Suppl. Table 2.1 Overview of EWAS associated with psychological stress during prenatal period

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Stress type****(Measurement)** | **Sample**  | **Tissue/cell** | **Author/year** | **Main results** | **Effect size/****Power** | **covariant** | **batch/position effect** | **Multiple correction** | **GO/KEGG** | **PMID** |
| prenatal depression/anxietyScale | 44 neonatal from women (15 current, 14 past stress,15 control) 62 adults (12 with,50 no maternal depression)(Canada) | Cord blood CD3+ T cellHippocampal | Nemoda et al.(2015) | Prenatal depression associated with145 DMP among neonates and 294 DMP among adults. 33 genes has overlap. | 145 DMP: FDR<0.05 (∆= 2~10%)294 DMR: FDR<0.1Small power | Plate assignment, cell purity | √/√ | √ | ImmunityIncludingNR3C1 | 25849984 |
| prenatal depression/anxietyMedical record | 33 exposed neonates (11 non-medicated vs.22 medicated)23 unexposed neonates(USA) | Cord blood  | Non et al. (2014) | The lower methylation of 42 CpG sites between neonates exposed vs. unexposed group. NFKB2, FKBP5, NR3C1, CRHR1 were validated. | FDR<0.1（EWAS)(∆= 9%~3.6%)(small power) | age of mother, BMI, family SES,maternal age at delivery height, sexweight  | √/× | √ | Transcriptionregulation ,Translation,Metabolicprocesses | 24751725 |
| prenatal anxietyquestionnaires | 23 high stress offspring 22 low stress offspring(Belgium) | Cord blood  | Vangeel et al.(2017) | 10 DMR between low vs high prenatal stress. Methylation of GABBR ↑ than control. | GABBR1: p=0.002r=0.517~0.462(large power) | gender, cell type, gestational age | √/× | √ | Braindevelopment | 29026448\* |
| prenatal depression/anxietymedical record | Discovery: 479 infants(In Project Viva)Validation: 999 infants(the Generation R Study)(USA) | Cord blood  | Cardenas et al. (2019)(longitudinal)  | Stressed infants 7.2% lower methylation of ZNF575,the association was replicated and persist into early childhood. | Discovery:∆β=7.2%Replication: (∆β=2.5%(large power) | maternal, BMI, self-reported race, smoking education and infant sex | √/× | √ | Transcriptional regulation | 30925934\* |
| **Stress type****(Measurement)** | **Sample**  | **Tissue/cell** | **Author/year** | **Main results** | **Effect size/****Power** | **covariant** | **batch/position effect** | **Multiple correction** | **GO/KEGG** | **PMID** |
| prenatalDepressionScale (EPDS) | 146 infants (6 weeks)128 infants (12 months)(Norwegian) | Saliva6 weeks 12 months | Wikenius et al. (2019)(longitudinal)  | No significant genome-wide association between prenatal stress and infantDNA methylation for both time points. | P=: 1.18e-07.Power: 65%  | cell type, sex,maternal depression age | √/√ | √ | / | 31070508\* |
| prenatalDepressionClinical assessment | 12 prenatal SRI antidepressant exposure neonates and 11 control(British) | Cord blood | Gurnot et al. (2015) | Maternal depressed in 3rd trimester associated with higher DNA methylation at CYP2E1 in the SRI-exposed neonates. | CYP2E1: r 2 : -0.81Large power | SRI exposure,maternal, prenatal mood | ×/× | √ | Metabolism | [25891251](https://www.ncbi.nlm.nih.gov/pubmed/25891251%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| prenatal psychiatric illness (SCID)  | 201 dyads(USA) | umbilical cord blood  | Schroeder et al.(2012)  | No large effects maternal psychological stress on neonatal DNA methylation. Exposure to an antidepressant associated with two CpG sites. | FDR=0.05>14.5% of variation Power: >80% | neonatal gender, race gestational age | √/× | √ | / | [22419064](https://www.ncbi.nlm.nih.gov/pubmed/22419064%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Maternal anxiety**Meta analysis** | 16 cohorts 7243 mother-child dyads(Multi-race) | umbilical cord blood. | Sammallahtinet al.(2021)  | no consistent evidence for any robust associations between maternal anxiety and DNAm in cord blood.  | Large power | child sex, maternal age, socioeconomic status, cell counts, ethnicity | √/√ | √ | / | 33414500\* |
| prenatal depressionquestionnaires | 178 mother with prenatal depression (13 with and165without SSRI treatment);195 HC(Scandinavia) | cord blood  | Kallak et al.(2021) | No DMP was associated with prenatal depression. There were DMG(CRBN, MDFIC) among children exposed to PND with SSRI treatment .There might be different consequences for the child depending on whether maternal PND was treated with SSRIs or not. | log2 fold change: −0.57; Low power | Child’ sex.cell proportion,maternal age at delivery, educational level, gestational age | √/√ | √ | brain development, stress response | 33845866 |
| **Stress type****(Measurement)** | **Sample**  | **Tissue/cell** | **Author/year** | **Main results** | **Effect size/****Power** | **covariant** | **batch/position effect** | **Multiple correction** | **GO/KEGG** | **PMID** |
| Maternal depressionEPDS Scale | 844 mother-child pairs from (ALSPAC) (UK) | cord blood  | Viuff et al. (2018) | 2 CpG sites &39 DMRs associated with maternal depression. But results were note replicated in Generation R Study | β: 0.01~0.05Low power(40%) | maternal age, BMI, parity, smoking, maternal education. cell proportion | √/× | √ | psychiatric disease, brain development. | 30405117 |
| Early life stressSCID, questionnaie (cross-species comparision) | 180 pair of mothers and infants (Germany) | CD34+ hematopoietic stem cells from cord blood | Nieratschker et al. (2014) | 3405 DMG (1786↓, 1750↑, 131mix direction). DMR in MORC1 was replicated in different species. | MORC1: P=0.0144Small power | Cell type | /MeDIP | √ | Cancer, gene expression | 25158004 |
| PrenatalExpose to IPV(Interview) | 122 mother and 120Neonates(Brazil) | Saliva | Serpeloni  et al. (2019) | 31 DMGs were uncovered. DNAm of NR3C1↓ and FKBP5 **↑** were replicated. The results were validated. | Large power  | age, sex, prenatal trauma, prenatal CDV | √/× | √ | Stressresponse;Psychiatricdisorders | 31040859\* |
| Prenatal Stress(life stress + contextual stress + personal stress + interpersonal stress) questionnaire | Generation R (N=912)(Netherlands)ALSPAC (N=828)(UK)Meta analysis: N=1740 | Cord blood  | Rijlaarsdam et al.(2016) | No any Bonferroni-corrected DMPs associated with prenatal maternal stress exposure.  | EWAS: meta-analysisEffect size: -0.06~0.04Large power | gestational age, sex, maternal smoking status, cell types | √/√ | √ | / | [26889969](https://www.ncbi.nlm.nih.gov/pubmed/26889969%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Prenatal Psychological stress(questionnaire) | 10 mother-child-pairsprospective mother-child cohort LINA(Germany) | cord blood | Trump et al. (2016) | High maternal stress was associated with an increased DNAm in infants. 2306 stress DMR were identified in children. | Large power | child’s gender,smoking during pregnancy, age of the mother, cell composition | / | √ | calcium- and Wnt-signaling wheeze | 27349968\* |
| **Stress type/****measure** | **Sample**  | **Tissue/cell** | **Author/year** | **Main results** | **Effect size/****Power** | **covariant** | **batch/position effect** | **Multiple****correction** | **GO/KEGG** | **PMID** |
| Maternal lifetime stress exposure(LSC-R,questionnaire) | 207 mother and newbabies(USA, diverse ethnity) | placental | Brunst et al.(2018) | 112 DMP associated with maternal stress.3 clusters response to high maternal lifetime stress. Especially for ANKFY1, TM6SF1 | Enough power | maternal race/ ethnicity, maternal age, children’s sex,cell heterogeneity | √/√ | √ | Endocytosis,Tight junction,metabolic pathways | 30001177\* |
| ExposureTo Quebec Ice Storm(questionnaire) | 36 stressed offspring (13.3yrs)(Canada) | T-cell andPBMC | Cao-Lei et al.(2014) | 1675 DMP (823 CpGs positive, 852 negative) associated with objective instead of subject stress were found. Results were validated across tissue. | cg12134633 r =-0.631, P<0.001 large power | / | ×/× | √ | Immuneprocesses | 25238154\* |
| PrenatalNatural disaster(questionnaire) | 34 adolescents whosemothers stressed (Canada) | T cell | Cao-Lei et al. (2015) | Maternal stress associated with 1564 DMG of offspring, persist into adolescence. | P=0.05,FDR=0.2not provided effect size | / | ×/× | √ | Immuneresponse | 25710121 |
| war exposure(semi-structured interviews) | 25 pair of mothers and infants(Congo) | Cord blood PlacentalMaternalvenous blood | Rodney et al.(2014) | War stress only associated with DNAm in maternal venous blood except for NR3C1.Placenta hypomethylated relative to maternal venous blood and newborn cord blood | r=-0.627P=0.001Large power  | Mean methylation, tissue | ×/× | √ | / | [25043696](https://www.ncbi.nlm.nih.gov/pubmed/25043696%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Prenatal socioeconomic status (questionnaire) | 422 mother–child pairsUSA(diverse ethnity) | cord blood | Laubach et al(2019)(longitudinal)  | Low prenatal SES was associated with methylation at CpG sites near ACSF3, TNRC6C, AS1, MTMR4 and LRRN4. The relationship with LRRN4 persisted into early childhood. | Large power | gestational agerace/ethnicity smoking habitsleukocytes composition etc. | √/√ | √ | CancerMetabolic,psychiatric disease, memory | 31509016\* |
| **Stress type/****measure** | **Sample**  | **Tissue/cell** | **Author/year** | **Main results** | **Effect size/****Power** | **covariant** | **batch/position effect** | **Multiple****correction** | **GO/KEGG** | **PMID** |
| prenatal maternal socioeconomic status (structured interviews) | 426 infantsUSA(diverse ethnity) | placenta | Santos et al. (2019) | SES adversity were associated with differential methylation at 33 CpG sites(19,57.6%) increased methylation, (14, 42.4%) decreased methylation. Sex differences were observed in DNAm. | Large power | maternal age, race, infant sex, birth weight, gestational age, maternal smoking  | √/× | √ | Gene transcriPtion, immunity, stress response | 31062658\* |
| Prenatal SEP(questionnaire) | 3 life stages (birth, n=914; childhood n=973; adolescence, n=974) from ALSPAC birth cohort(U.K) | cord blood  | Alfano et al. (2019)(longitudinal) | maternal education was associated with 4 CpGs methylation levels at birth (SULF1, GLB1L2 and RPUSD1).Two CpG sites at birth and during adolescence were identified.These results were failed to replicated. | Large power | Parental and maternal demorgraphical status  | √/√ | √ | Signal pathways | 30590607\* |

Note: \* means EWAS with statistical power>75%.

Suppl. Table 2.2 Overview of EWAS associated with psychological stress postnatal period

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| **Stress type****(Measurement)** | **Sample** | **Tissue/cell** | **Author/year** | **Main results** | **Effect size/ power** | **covariant** | **batch/position effect** | **Multiple correction** | **GO/KEGG** | **PMID** |
| Child maltreat/neglect(Multiple data sources)  | 96 stressed vs.96 controlchildren USA(mixed race) | saliva | Yang et al. (2013) | 2868 DMP in maltreated children compared to controls | P<5.0×10-7∆= 17% Power:76% | age, genderrace | √/× | √ | Psychiatric/ physical disorders heart disease, stroke, cancer | 23332324\* |
| Childhood abuse (Multiple informants and data sources) | 94 stressed 96 control children USA(mixed race) | saliva | Weder et al(2014) | 11 DMP from ID-3 , GRIN1and TPPP emerged associating with maltreatment Hypomethylation of BDNF, NR3C1, FKBP5 were identified among stress group (different loci, not comparable) | P<5.0×10-7large power | age, race, sex  | √/× | √ | ID-3: stress responseGRIN1: neural plasticity TPPP: neural circuitry development. | [24655651](https://www.ncbi.nlm.nih.gov/pubmed/24655651%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Child maltreat(MCS record) | 298 stressed 250 control childrenUSA(multi race) | saliva  | Cicchetti et al. (2016) | Over 1800 DMP between two groups after whole genome-wide correction. Methylation of ALDH2, ANKK1, NR3C1 were identified | P< 5.0×10-7∆= 6.2%(1%–64%)large power | Sex, race | ×/× | √ | mental health, cancer, cardiovascular systems, immune functioning  | [27691979](https://www.ncbi.nlm.nih.gov/pubmed/27691979%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Maltreatment,neglect,witnessviolence(interview) | Discovery: 1656 adolescents Replication: 818 adults (British) | Peripheral blood  | Marzi et al(2018)(Longitudinal) | No DMG associated with polyvictimi- zation. 48 loci associated with SA, but not been replicated. Results of NR3C1, FKBP5, BDNF, AVP, CRHR1, SLC6A4 did notrevealed. | large power | sex, cell-typesmoking  | √/√ | √ | / | [29325449](https://www.ncbi.nlm.nih.gov/pubmed/29325449%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Childhood abuse + child adversities + SEP (questionnaire) | 691~774 Child from ALSPAC (UK) | cord bloodleukocytes | Dunn et al.(2019) (longitudinal) | Neighbourhood disadvantage:10 CpG sites, Financial stress: 9 CpG sites;sexual or physical abuse: 38CpG sites | Small-medium power (5~19%) | cell type, child race/Ethnicity, birth weight, maternal age  | √/× | √ | regulation of developmental growth;axon development, and neuron apoptotic  | [30905381](https://www.ncbi.nlm.nih.gov/pubmed/30905381%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank) |
| **Stress type****(Measurement)** | **Sample** | **Tissue/cell** | **Author/year** | **Main results** | **Effect size/ power** | **covariant** | **batch/position effect** | **Multiple correction** | **GO/KEGG** | **PMID** |
| Child maltreat(CTQ questionnaire) | 124 high-risk youth (16~24 yrs)(UK diverse ethnicity) | Buccal cells | Cecil et al. (2016) | PA has strongest effect of methylation changes of epigenome. Different abuse sub-type has unique and common methylation changes. | Physical abuse：large power | age, sex, ethnity | √/√ | √ | PA: cardiovascular function fear, wound healing. PN: nutrient metabolism. Common: nervous development, tissue growth. | 27643477\* |
| Childhood trauma(PCA) | 188 adults (27 yrs)USA89% Caucasian  | blood | O’Donnell (2018)(Longitudinal) | PC analysis showed history of abuse/neglect significantly associated with DNA methylome variation at 27 years. | Power:10.3%, 3.3% of variance (PC1, PC2)Large power | sex, ancestry, cellular heterogeneity, risk of psychiatric disorder | √/× | × | PC1: protein phosphorylation,Immune activation/ differentiation. PC2: transcription regulation | 29317599\* |
| Childhood abuse(questionnaire) | 12 stressed males28 control males(England & Scotland) | whole blood | Sudermanet al.(2014) | 997 DMG (311 hypermethylated and 686 hypomethylated) associated with child abuse. Results of PM20D1 were validated. DMG associated with low social-economic and maltreatment little overlap. | Cut off : FDR<0.2p<0.01: hyper-q<0.05: hypo-Small power | socio-econmic position  | √/× | √ | Signaling pathways | [24618023](https://www.ncbi.nlm.nih.gov/pubmed/24618023%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank) |
| Physical/sexual, emotional abuse (CTQ questionnaire)  | 34 male (USA) | Sperm | Roberts et al.(2018)(longitudinal) | Differential methylation between those exposed to CM and control; adulthood trauma exposure and mental health partially mediated by the methylation changes | 6.2% variance Small power  | age at sample collection, month of birth, race/ethnicity  | √/√ | √ | neuronal function.fat cell regulation immune function (SDK1) | [30279435](https://www.ncbi.nlm.nih.gov/pubmed/30279435%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank) |
| **Stress type****(Measurement)** | **Sample** | **Tissue/cell** | **Author/year** | **Main results** | **Effect size/ power** | **covariant** | **batch/position effect** | **Multiple correction** | **GO/KEGG** | **PMID** |
| Child trauma(SCID interview)  | 54 pregnant women (32.3 yrs) (USA) | Buccal cells | Robakis  | CM associated with methylation density in 162 regions; not associated with mean DNAm over entire region of OXTR | Cohen’s d = 0.94large power | / | /Illumina HiSeq 4000 platform | √ | metabolic, cellular process, and regulatory functions;  | [32066670](https://www.ncbi.nlm.nih.gov/pubmed/32066670%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Child trauma(CTQ questionnaire) | Discovery: 85 adults NetherlandsReplication: 45 +255 adults(diverse ethnity)  | Discovery;bloodValidation:blood+buccalCross tissue  | Houtepenet al. (2016) | KITLG methylation mediates childhood trauma and cortisol stress reactivity (discovery). Hypomethylation of KITLG were replicated. | KITLG:small power :7~9%  | age, sex, ethnicity age of trauma | √/√ | √ | Cortisolstress reactivity | [26997371](https://www.ncbi.nlm.nih.gov/pubmed/26997371%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank) |
| Child trauma(CTQ questionnaire)  | 60 stressed adults, 30 control Germany | CD14+ monocytes | Frach et al.(2020) | Neither individual sites nor KITLG methylation significantly associated with child trauma after multiple testing. | p = 0.817β=−0.032low power:38% | age, sex cell composition | √/√ | √ | / | [32203862](https://www.ncbi.nlm.nih.gov/pubmed/32203862%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank) |
| Childhood abuse (record) | 24 abused 19 non abused suicide completer | hippocampal neurons | Labontéet al.(2012) | 307 DMP among abused group (248 ↑,114↓), especially for ALS2 (hypermethylation) | P<7.07\*E−5(after FDR)Power: >50% | age, pH, and postmortem interval | /MeDIP | √ | cellular/ neuronal plasticity | [22752237](https://www.ncbi.nlm.nih.gov/pubmed/22752237%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank) |
| Child maltreatment (CTQ ) | 96 stressed BPD 93 low-stress MDD switzerland | blood | Prados et al. (2015) | Child maltreatment predict higher methylation of multiple loci across genome, especially for MIR-137. | adequate power | age,comorbidity frequently,cell type | √/× | ×P=0.05 | inflammatory, regulatorof expression， neuronal /cell development, HPA | [25612291](https://www.ncbi.nlm.nih.gov/pubmed/25612291%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Child abuse(CTQ questionnaire) | 61 PTSD 32 abused, 108control with trauma USA(diverse ethnicity) | blood | Mehta et al.(2013) | DNA methylation of abused vs. non-abuse: 69% vs 34%. DNAm associated with abuse did not overlap with those for PTSD. | **∆**m**=** 35% large power | age, sex, ethnicity, adult trauma severity substance abuse | √/× | √ | central nervous system development tolerance induction pathways | [23630272](https://www.ncbi.nlm.nih.gov/pubmed/23630272%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| **Stress type****(Measurement)** | **Sample**  | **Tissue/cell** | **Author/year** | **Main results** | **Effect size/ power** | **covariant** | **batch/position effect** | **Multiple correction** | **GO/KEGG** | **PMID** |
| Child abuse(record) | 27 abused suicide complet er; 26 controls(Canada) | ACC(cross cell/ species compare) | Lutz et al. (2017)  | 115 DMR between stressed vs. controls. Hypomethylation in LINGO3 and POU3F1 for oligodendrocyte .  | large power | age, gender, RNA integri-ty number | /RRBS | √ | reduced white matter density and myelin axonal thickness. | [28750583](https://www.ncbi.nlm.nih.gov/pubmed/28750583%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| childhood trauma (Questionnaire) | 30 older with stress, 15 HC(Zurich) | buccal cells | Marinova(2017) | 71 differentially methylated CpG were identified between the two groups. | large power | age, gender, psychopathology | √/× | √ | cellular SignalingBrain development | 28241754\* |
| Child life stress(Interview) | 11 high vs.11 low stress girls USA(half Caucasian) | saliva | Papale et al. (2018)  | 122 DMG among high stress girls, enriched for GRHL1 POU3F3, RHOFX1, TBX20, TBX21 | FDR < 0.05medium-largepower | cell type/count, age,ethnicity  | √/√ | √ | stress response.Transmitter secretion | [30018309](https://www.ncbi.nlm.nih.gov/pubmed/30018309%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Institutional care(Data source) | 14 stressed, 14 control children(diverse ethnity) (Russian) | blood  | Naumova et al. (2012) | Higher methylation in stressed group. 914 DMG (815↑ 99 ↓)  | P=0.01large power | / | √/× | √ | immune response cellular signaling, brain development | [22123582](https://www.ncbi.nlm.nih.gov/pubmed/22123582%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Early deprivation(record) | 33 stressed &16 Control children Romania | buccal cell | Kumsta et al. (2016) | No DMP were significant. An DMR was identified. | r=0.52large power |  ethnity, sex | √/× | √ | / | [27271856](https://www.ncbi.nlm.nih.gov/pubmed/27271856%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Early life stress(questionnaire, scale) | 109 adolescents(USA) | buccal cell | Essex et al. (2013)(longitudinal) | Maternal stress in infancy increased DNAm in 139 sites; paternal stress in preschool increased DNAm in 31 sites. No effect of ELS on methylation DRD4, 5-HTT, COMT, BDNF, DAT1, NR3C1. | Maternal corr：0.21 ~0 .40Paternal corr：0.34 ~0 .45large power | / | √/× | √ | biosyntheticMetabolic processes. | 21883162\* |
| **Stress type****(Measurement)** | **Sample**  | **Tissue/cell** | **Author/year** | **Main results** | **Effect size/ power** | **covariant** | **batch/position effect** | **Multiple correction** | **GO/KEGG** | **PMID** |
| Social deprivation(record) | 29 orphanages & 29 biological raised childrenEastern Slavic(diverse ethnicity)  | PBMC | Naumova (2019) | Children residing in orphanages were significant differences in DNA methylation states in 164 CpGs (82 Hypermethylation,82 hypomethylation). | large power | cell-specific | √/× | √ | immune cells function, cytokine signaling | 30913238\* |
| Early life deprivation**(checklist)** | 50 stressed adolescents33 control(Europe or Russia) | whole blood | Esposito et al. (2016)  | 30 DMP spanning 19 genes, including CYP1A1 more methylated in the adopted group  | mean ∆β>0.02Small power | negative life experience,age, sex | √/√ | √ | neural development and developmental biology | [26847422](https://www.ncbi.nlm.nih.gov/pubmed/26847422%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank) |
| Psycho-social stress(Questionnaire) | Discovery:1287 teenage Validation: 413 adolescents(IMAGENfrom European) | peripheral blood | Tay et al. (2019) | Great number of life stress associated with hypermethylation of sterile alpha motif/pointed domain (SPDEF). This result was replicated. | cg16527629:r=0.094, cg01395541r=0.082large power | recruitment site, gender, cell count, acquisition waves | √/√ | √ | subustance abusealcoholism, tobacco use disorder | 30525907 \* |
| Total Life Stress(Questionnaire) | 49 PTSD60 HC(African American)  | PBMC | Smith, (2011) | A CpG site in NPFFR2 was inverselyassociated with TLS after adjustment for multiple testing. | large power | age, sex  | √/× | √ | Immune inflammation | 21714072\* |
| Early life stress(Experienced violence) | 375 individuals(126grandmothers 125mothers 124adolescents)(Brazil) | saliva | Serpeloni et al.(2019) | lifetime exposure to community and domestic violence associated with BDNF\_cg06260077, CLPX\_cg01908660 | medium power | Age, cell type, Heterogeneity,Exposure to other traumatic events | ×/× | √ | neural development | 31059136 |
| **Stress type****(Measurement)** | **Sample**  | **Tissue/cell** | **Author/year** | **Main results** | **Effect size/ power** | **covariant** | **batch/position effect** | **Multiple correction** | **GO/KEGG** | **PMID** |
| child adverse stress questionnaires +interview | Dis: 552 adults (NSHD) UKRepli: 780 adults (ALSPAC)  | Discovery: blood Replication:buccal  | Houtepenet al. (2018) | 9 DMRs associated with ACE score. DMRs associated with child maltreat were replicated in both cohort. Differential DMR relate to sub-types of abuse. | medium~large power | smoking,age at sampling,Cell heterogeneity | √/× | √ | smoking | [30510187](https://www.ncbi.nlm.nih.gov/pubmed/30510187%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Childhood adversities/ SEP(parent report) | 192 child (F: 98 M: 94)(diverse ethnicity)  | Buccal  | Bush et al. (2018) (longitudinal) | 488, 354, and 102 DMP associated with family income, parental education and family psycho-social adversity respectively. Each adversity had distinct DNAm, 9 common DMG | large power | genetic ancestry, age, sex, twin status  | √/√ | √ | family adversity and income level:immunity parental education: regulation of development | [30351206](https://www.ncbi.nlm.nih.gov/pubmed/30351206%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Childhood SEP (scale) | 398 adolescents(USA) | PBMCs | Beach et al(2016） | 28,640 loci associated with SEP  | r=-0.040(SES);large power | age, sex  | √/× | √ | regulation of signaling pathway | [26822447](https://www.ncbi.nlm.nih.gov/pubmed/26822447%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Child SEP (4 independent sources of data collection) | 1619 (F: 50%)From 5 to 18 yrs(England & Wales) | Peripheral blood | Reuben et al. A(2020)(longitudinal Twin Study) | Family SES associated with DNAm of multiple CpG sites (CNTNAP2, AHRR, CYP1A1, OR4C13). Results of NR3C1, SLC6A4, BDNF, FKBP5, OXTR were not replicated. | inflammationβ= 0.12Smoking:β:0.18(EWAS) large power | sex, cell type, maternal smoking, twin zygosity status | √/√ | √ | Inflammation;Smoking; metabolism of hydrocarbons,cancer | [32478847](https://www.ncbi.nlm.nih.gov/pubmed/32478847%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Child disadvantaged SEP(scale) | 40 males (45 years )(UK) | Peripheral blood | Borgholet al.(2012) | 1252 DMG associated with child SEP vs 545 DMG associated with adulthood SEP; 63 promoters overlap among them | large power | / | /MeDIP | ×=0.05 | key cell signalling pathways (MAPK); metabolism. | [22422449](https://www.ncbi.nlm.nih.gov/pubmed/22422449%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Childhood SEP, perceived stress | 92 adults (F: 62, M: 38)(Canada) | PBMCs | Lam et al. (2012) | 3 CpG sites associated with early life SEP, 5 CpG DNA methylation associated with perceived stress. DNAm affected by cell type. | Large power | cell compositionsex, age, ethnicity  | √/× | √ | inflammatory response | [23045638](https://www.ncbi.nlm.nih.gov/pubmed/23045638%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| **Stress type****(Measurement)** | **Sample**  | **Tissue/cell** | **Author/year** | **Main results** | **Effect size/ power** | **covariant** | **batch/position effect** | **Multiple correction** | **GO/KEGG** | **PMID** |
| Childhood SEP(scale or record) | 141 adults (Female: 74 Male: 67 )(USA) | blood leukocytes& Adipose | Loucks et al.(2016) | Adipose: Men- 91 CpG sites differentially methylated Women- 71CpG sites differentially methylated Blood: none | large power | BMI, age, sex, ethnicity, cell type proportion, smoking | ×/× | √ | development of obesity | [27768648](https://www.ncbi.nlm.nih.gov/pubmed/27768648%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Childhood SEP (scale or record) | 464 adult(F: 395 M: 99)(Philippines) | whole blood  | McDade et al.(2017)  | Fewer household assets associated with lower DNAm for probe in C1S, and higher in GNG2. Parental absence predicted higher DNAm in EGR4. | large power:>95%  | sex,inflammation index, blood cell composition  | √/√ | √ | inflammation | [28673994](https://www.ncbi.nlm.nih.gov/pubmed/28673994%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| Child abuse + child SEP (multiple source of data) | 40 male adult (England, Scotland) | whole bloodLymphoblast-oid cell  | Suderman et al. (2015) | WB: 29 DMP, LCL: 39 DMP Both in regulation and development: most of DMG hypomethylated in abused males. | small power(8~9%) | / | √/× | √ | transcription regulatory;Signaling pathwaydevelopment | [26351305](https://www.ncbi.nlm.nih.gov/pubmed/26351305%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank) |
| life-course SES(questionnaires) | 178  adults(Italy) | blood | Castagn et al. (2020) | Less-advantaged SEP in young adulthood associated with a lower inflammatory methylome score later in life. | β:-0.006~-0.004Low power | Age, gender, cell type，BMISmoking，Physical activity,  | √/√ | √ | inflammation | 32875816 |
| life-course SES(multidimensional summary measure) | 489 youth (20yrs)(Philippines) | Blood white cell | McDade et al.(2019)(Longitudinal) | 2,546 CpG sites were differentially methylated in association with low life SES（increased 1,777 sites, decreased 769 sites). | FDR:0.05large power | Blood cell , gender，principal components of genetic variation | √/√ | √ | immune function,skeletal development, development of the nervous system | 30771258\* |

Note: \* means EWAS with statistical power>75%. SES/SEP: socioeconomic status/position

Suppl. Table 2.3 Overview of EWAS associated with psychological stress during adulthood

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Stress type****(Measurement)** | **Sample**  | **Tissue/cell** | **Author/year** | **Main results** | **P value/power** | **covariant** | **batch/position effect** | **Multiple correction** | **GO/KEGG** | **PMID** |
| adult SES 18 candidate genes | 1,226 adults from MESA(Multi-Ethnic Atherosclerosis Stress Study) | blood | Smith et al.(2017) | Neighborhood socioeconomic disadvantage associated with DNA methylation in two stress related gene (CRF, SLC6A4) and two inflammation genes( F8, TLR1). | β: 0.001 Low power | sex, race ethnicity, age, child SES, adult SES | √/√ | √ | inflammationstress-related | 28678593 |
| life-course SES(18 genes related to stress/ inflammation)(record) | 1,264 adultsNon Hispanic white, African-American, and Hispanic  | blood monocytes | Needham et al. (2015) | low adult SES was associated with DNAm in one stress-related gene (AVP) and 5 inflammation- related genes (CD1D, F8, KLRG1, NLRP12, TLR3).  | Large power | sex, race/ethnicity age, | √/√ | √ | inflammationstress-related | 26295359\* |
| perceived stressearly-life SES(record) | 92 individuals(24~45years） | PBMC | Lam et al.(2012) | Perceived stress and early-life socioeconomic status both associated with epigenome-wide patterns of DNA methylation. | Spearman P <0.05Small power<7% | age, gender, ethnity,Blood cell composition | √/× | √ | Inflammatory response | 23045638 |
| life-course SES(questionnaires) | 178  adults(Italy) | blood | Castagn et al. (2020) | Less-advantaged SEP in young adulthood associated with a lower inflammatory methylome score later in life. | β:-0.006~-0.004Low power | Age, gender, cell composition,Smoking/alcohol status, Physical activity, BMI | √/√ | √ | inflammation | 32875816 |
| **Stress type****(Measurement)** | **Sample**  | **Tissue/cell** | **Author/year** | **Main results** | **P value/****power** | **covariant** | **batch/position effect** | **Multiple correction** | **GO/KEGG** | **PMID** |
| chronic job stress(interviews) | 117 female  | peripheral blood | Zhu et al.(2011) | Wide spread methylation changes in chronic stressed workers (66.4%↑，33.6%↓),especially in the promoter of CLOCK ↓ and CRY2 ↑ | CLOCK: OR, 0.36CRY2: OR:0.32Large power | age, folate intake | ×/× | √ | Cancer-related pathways | [22080730](https://www.ncbi.nlm.nih.gov/pubmed/22080730%22%20%5Ct%20%22https%3A//www.geenmedical.com/_blank)\* |
| shift work(interviews) | 65 dayshift workers59 nightshift workers | lymphocytescell | Bhatti et al. (2015) | 21 loci across circadian genes average methylation was consistently decreased among nightshift workers compared to dayshift workers. Especially for three loci located in PER3. | ∆=11%Large power | gender, age, BMI, race, current smokingStatus, leukocyte cell proportion | ×/× | √ | host defense and immunity, cancer | 25187986\* |
| shift work | 111 nightshift 86 dayshift female  | peripheral blood  | Adams et al.(2017) | No statistically significant associations at the genome-wide level were observed with shift work. | Low power | Age, BMI, race, alcohol consumption , smoking, mixture of leukocytes | √/√ | √ | **/** | 28837395 |
| Shift work | 2574 women 935–74 yrs) | whole blood  | White et al. (2019） | 85 CpGs significantly associated with years of night-shift work. 66 CpGs significantly associated with years of overall shift work.36 CpGs overlap. | Β：0.005~–0.003Low power | case status, age at baseline, alcohol consumption,education, smoking status | √/√ | √ | circadian rhythm | 30879037 |

Note: \* means EWAS with statistical power>75%. SES/SEP: socioeconomic status/position