcn, *M* (*SD*)	1.12 (0.23)	1.11 (0.21)	1.07 (0.2)	0.98 (0.25)	$p = .15$
Platelet-to-leukocyte ratio, *M* (*SD*)	45.54 (14.13)	40.74 (13.62)	39.87 (15.58)	36.12 (11.92)	$p = .22$

Notes: ACE: adverse childhood experiences; BMI: body mass index; BDI: Becks Depression Inventory; CTQ: Childhood Trauma Questionnaire; ETI: Early Trauma Interview; MADRS: Montgomery Asberg Depression Rating Scale; MDD: major depressive disorder; M: mean; *SD*: Standard deviation. Statistically significant *p* values are given in bold.
[a,b]Same superscripts within the same line indicate groups are not significantly different from one another.

2.2. Study protocol

All participants attended one study appointment for psychiatric and medical diagnostics by physical examination, blood sampling and clinical interviews (including SCID-I and –II, MADRS as well as the ETI to assess ACE). Participants also completed MDD- and ACE-related questionnaires (BDI-II and CTQ, respectively). Non-fasting blood samples were collected in BD Vacutainer EDTA tubes (BD Vacutainer, Cat. 366643) and immediately sent to the to the Labour Berlin–Charité Vivantes GmbH, Berlin, Germany for assessment of complete blood counts and to the Laboratory of the Institute of Medical Psychology, Campus Mitte, Charité–Universitätsmedizin Berlin, Germany for further processing. Whole EDTA blood was aliquoted within 4 h and stored at −80 °C until mtDNAcn analysis.

2.3. Mitochondrial DNA copy number variations

Mitochondrial DNAcn was measured at the laboratory of the Centre for Environmental Sciences, University Hasselt, Belgium in DNA extracted from whole blood using QIAamp DNA Mini Kit (Qiagen) according to the manufacturer's instruction. mtDNA content was measured by determining the ratio of two mitochondrial gene copy numbers, *MT-ND1* (mitochondrial encoded NADH dehydrogenase 1) and *MTF3212/R3319* (mitochondrial forward primer from nucleotide 3212 and reverse primer from nucleotide 3319) to a single-copy nuclear control gene, *RPLP0* (acidic ribosomal phosphoprotein P0), using a quantitative real-time polymerase chain reaction (qPCR) assay (Janssen et al. 2012). More detailed information on the used primer and cycling conditions and calculations of the relative average mtDNAcn are provided in the supplementary material.

2.4. Complete blood counts

A standard clinical complete blood count was performed with the Sysmex XN 1000 (Sysmex). Due to technical reasons, hemogram data was missing for 9 individuals ($n=1$ MDD−/ACE−, $n=2$ MDD+/ACE−, $n=2$ MDD−/ACE+, $n=4$ MDD+/ACE+). Chi^2 test results indicated there were no significant group differences regarding the number of missing biological measurements (X^2 (3, 91) = 3.01, $p = .38$).

2.5. Statistics

Demographic and clinical characteristics, including the severity of depressive symptoms and childhood trauma scores of the MADRS, BDI-II, ETI and the CTQ were analysed with one-way ANOVA (BDI-II, CTQ) or, if appropriate, Kruskal-Wallis tests (MADRS, ETI) for continuous variables or chi2 test for dichotomous variables across groups. Two general linear models with the between-subjects factors 'ACE' (ACE+ vs. ACE−) and 'MDD' (MDD+ vs. MDD−) were used to investigate the effect of ACE and MDD on mtDNAcn (dependent variable). In Model 1, we adjusted for BMI as it differed significantly between groups and was associated with mtDNAcn in the control group ($r = .44$, $p = .046$). In Model 2, we, in addition to BMI, adjusted for the platelet-to-leukocyte ratio, obtained from the standard clinical complete blood count, which in our study showed a strong association with whole blood mtDNAcn ($r = .64$, $p < .001$, Figure 1). Pearson's correlations between other blood cell composition variables and

mtDNAcn are presented in Table S1. Furthermore, associations between depression severity (MADRS, BDI-II sum score), trauma load (ETI sum score, CTQ sum score) and the platelet-to-leukocyte ratio and mtDNAcn were explored through Pearson's (partial) or Spearman's rank correlations, where appropriate. Data analysis was performed using the SPSS statistical software (SPSS 26.0, Inc., Chicago, IL, USA). The significance level was set at $p < .05$ for all analyses.

3. Results

3.1. Whole blood mtDNAcn in the context of ACE and MDD

In Model 1, a significant effect of ACE was observed on whole blood mtDNAcn, indicating lower relative mtDNA/S ratios in individuals exposed to ACE compared to non-exposed individuals ($F_{1, 86} = 4.57$, $p = .035$, $\eta^2=0.05$, Figure 2). The effect of MDD ($F_{1, 86} = 0.89$, $p = .35$, $\eta^2=0.01$) and the interaction effect between ACE and MDD ($F_{1, 86} = 1.14$, $p = .29$, $\eta^2=0.01$) with mtDNAcn were not significant, see also Table 2. After additionally adjusting for the platelet-to-leukocyte ratio in Model 2, the association of ACE with mtDNAcn was no longer significant ($F_{1, 77} = 2.32$, $p = .13$, $\eta^2=0.03$). The platelet-to-leukocyte ratio was highly associated with mtDNAcn ($F_{1, 77} = 52.93$, $p < .001$, $\eta^2=0.41$, Table 3).

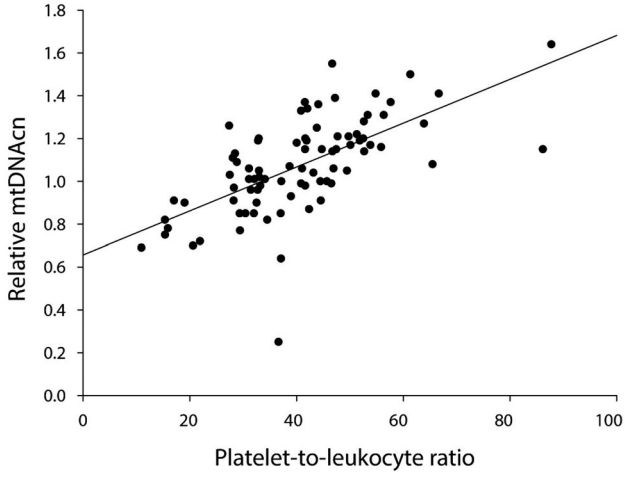

Figure 1. Scatterplot illustrating the relationship between platelet-to-leukocyte ratio and relative mtDNAcn ($r=.64$, $p <.001$, $n=83$). mtDNAcn: mitochondrial DNA copy number.

Table 2. Model 1, ANCOVA summary table for determining the effects of ACE, MDD, their interaction term and BMI.

Source of variation	Mean square	*df*	*F*	*p*	η^2
ACE	0.23	1	4.57	**.035**	.05
MDD	0.04	1	0.89	.35	.01
ACE*MDD	0.06	1	1.14	.29	.01
BMI	0.06	1	1.11	.29	.01

Note: mtDNAcn is the dependent variable in this analysis. ACE: adverse childhood experiences; BMI: body mass index; MDD: major depressive disorder. Statistically significant p-values are given in bold.

3.2. Associations of trauma and depression severity with mtDNAcn and the platelet-to-leukocyte ratio

Analyses of trauma severity indicated a trend towards a significant negative association of the CTQ sum score ($r=-.20$, $p = .059$) and a significant negative association of the subscale physical abuse ($r=-.22$, $p = .04$) with mtDNAcn. An overview of associations between all the CTQ subscales and mtDNAcn is reported in Table S2. Furthermore, a negative but non-significant association of the ETI score with mtDNAcn was observed ($r_s = -.17$,

Table 3. Model 2, ANCOVA summary table for determining the effects of ACE, MDD, their interaction term and the covariates BMI and platelet-to-leukocyte ratio.

Source of variation	Mean square	*df*	*F*	*P*	η^2
ACE	0.07	1	2.32	.13	.03
MDD	001	1	0.02	.88	.0003
ACE*MDD	0.04	1	1.3	.26	.02
BMI	0.08	1	2.73	.10	.03
Platelet-to-leukocyte ratio	1.57	1	52.93	**<.0001**	.41

Note: mtDNAcn is the dependent variable in this analysis. ACE: adverse childhood experiences; BMI: body mass index; MDD: major depressive disorder. Statistically significant p-values are given in bold.

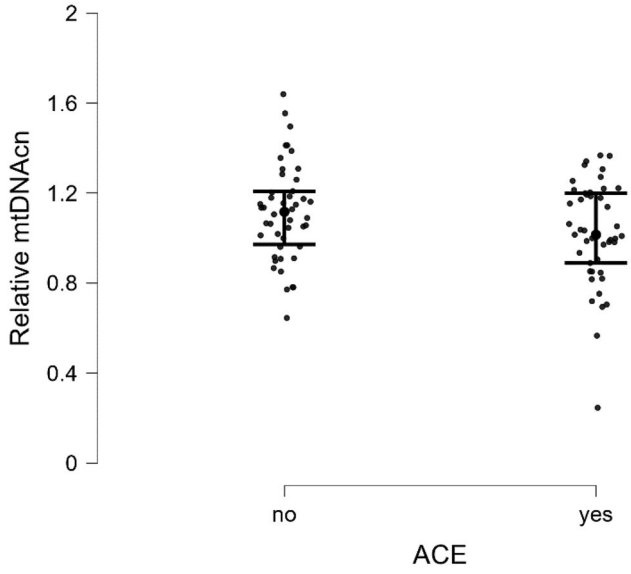

Figure 2. Difference in relative mtDNAcn (unadjusted) between individuals exposed to ACE and non-exposed individuals. Bars represent the interquartile range. The median mtDNAcn was 1.12 (1.22–0.96) for the group with no ACE ($n=46$) and 1.01 (1.20–0.87) for the group with (yes) ACE ($n=45$). ACE: adverse childhood experiences; mtDNAcn: mitochondrial DNA copy number.

p = .12). As expected, no significant associations of depression severity indicated by the BDI-II sum score (r=−.10, p = .35) and MADRS (r_s = −.09, p =.43) were seen with mtDNAcn.

Trauma severity, as measured by the ETI score, showed a significant negative association with platelet-to-leukocyte ratio (r_s = −.29, p = .008), but no significant association was observed with the CTQ sum score (r=−.16, p = .14) or its subscales (all p-values > .05). The BDI-II sum score and MADRS were also negatively associated with the platelet-to-leukocyte ratio, but these associations did not reach statistical significance (BDI-II, r=−.18, p = .11; MADRS, r_s = −.20, p = .08).

After controlling for the platelet-to-leukocyte ratio, no significant associations of trauma and depression severity with mtDNAcn were observed (all p values > .05).

4. Discussion

Previous research addressing mtDNAcn in blood samples from individuals with and without ACE and MDD reported heterogenous findings. In the current study, we initially observed lower whole blood mtDNAcn in individuals exposed to ACE compared to non-exposed subjects, whereas MDD as well as the interaction of ACE and MDD had no significant effect. However, after adjusting for the platelet-to-leukocyte ratio, the effect of ACE on mtDNAcn was no longer significant. Previously published results in the same study cohort showed increased levels of inflammation, including elevated total leukocytes counts, in individuals exposed to ACE, with the highest level in the group with MDD (de Punder et al. 2018). This likely reduced the platelet-to-leukocyte ratio in these individuals, as further evidenced by the observed negative association between trauma severity and the platelet-to-leukocyte ratio, which correspond with lower measures of mtDNAcn (Hurtado-Roca et al. 2016; Knez et al. 2016; Shim et al. 2020; Picard 2021). Therefore, our initial finding of lower whole blood mtDNAcn in individuals exposed to ACE may be attributed to inflammation-related shifts in blood cell composition associated with childhood trauma exposure (Baumeister et al. 2016; Danese and van Harmelen 2017; de Punder et al. 2018). A similar observation has been reported in a study with patients with obsessive-compulsive disorder (OCD) and healthy controls. Here, correlation analyses of the entire study population showed a negative correlation between trauma severity and whole blood mtDNAcn (without accounting for the platelet-to-leukocyte ratio). Moreover, lower whole blood mtDNAcn in the OCD group was significantly correlated with an increase in systemic inflammation (Kang et al. 2021).

Our results contrast with those of other studies, which reported higher mtDNAcn in ACE-exposed individuals (Tyrka et al. 2016; Ridout et al. 2020). Although these studies had larger sample sizes, they did not account for the platelet-to-leukocyte ratio.

The lack of an observed association between MDD and whole blood mtDNAcn in our study aligns with previous research findings (He et al. 2014). However, other studies reported conflicting results, with some showing increased whole blood mtDNAcn (Tyrka et al. 2016; Chung et al. 2019; Tsujii et al. 2019; Ryan et al. 2023) and others reporting decreased levels (Kim et al. 2011) in the context of depression or depression symptomology. Lower whole blood mtDNAcn was also observed in individuals with bipolar disorder (BD) compared to a healthy control group (Spano et al. 2022). This heterogeneity in findings may be attributed to differences in study designs, participant characteristics and measurement methodologies. Notably, most studies did not include measures of childhood adversity, and none of the mentioned studies considered blood cell composition (i.e. the platelet-to-leukocyte ratio), a known source of variation in whole blood mtDNAcn calculations (Picard 2021).

As most previous studies investigating MDD did not assess experiences of childhood adversity, a key strength of the study was the systematic inclusion of this factor using a full factorial design. Furthermore, none of the patients and participants took psychotropic medication that may impair mitochondrial function (Chan et al. 2020). Finally, mtDNAcn measured in whole blood is confounded by platelet abundance, for which we, in contrary to previous studies investigating ACE and MDD, statistically controlled in our analyses. Still, measuring mtDNAcn directly in isolated immune cells might have resulted in different findings.

This study has also several limitations. First, the cross-sectional design does not allow any causal conclusions. Second, the relatively small sample size, might have led to insufficient power to detect a significant effect of ACE, especially when adjusting for a strong predictor of whole blood mtDNAcn such as the platelet-to-leukocyte ratio. Additionally, it is not possible to distinguish the effects of ACE, BMI and other ACE-related variables, including smoking and SES, as these factors are interconnected and may have contributed to the observed associations. Moreover, the sample size was insufficient to enable us to compare sex differences.

To conclude, after adjusting for the platelet-to-leukocyte ratio, we found no evidence supporting an association between ACE or MDD and whole blood mtDNAcn. Furthermore, this underlines the importance to consider

blood cell composition when measuring whole blood mtDNAcn in trauma- and MDD-related research or other conditions associated with inflammation.

Acknowledgements

None.

Statement of interest

None to declare.

Funding

This work was supported by the Deutsche Forschungsgemeinschaft (DFG) under Grant number KU 3106/2-1 (Linn K. Kuehl, Christian Otte, Katja Wingenfeld). Dries Martens is supported by a postdoctoral grant from the Research Foundations Flanders (FWO grant 12X9623N).

ORCID

Karin de Punder http://orcid.org/0000-0003-0510-9147
Sonja Entringer http://orcid.org/0000-0002-9926-7076
Dries S. Martens http://orcid.org/0000-0001-7893-3642
Alexander Karabatsiakis http://orcid.org/0000-0002-5822-0108
Bilbo Kipka http://orcid.org/0009-0009-8976-8115
Christine Heim http://orcid.org/0000-0002-6580-6326
Christian E. Deuter http://orcid.org/0000-0001-6880-5946
Christian Otte http://orcid.org/0000-0002-4051-997X
Katja Wingenfeld http://orcid.org/0000-0001-7457-0370
Linn K. Kuehl http://orcid.org/0000-0001-6871-6302

References

Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. 2016. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-alpha. Mol Psychiatry. 21(5): 642–649. https://doi.org/10.1038/mp.2015.67

Beck AT, Steer RA, Ball R, Ranieri W. 1996. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess. 67(3):588–597. https://doi.org/10.1207/s15327752jpa6703_13

Behnke A et al. 2023. Circulating inflammatory markers, cell-free mitochondrial DNA, cortisol, endocannabinoids, and N-acylethanolamines in female depressed outpatients. World J Biol Psychiatry. 24(1):58–69. https://doi.org/10.1080/15622975.2022.2070666

Bernstein DP et al. 2003. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. Child Abuse Negl. 27(2):169–190. https://doi.org/10.1016/s0145-2134(02)00541-0

Boeck C et al. 2016. Inflammation in adult women with a history of child maltreatment: the involvement of mitochondrial alterations and oxidative stress. Mitochondrion. 30:197–207. https://doi.org/10.1016/j.mito.2016.08.006

Boeck C et al. 2018. The association between cortisol, oxytocin, and immune cell mitochondrial oxygen consumption in postpartum women with childhood maltreatment. Psychoneuroendocrinology. 96:69–77. https://doi.org/10.1016/j.psyneuen.2018.05.040

Bremner JD, Vermetten E, Mazure CM. 2000. Development and preliminary psychometric properties of an instrument for the measurement of childhood trauma: the Early Trauma Inventory. Depress Anxiety. 12(1):1–12. https://doi.org/10.1002/1520-6394(2000)12:1<1::AID-DA1>3.0.CO;2-W

Calarco CA, Keppetipola SM, Kumar G, Shipper AG, Lobo MK. 2024. Whole blood mitochondrial copy number in clinical populations with mood disorders: a meta-analysis: blood mitochondrial copy number and mood disorders. Psychiatry Res. 331:115662. https://doi.org/10.1016/j.psychres.2023.115662

Castellani CA, Longchamps RJ, Sun J, Guallar E, Arking DE. 2020. Thinking outside the nucleus: mitochondrial DNA copy number in health and disease. Mitochondrion. 53:214–223. https://doi.org/10.1016/j.mito.2020.06.004

Chan S, McCarthy M, Vawter MP. 2020. Psychiatric drugs impact mitochondrial function in brain and other tissues. Schizophr Res. 217:136–147. https://doi.org/10.1016/j.schres.2019.09.007

Chin Fatt CR et al. 2025. Cellular immune phenotype of major depressive disorder - findings from the EMBARC study. World J Biol Psychiatry. 26(5):179–188. https://doi.org/10.1080/15622975.2025.2486137

Chung JK, Lee SY, Park M, Joo E-J, Kim SA. 2019. Investigation of mitochondrial DNA copy number in patients with major depressive disorder. Psychiatry Res. 282:112616. https://doi.org/10.1016/j.psychres.2019.112616

Danese A, van Harmelen AL. 2017. The hidden wounds of childhood trauma. Eur J Psychotraumatol. 8(sup5):137584. https://doi.org/10.1080/20008198.2017.1375840

de Punder K et al. 2018. Inflammatory measures in depressed patients with and without a history of adverse childhood experiences. Front Psychiatry. 9:610. https://doi.org/10.3389/fpsyt.2018.00610

Entringer S et al. 2020. Immediate and longitudinal effects of maltreatment on systemic inflammation in young children. Dev Psychopathol. 32(5):1725–1731. https://doi.org/10.1017/S0954579420001686

Filograna R, Mennuni M, Alsina D, Larsson N-G. 2021. Mitochondrial DNA copy number in human disease: the more the better? FEBS Lett. 595(8):976–1002. https://doi.org/10.1002/1873-3468.14021

Gumpp AM et al. 2020. Childhood maltreatment is associated with changes in mitochondrial bioenergetics in maternal, but not in neonatal immune cells. Proc Natl Acad Sci U S A. 117(40):24778–24784. https://doi.org/10.1073/pnas.2005885117

He Y et al. 2014. Leukocyte mitochondrial DNA copy number in blood is not associated with major depressive disorder in young adults. PLoS One. 9(5):e96869. https://doi.org/10.1371/journal.pone.0096869

Heim C, Shugart M, Craighead WE, Nemeroff CB. 2010. Neurobiological and psychiatric consequences of child abuse and neglect. Dev Psychobiol. 52(7):671–690. https://doi.org/10.1002/dev.20494

Hurtado-Roca Y, Ledesma M, Gonzalez-Lazaro M, Moreno-Loshuertos R, Fernandez-Silva P, Enriquez JA, Laclaustra M. 2016. Adjusting MtDNA Quantification in Whole Blood for

Peripheral Blood Platelet and Leukocyte Counts. PLoS One. 11(10):e0163770. https://doi.org/10.1371/journal.pone.0163770

Janssen BG et al. 2012. Placental mitochondrial DNA content and particulate air pollution during in utero life. Environ Health Perspect. 120(9):1346–1352. https://doi.org/10.1289/ehp.1104458

Kang JI et al. 2021. Alterations of cellular aging markers in obsessive–compulsive disorder: mitochondrial DNA copy number and telomere length. J Psychiatry Neurosci. 46(4):E451–E458. https://doi.org/10.1503/jpn.200238

Karabatsiakis A et al. 2014. Mitochondrial respiration in peripheral blood mononuclear cells correlates with depressive subsymptoms and severity of major depression. Transl Psychiatry. 4(6):e397–e397. https://doi.org/10.1038/tp.2014.44

Kim M-Y, Lee J-W, Kang H-C, Kim E, Lee D-C. 2011. Leukocyte mitochondrial DNA (mtDNA) content is associated with depression in old women. Arch Gerontol Geriatr. 53(2):e218–e221. https://doi.org/10.1016/j.archger.2010.11.019

Knez J, Winckelmans E, Plusquin M, Thijs L, Cauwenberghs N, Gu Y, Staessen JA, Nawrot TS, Kuznetsova T. 2016. Correlates of Peripheral Blood Mitochondrial DNA Content in a General Population. Am J Epidemiol. 183(2):138–146. https://doi.org/10.1093/aje/kwv175

Montgomery SA, Asberg M. 1979. A new depression scale designed to be sensitive to change. Br J Psychiatry. 134(4):382–389. https://doi.org/10.1192/bjp.134.4.382

Otte C et al. 2016. Major depressive disorder. Nat Rev Dis Primers. 2(1):16065. https://doi.org/10.1038/nrdp.2016.65

Picard M. 2021. Blood mitochondrial DNA copy number: what are we counting? Mitochondrion. 60:1–11. https://doi.org/10.1016/j.mito.2021.06.010

Picard M, McEwen BS. 2018. Psychological stress and mitochondria: a systematic review. Psychosom Med. 80(2):141–153. https://doi.org/10.1097/PSY.0000000000000545

Ridout KK et al. 2020. Molecular markers of neuroendocrine function and mitochondrial biogenesis associated with early life stress. Psychoneuroendocrinology. 116:104632. https://doi.org/10.1016/j.psyneuen.2020.104632

Ryan KM, Doody E, McLoughlin DM. 2023. Whole blood mitochondrial DNA copy number in depression and response to electroconvulsive therapy. Prog Neuropsychopharmacol Biol Psychiatry. 121:110656. https://doi.org/10.1016/j.pnpbp.2022.110656

Shim HB, Arshad O, Gadawska I, Côté HCF, Hsieh AYY. 2020. Platelet mtDNA content and leukocyte count influence whole blood mtDNA content. Mitochondrion. 52:108–114. https://doi.org/10.1016/j.mito.2020.03.001

Spano L et al. 2022. Telomere length and mitochondrial DNA copy number in bipolar disorder: identification of a subgroup of young individuals with accelerated cellular aging. Transl Psychiatry. 12(1):135. https://doi.org/10.1038/s41398-022-01891-4

Tsujii N et al. 2019. Mitochondrial DNA copy number raises the potential of left frontopolar hemodynamic response as a diagnostic marker for distinguishing bipolar disorder from major depressive disorder. Front Psychiatry. 10:312. https://doi.org/10.3389/fpsyt.2019.00312

Tyrka AR et al. 2016. Alterations of mitochondrial DNA copy number and telomere length with early adversity and psychopathology. Biol Psychiatry. 79(2):78–86. https://doi.org/10.1016/j.biopsych.2014.12.025

Williams JB, Kobak KA. 2008. Development and reliability of a structured interview guide for the Montgomery Asberg Depression Rating Scale (SIGMA). Br J Psychiatry. 192(1):52–58. https://doi.org/10.1192/bjp.bp.106.032532

Wingenfeld K et al. 2010. [The German version of the Childhood Trauma Questionnaire (CTQ): preliminary psychometric properties]. Psychother Psychosom Med Psychol. 60(8):e13. https://doi.org/10.1055/s-0030-1253494

[WHO] World Health Organization. 2024. Depressive disorder [Internet]; [accessed 2024 Nov 19]. https://www.who.int/news-room/fact-sheets/detail/depression

Wingenfeld K et al. 2011. Associations of childhood trauma, trauma in adulthood and previous-year stress with psychopathology in patients with major depression and borderline personality disorder. Child Abuse Negl. 35(8):647–654. https://doi.org/10.1016/j.chiabu.2011.04.003

Wittchen H-U, Zaudig M, Fydrich T. 1997. Skid. Strukturiertes klinisches Interview für DSM-IV. Achse I und II. Handanweisung. Göttingen: Hogrefe.

Zitkovsky EK, Daniels TE, Tyrka AR. 2021. Mitochondria and early-life adversity. Mitochondrion. 57:213–221. https://doi.org/10.1016/j.mito.2021.01.005