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Peer victimization in adolescence alters gene expression and cytokine profiles during transition to adulthood

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ABSTRACT

Adolescents who experience peer victimization (PV) often report psychosomatic complaints; however, little is known about possible underlying molecular effects. Social adversity has already been shown to downregulate immune genes and upregulate inflammatory genes. This study investigated PV for potentially enduring molecular effects, in terms of gene expression, leukocyte composition, and cytokine levels in young adulthood. Participants (n = 144; 47% female) were drawn from the Zurich Brain and Immune Gene Study (z-GIG). PV was studied from age 11 to 20, and molecular data were collected at age 22. A counterfactual framework with genetically informed inverse probability weighting was applied to account for individual and environmental confounders. Compared to non-PV controls, victims showed extensive immune changes. *In silico* deconvolution revealed shifts in leukocyte composition, including an M2-like monocyte–skewed profile. Differentially expressed genes were enriched in several Reactome pathways, including *Interferon signaling*, *Metabolism*, *Signal transduction*, *Chromatin Organization*, and *Metabolism of Proteins*. Transcription factors STAT2 and IRF2 emerged as key regulators, with target genes primarily in the *Interferon Signaling* and *Chromatin Organization* pathways. Cytokine levels also differed, including elevated pro-inflammatory markers such as CCL4, TNF, CXCL9, and CXCL10. The findings provide preliminary evidence of the immunomodulatory potential of PV and highlight the importance of public health strategies aimed at prevention, building resilience, and mitigating long-term effects.

1. Introduction

PV among adolescents, such as verbal and physical violence or systematic exclusion, is not only a common difficult experience in youth, but also causes significant stress and may lead to stress-related pathology, with similar effects as forceful social subordination (Sapolsky, 2004). Health problems reported by PV victims include psychological conditions such as anxiety, depression, agoraphobia, externalizing problems, generalized anxiety disorder, panic disorder, psychosis, substance use, and self-harm (Klomek et al., 2015; Lereya et al., 2015; Moore et al., 2017; Reijntjes et al., 2010, 2011) and in some cases even suicide (Cha et al., 2018; Koyanagi et al., 2019; Van Geel et al., 2022); importantly, victims also commonly report physical stress symptoms, including headaches, asthma, skin problems, loss of appetite, abdominal pain, vomiting, stiffness, back pain, dizziness, sleep disorders and fatigue (Gini and Pozzoli, 2009, 2013; Hager and Leadbeater, 2016; Murphy et al., 2015). With a global prevalence of around 30% (Biswas et al., 2020) and documented physical impairments, PV warrants closer investigation at the molecular level to inform targeted public health initiatives.

PV constitutes a potent social stressor during adolescence with the potential for system-wide biological effects. This developmental period involves significant—and potentially lasting—changes in neuroendocrine and immune systems, along with transcriptional regulation

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processes that shape cytokine production and stress responsivity (Casey et al., 2008; Rowson et al., 2019). These cytokines can, in turn, feed back into neuroendocrine processes (Chiang et al., 2012; Dantzer et al., 2008; Giletta et al., 2018; Polacchini et al., 2018), forming a "neuroimmune pipeline" that impacts health over the life course (Miller and Cole, 2012).

While biologically informed PV research has focused on individual differences in the stress response—including hair cortisol levels (e.g., Brendgen et al., 2023; Ouellet-Morin et al., 2021), cytokine activity (e.g., Chiang et al., 2012; Copeland et al., 2014; Giletta et al., 2018), epigenetic aging (e.g., Perret et al., 2023; Shalev et al., 2013), and DNA methylation as well as other epigenetic mechanisms (e.g., Marzi et al., 2018)—only one study has investigated immunomodulatory gene expression, and that in the context of homophobic victimization (Li et al., 2020). No such analysis exists for PV. Yet transcriptomic analysis may provide critical insight into how PV influences health by identifying the molecular pathways through which it modulates immune function.

Prior research has been constrained by analyzing biological measures in separate samples and by cross-sectional designs that limit the ability to account for dynamic socio-environmental confounders (Zuber et al., 2023). Findings on the impact of PV may also be biased by common-method variance, as many studies rely on self-reported measures for both PV and health-related outcomes (Gini and Pozzoli, 2013). Additionally, as PV studies are observational for ethical reasons, their inherent susceptibility to treatment selection bias should be acknowledged and methodologically addressed (Schoeler et al., 2018).

Social adversity is often associated with a characteristic transcriptomic profile shaped by evolutionary adaptation and characterized by upregulated proinflammatory genes and downregulated type I interferon genes (antiviral genes)—a pattern referred to as *conserved transcriptional response to adversity* (CTRA; Cole, 2019)—which is linked to an increased risk of mental health conditions (e.g., depression and anxiety), inflammatory diseases (i.e., cardiovascular, metabolic and tumor diseases), and impaired immune response (e.g., increased susceptibility to viral infections and reduced vaccine efficacy) (Cole, 2013, 2019). In addition, studies show significant variations in transcription factor (TF) activity under chronic social stress, such as higher NF-κB and CREB activity and lower GR activity (Miller et al., 2009; Ravi et al., 2024). Research into CTRA and TF activity in the context of PV, however, remains nascent, underscoring the rationale for incorporating transcriptomic and regulatory genomic approaches in the present study.

In this study, 22-year-olds who had experienced PV between 11 and 20 years (victims) were compared with non-PV controls using a longitudinal design that accounted for time-varying confounders. Leukocyte composition was estimated using *in silico* cell type deconvolution (Avila Cobos et al., 2020). Analyses focused on the regulation of CTRA profile and enrichment in pre-selected functional Reactome pathways—including immune-related processes—based on a genome-wide analysis of differentially expressed (DE) genes. Additionally, an exploratory Reactome-wide query identified further enriched signaling pathways. TF activity and target genes were analyzed using the TF binding sites of DE genes. Finally, cytokine profiles—including 16 proinflammatory and other cytokines measured by multiplex immunoassay—were analyzed.

To address potential selection bias, genetically informed inverse probability weighting (IPW) was applied across all analyses. The weighing model incorporated pre-victimization characteristics, polygenic risk scores (PRS) for attention-deficit/hyperactivity disorder (ADHD), generalized anxiety disorder (GAD), major depressive disorder (MDD), and panic disorder (PD), as well as genetic ancestry principal components to account for underlying population structure.

2. Materials and methods

2.1. Sample characteristics

Data come from the Zurich Brain and Immune Gene Study (z-GIG). z-GIG is a subsample from z-proso (Ribeaud et al., 2022; z-proso Project Team, 2024), a longitudinal panel (baseline $n \approx 1500$) started in 2004 with Zurich elementary school children aged 7–9, notable for high ethnic heterogeneity (> 60% of parents born abroad in 90 countries). In 2018, when eight waves had been completed (average age 20.5 years), for the z-GIG study, participants in z-proso were stratified based on self-reported peer adversity as well as relevant characteristics such as sex, teacher-rated peer adversity, aggression level, anxiety level, and conflict resolution skills. Individuals were assigned to the same stratum if they had the same sex and fell into the same median split on each of these variables (see Supplementary Table S1 for the full list of variables and details of the 23 strata used for sample selection). 500 eligible subjects were randomly drawn from 23 strata and 200 finally participated in z-GIG at age 21 (response rate 40%), of whom 186 consented to blood sampling. No evidence of systematic nonparticipation was detected. IPW addressed selection bias from sample stratification and baseline confounders (explained *infra*, 2.4). Valid mRNA and cytokine samples were obtained from 153 z-GIG participants. After one exclusion due to pregnancy and eight exclusions for statistical reasons related to IPW, the analytic sample comprised 144 participants, including 16 (11.1%) victims of PV (explained *infra*, 2.3). The mean age was 21.8 (SD = 0.47), and the sex ratio was 74 men to 70 women.

2.2. Procedures

Participants were invited to the laboratory for blood sampling. Protocols were approved by the Zurich Cantonal Ethics Committee (KEK, BASEC No. 2017–02083), and informed consent was obtained. Trained phlebotomists from the Laboratory for Social and Neural Systems Research (SNS Lab) at the University of Zurich collected 32.5 mL of peripheral blood from the antecubital vein. Blood was stored in serum, EDTA and PAXgene RNA tubes. The serum and EDTA samples were immediately centrifuged at $2000 \times g$ 10 min to extract serum and plasma, and all samples including PAXgene tubes were stored at −80 °C until analysis.

A total of 153 samples with sufficient mRNA/DNA were processed at LIFE & BRAIN GmbH, Bonn, Germany, for high-throughput bulk analysis. mRNA was extracted from PAXgene following the protocol previously described (Becker et al., 2022), converted to cDNA using the Lexogen QuantSeq 3′ mRNA FWD kit (Corley et al., 2019), and sequenced at 15M reads (1 × 100 bp) on a NovaSeq 6000. Adapter sequences and low-quality bases were trimmed with cutadapt v1.16, and mRNA-seq data were mapped to the GRCh38 human reference genome using STAR v2.7.6a, and Salmon (Patel et al., 2023). Gene expression was quantified using featureCounts v2.0.1 (subread package), with quality control (QC) metrics assessed via MultiQC v1.9. The resulting mRNA gene count matrix was generated using the nf-core/rnaseq pipeline. Potential batch effects were assessed via principal component analysis (Leek et al., 2010), with the first four components explaining 13.2% of the variance, indicating no systematic clustering.

DNA was isolated from EDTA blood following the method previously described (Jagannath et al., 2020). Isolated DNA was genotyped using the Illumina Infinium GSA Array mapped to GRCh38. PED files were subjected to basic QC (maf > 0.01; info > 0.8), strand flipping, sex check, and clumping (Choi, 2020). PRS were calculated from summary statistics of recognized GWAS in European populations (ADHD: Demontis et al., 2023; PD: Forstner et al., 2021; GAD: Otowa et al., 2016; MDD: Wray et al., 2018) lifted to GRCh38 using the UCSC LiftOver tool. Principal components of genotyping were calculated, with both analyses conducted using PLINK 1.90b7 (Purcell et al., 2007) and GNU awk 5.1.0.

Blood plasma cytokines were quantified in triplicates using the Bio-

Plex Human Cytokine Screening Panel, 48-Plex (BioRad, #12007283), following the manufacturer's protocols. Raw fluorescence data were processed in Bio-Plex Manager version 6.1 (Bio-Rad Laboratories, Inc., 2023) to generate cytokine concentrations using standard curves, and subsequent analyses R 4.4.1 (R Development Core Team, 2023) Supplementary Table S8 reports median plasma concentrations, the percentage of out-of-range values for each cytokine (mean = 2.31%; SD = 0.64%), and the manufacturer-reported detection thresholds).

The experimenter and wet lab personnel were blinded to PV conditions, with only the data analyst informed of group assignments.

2.3. Peer victimization profile

From waves four (age 11) to eight (age 20) of the z-proso panel, a binary treatment variable was constructed prospectively using self-reported data on social peer adversity, including exclusion, insult, physical violence, and property damage. Items were measured on a Likert scale to assess incidence over the last 12 months (1 = never, 2 = 1 time, 3 = 3 times, 4 = about once a month, 5 = about once a week, 6 = about every day). In each wave, the same questions had been asked regarding how much adversity participants had *experienced* (subordinate experiences, SE) and how much adversity they had *exerted* on others (dominant behavior, DB). Composite scores for SE and DB were created by summing up the respective Likert-scale variables for each adversity type in each wave. Next, totals were normalized to derive scores quantifying social peer adversity. To classify individuals as severely affected from SE or DB, the 90th percentile and above for each survey year was used (SE: 2009 = 0.36, 2011 = 0.36, 2013 = 0.28, 2015 = 0.20, 2018 = 0.20; DB: 2009 = 0.24, 2011 = 0.36, 2013 = 0.28, 2015 = 0.20, 2018 = 0.16) to remove trends and dynamically capture individuals with the most severe experiences with presumably significant impacts on their well-being. Ultimately, 16 individuals (11.1% of the analytic sample) were identified as being exclusively exposed to SE without exhibiting DB, and a binary variable was created to represent this PV profile. This binary profile was used to approximate a persistent PV phenotype—reflecting individuals with a stable pattern of social subordination across adolescence, even in years without assessments (Supplementary Fig. S1A visualizes the derivation of the PV profile). The remaining non-PV controls included youth with neither SE nor DB (n = 23; 57.4%), DB only (n = 32; 17.8%), and both SE and DB (n = 74; 24.8%). These subgroups, along with other social adversities, were statistically controlled for in the weighted models (explained *infra*, 2.5). Supplementary Fig. S1B and Table S2 present initial differences between the PV and non-PV control groups, including absolute standardized differences pre- and post-IPW.

2.4. Inverse probability weighting

In the analyses, IPW (Hernán and Robins, 2020) was applied to adjust for biopsychosocial confounders related to treatment (PV) and stratified sample selection. By weighting non-PV controls to balance characteristics, IPW creates a pseudo-population that approximates a randomized trial, enhancing causal inference. This method is widely recommended for observational studies to adjust for confounding—particularly in PV research (Baldwin et al., 2023)—and is effective in genomic analyses for improving variance estimation reliability (Reifeis et al., 2020). Specifically, a logit model was applied to confounders associated with both the treatment and outcome (Rubin, 1997) to derive propensity scores for PV. These scores were used to calculate weights for estimating the average treatment effect on the treated (ATT; Eq. 1),

$$w_i = D_i + (1 - D_i)\left(\frac{e_i}{1 - e_i}\right) \tag{1}$$

where D denotes victim status and e is the propensity score (Morgan and Winship, 2015). The ATT was chosen to estimate the effect of PV on those directly exposed, as they represent the primary population of interest. Weights were trimmed at the 5th and 95th percentiles to reduce the influence of extreme values. Baseline data for the propensity score model were drawn from reports by the young person, teachers, and parents during the first three z-proso waves (ages 7–9), prior to measuring victimization. Missing data (0.5–6% across variables) were addressed using random forest imputation (missRanger 2.6.0; Stekhoven and Buhlmann, 2012). PRS for ADHD, GAD, MDD, and PD were included (detailed in Section 2.2). To account for ancestry-related population structure within the sample, we included principal components derived from genome-wide genotype data. The first four components were selected based on eigenvalue analysis, which showed a clear inflection point at the fourth component with an eigenvalue near 1 (Supplementary Fig. S2; Cattell, 1966; Price et al., 2006). See Supplementary Fig. S1A, Tables S2 and S3 for a complete list of the confounding factors and rationale. To minimize extrapolation bias, ATT estimation was restricted to victims with propensity scores within the range of the non-PV controls (common support) and excluded eight of the initial 24 victims with valid mRNA due to lacking suitable matches (Austin and Stuart, 2017; Stuart, 2010), yielding the final group of 16 victims. In complex survey designs (Lumley, 2023), IPW weights w were used as sampling weights throughout the analyses.

2.5. Data analysis

The aim of the analyses was to investigate the consequences of PV on biological stress indicators via: (1) *in silico* cell-type deconvolution; (2) differential expression and TF analyses; and (3) cytokine dysregulation. Statistical analyses were performed using R 4.4.1 (R Development Core Team, 2023). A *base* model (Eq. 2) included the PV dummy with adjustments for subjects involved in DB or both SE and DB. Sexual harassment victimization (*sexv*), perpetration (*sexp*), and sexual assault victimization (*assltv*) were adjusted for but excluded from the initial PV profile due to distinct causal mechanisms (Frøyland et al., 2023). Adjustments were made for time-varying confounders ($X\gamma$) including body-mass-index (Puhl et al., 2011), exercise (Harrison and Baune, 2014; O'Connor et al., 2021; Schoeler et al., 2018), psychological help-seeking (Antoni et al., 2012; Harrison and Baune, 2014), and psychoactive substance use (Lovallo et al., 2000; O'Connor et al., 2021); to enhance statistical power, principal components were derived for each of these four domains, reducing dimensionality while capturing about 75% of the variance. Diurnal and annual variation were controlled by including sine and cosine terms: for diurnal variation, $\sin(2\pi/24 \times \text{daytime})$ and $\cos(2\pi/24 \times \text{daytime})$; for annual variation, $\sin(2\pi/365 \times \text{doy})$ and $\cos(2\pi/365 \times \text{doy})$. All models accounted for chronic and metabolic diseases, and long-term medication use (binary). The model equation, weighted by w (Eq. 1), is as follows:

$$y = \beta_0 + \beta_1 \text{pv} + \beta_2 \text{db} + \beta_3 \text{db\_se} + \beta_4 \text{sexv} + \beta_5 \text{sexp} + \beta_6 \text{assltv} + X\gamma + \varepsilon, \text{ weighted by } w \tag{2}$$

In an extended model, principal components from genes *CD14*,

CD19, *CD3D*, *CD4*, *CD8A*, *FCGR3A*, and *NCAM1* were included to control for leukocyte composition, based on prior research (Cole et al., 2007; Fredrickson et al., 2013; Li et al., 2020). P values were adjusted for multiple comparisons using the false discovery rate (FDR) method (Benjamini and Hochberg, 1995) to control for type I errors.

As a sensitivity analysis, all main analyses were repeated excluding individuals with both subordinate and dominant factors (SE+DB) from the controls. Results remained consistent with the original findings—albeit with low statistical power—and confirmed that the findings were not driven by a salient yet non-exhaustive combination of adversity (see Supplementary Figs. S5 and S6).

2.5.1. *In silico deconvolution*

Potential differences in leukocyte composition between victims and non-PV controls were assessed using *in silico* cell-type deconvolution with the FARDEEP algorithm (Avila Cobos et al., 2020; Hao et al., 2019). The primary analysis used the LM22 basis matrix (Newman et al., 2015) for its more detailed cell reference profile, which surpasses that of quanTIseq. Despite being designed for microarray data, LM22 was deemed suitable due to similarities in transcript quantification between microarrays and 3′ RNA-seq, along with the latter's broader dynamic range and enhanced detection of low-abundance transcripts (Corley et al., 2019). Results were additionally compared with quanTIseq, optimized for RNA-seq (Finotello et al., 2019), to assess agreement. LM22 (and similarly quanTIseq) includes expression data from cells not found in peripheral blood but whose precursors are. For instance, monocytes in peripheral blood, before migrating to tissues and differentiating into M0 macrophages, exhibit precursor characteristics that influence polarization into M1 or M2 macrophages (M1, M2; Boyette et al., 2017). Consequently, M1 and M2 signals were interpreted as originating from monocytes and are referred to as M1-like and M2-like monocytes. Similarly, follicular T helper cell (Th) signals were interpreted as originating from follicular-like Th.

2.5.2. *Gene expression analysis*

The mRNA count matrix was normalized using the edgeR 4.2.2 TMM method (Robinson et al., 2010), with a minimum count of 5 and a proportion of 5%, followed by log2-transformation resulting in a matrix of 17,333 genes. DE genes were analyzed through two approaches: an *a priori* analysis focusing on CTRA genes and preselected Reactome pathways (v88; Gillespie et al., 2022) with known CTRA activity, and an *exploratory* analysis querying genome-wide Reactome pathway enrichment.

2.5.2.1. A priori analysis. Following established methods (Li et al., 2020; Ross et al., 2021), CTRA genes (Cole, 2019) were analyzed as repeated measures, with sign-inverted counts for genes expected to be stress-downregulated. Analyses employed a complex survey design (Lumley, 2023) incorporating IPW and subject-specific intercepts. Genome-wide DE analysis was then performed using limma (Smyth et al., 2022) with IPW applied. Variance adjustments for the IPW pseudo-population were calculated using empirical sandwich estimators from geex v1.1.1 (Reifeis et al., 2020; Reifeis and Hudgens, 2022; Saul and Hudgens, 2020). Significantly DE genes ($|\log_2(FC)| > \log_2(1.2)$; $p < 0.05$) were analyzed via Fisher's exact tests to identify overrepresentation in top-level Reactome pathways containing CTRA genes, including *Hemostasis* (R-HSA-109582), *Immune System* (R-HSA-1430728), *Metabolism* (R-HSA-162582), and *Signal Transduction* (R-HSA-168256), with a particular focus on antiviral and pro-inflammatory subpathways. Importantly, only 43 of the 61 CTRA genes are currently annotated in Reactome. P values were FDR-adjusted within the preselected pathways ($p < 0.05$).

2.5.2.2. Exploratory analysis. Significantly up- and downregulated DE genes were used to query pathway enrichment across the entire Reactome database (annotations dated 2024-01-25) via the gprofiler2 API (Raudvere et al., 2019), to identify significant pathways across all hierarchical levels. Enrichment significance was FDR-corrected across the 2,562 Reactome pathways ($p < 0.05$).

2.5.3. *Transcription factor activity analysis*

Activity of TFs was inferred from predicted transcription factor binding sites in significantly DE genes using the TRANSFAC® database (Matys et al., 2003) via gprofiler2 v0.2.3, focusing on high-confidence matches within ±1 kb of the transcription start site, categorized as match class 1 to ensure credibility. The Harmonizome database (Rouillard et al., 2016) was then queried to retrieve TF target genes (TFTGs). Significantly DE TFTGs were mapped to genes from Reactome-wide identified pathways to calculate the pooled gene ratio of TFs and identify potential TF–pathway associations.

2.5.4. *Cytokine analysis*

Absolute concentrations of 16 cytokines (CCL11, CCL27, CCL4, CCL5, CLEC11A, CSF1, CXCL10, CXCL12, CXCL9, HGF, IL16, IL9, KITLG, LTA, PDGFB, and TNF) were obtained from multiplex immunoassays. Cytokine data were log2-transformed and analyzed using IPW-adjusted regression models. Statistical significance was determined with FDR-corrected p values ($p < 0.05$).

3. Results

3.1. *IPW and model performance*

The maximum absolute standardized difference between treated and non-PV controls for IPW covariates was 0.194, indicating satisfactory balance for the sample size (Austin, 2009). Table 1 provides a summary of key demographic and health-related variables by group. The logistic regression model generated valid propensity scores without perfect predictions. Supplementary Fig. S1B shows improved balance after weighting, and Supplementary Fig. S3 illustrates sufficient overlap in propensity scores between groups. Variance inflation was assessed, showing no evidence of multicollinearity or inflated standard errors. The difference between the mean of the estimated weights and their expected value was −0.009, reflecting high agreement and stability of the weighting procedure (Reifeis and Hudgens, 2022).

3.2. *In silico deconvolution*

In silico cell-type deconvolution revealed several differences in the leukocyte profile of victims compared to non-PV controls, suggesting the inclusion of leukocyte-encoding genes in subsequent analyses. The

Table 1
Sample characteristics of peer victims and non-PV controls.

	Controls	PV	*p*
Female*	0.481 (0.50)	0.500 (0.52)	1.0000
Age	21.807 (0.47)	21.737 (0.53)	0.6163
BMI	22.879 (4.20)	23.931 (5.05)	0.4343
SES*	0.512 (0.19)	0.512 (0.20)	0.9955
Immigration background*	0.411 (0.49)	0.625 (0.50)	0.1156
Number of siblilngs*	1.109 (0.89)	1.062 (1.00)	0.1669
Chronic diseases	0.450 (0.50)	0.375 (0.50)	0.6048
Metabolic diseases	0 (0)	0.062 (0.25)	0.1106
Longterm medication use	0.287 (0.45)	0.312 (0.48)	1.0000
PRS ADHD*	0.001 (<0.01)	0.001 (<0.01)	0.7935
PRS GAD*	−0.005 (<0.01)	−0.005 (<0.01)	0.6720
PRS MDD*	−0.007 (<0.01)	−0.007 (<0.01)	0.6824
PRS PD*	−0.004 (<0.01)	−0.005 (<0.01)	0.5426

Note: Values are means (SD). *Baseline characteristics. BMI = body mass index at age 22; SES = socio-economic status; PRS = polygenic risk score. For full variable definitions, balance diagnostics, and the complete list of IPW covariates, see Supplementary Table S2 and Fig. S1B.

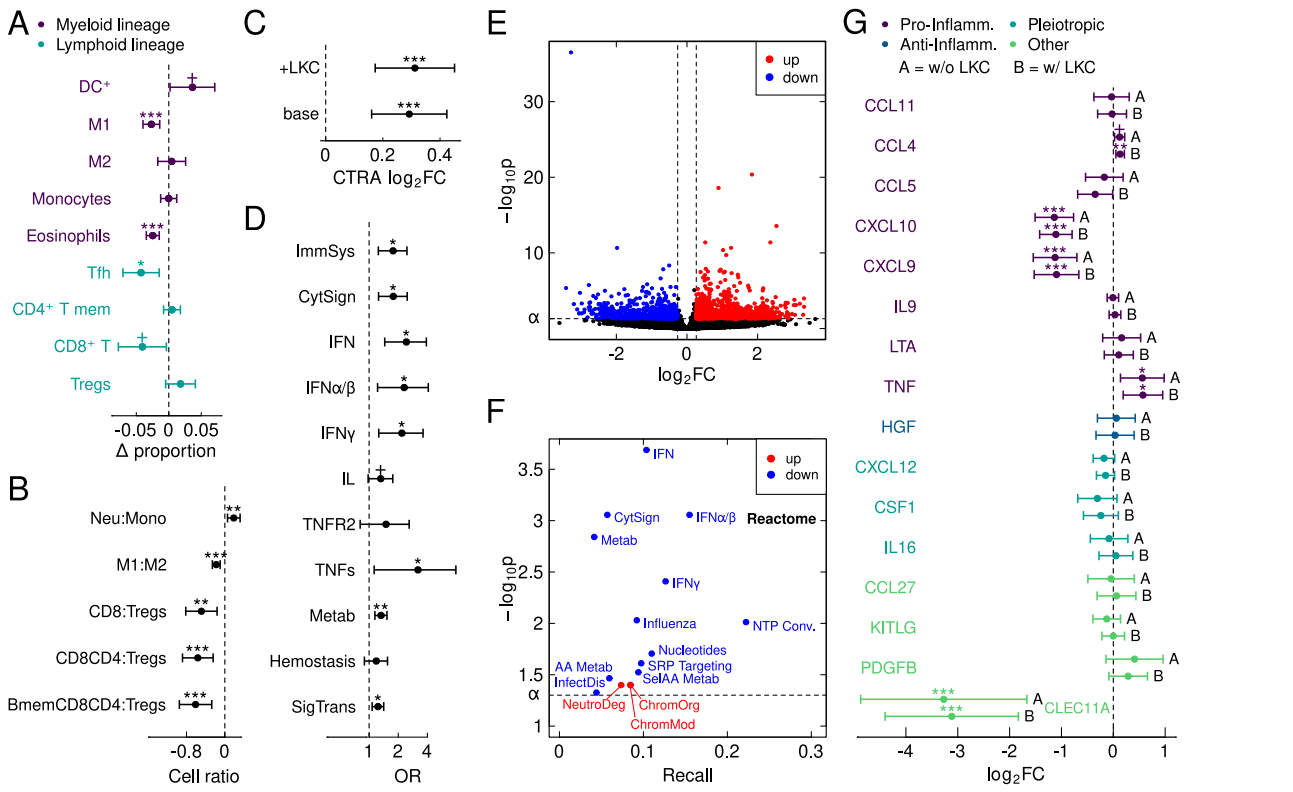

Fig. 1. Leukocytes and gene expression. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$, $^{+}p < 0.1$. ***(A)*** Changes in relative leukocyte proportions in victims compared to controls with 95% CIs. DC^{+} = activated dendritic cells, M1 and M2 = M1-like and M2-like monocytes, Tfh = follicular-like Th, $CD4^{+}$ T mem = memory $CD4^{+}$ T cells, $CD8^{+}$ T = $CD8^{+}$ T cells, Tregs = regulatory T cells. ***(B)*** Ratios of specific cell types in the deconvolution analysis with 95% CIs. Neu = neutrophils, mono = monocytes, Bmem = memory B cells. ***(C)*** Upregulation of the CTRA profile compared to controls with 95% CIs. base = base model, +LKC = leukocyte encoding genes added in model. ***(D)*** Odds ratios for enrichment in preselected Reactome pathways from Fisher's exact tests with 95% CIs. The *x* axis is on a log scale. ***(E)*** Volcano plot of DE genes from genome-wide analysis. ***(F)*** Pathways identified from the Reactome-wide query. ***(G)*** Comparison of absolute cytokine levels in victims vs. controls with 95% CIs. A = base model, B = leukocyte encoding genes included in model. ChromMod = *Chromatin modifying enzymes*, ChromOrg = *Chromatin organization*, CytSign = *Cytokine Signaling in Immune system*, ImmSys = *Immune System*, InfectDis = *Infectious disease*, Influenza = *Influenza Infection*, InnateImm = *Innate Immune System*, NTP Conv. = *Interconversion of nucleotide di- and triphosphates*, IFNα/β = *Interferon alpha/beta signaling*, IFNγ = *Interferon gamma signaling*, IFN = *Interferon Signaling*, Metab = *Metabolism*, AA Metab = *Metabolism of amino acids and derivatives*, Nucleotides = *Metabolism of nucleotides*, Protein Metab = *Metabolism of proteins*, NeutroDeg = *Neutrophil degranulation*, SelAA Metab = *Selenoamino acid metabolism*, SigTrans = *Signal Transduction*, IL = *Signaling by Interleukins*, SRP Targeting = *SRP-dependent cotranslational protein targeting to membrane*, TNFR2 = *TNFR2 non-canonical NF-kB pathway*, TNFs = *TNFs bind their physiological receptors*, Translat = *Translation*, ViralPath = *Viral Infection Pathways*.

following β coefficients reflect the relative abundance of the respective cell type. Deconvolution estimated lower proportions of M1-like monocytes ($\beta = -0.027$; 95% CI = [−0.040, −0.014]; $p = 0.0008$), eosinophils ($\beta = -0.025$; 95% CI = [−0.035, −0.015]; $p = 0.0001$), and follicular-like Th ($\beta = -0.043$; 95% CI = [−0.071, −0.015]; $p = 0.0221$) in victims (Fig. 1A). The model also estimated higher proportions of activated dendritic cells (DC^{+}), although this difference did not reach statistical significance ($\beta = 0.036$; 95% CI [0.002, 0.071]; $p = 0.0950$). LM22-derived estimates for M1-like monocytes and neutrophils showed similar significance patterns to supplementary quanTIseq results, supporting robustness (Supplementary Tables S4 and S5). Several ratios of certain cell types differed in victims compared to controls: A higher ratio was observed for neutrophils:monocytes ($\beta = 0.187$; 95% CI = [0.558, 0.318]; $p = 0.0056$), while lower ratios were observed for M1:M2-like monocytes ($\beta = -0.179$; 95% CI = [−0.260, −0.098]; $p = 0.0001$), $CD8^{+}$ T cells:Tregs ($\beta = -0.489$; 95% CI = [−0.815, −0.162]; $p = 0.0046$), ($CD8^{+}$ T, $CD4^{+}$ T cells):Tregs ($\beta = -0.564$; 95% CI = [−0.833, −0.244]; $p = 0.0011$), and (B memory, $CD8^{+}$ T, $CD4^{+}$ T cells):Tregs ($\beta = -0.611$; 95% CI = [−0.949, −0.273]; $p = 0.0011$) (Fig. 1B). The resulting M2-like skew might contribute to conditions such as autoimmune reactions and various allergic and skin disorders (Martinez et al., 2009); indeed, *post hoc* analyses of average marginal effects derived from IPW-weighted quasibinomial logistic regression indicated that victims had a 18.6% higher probability of reporting allergies, including asthma, compared to controls (AME = 0.186; 95% CI = [0.188, 0.543]; $p = 0.0405$). We also noted frequent reports of skin problems among victims (results not shown).

3.3. Differential gene expression

The CTRA profile of victims was upregulated compared to controls, with victims in the base model showing an average log2FC of 0.292 (95% CI = [0.161, 0.424]; $p < 0.0001$), equivalent to a fold change of approximately 1.22 (Fig. 1B). After controlling for leukocyte-encoding genes, the extended model indicated a slightly higher log2FC of 0.312 (95% CI = [0.173, 0.451]; $p < 0.0001$), corresponding to a fold change of about 1.24. In the genome-wide DE analysis, victims exhibited 817 upregulated and 591 downregulated genes ($|\log2(FC)| > \log2(1.2)$ and $p < 0.05$) (Fig. 1E). This analysis confirmed repeated measures with 26 of 61 (42.6%) DE CTRA genes in victims. Among these, 4 of 25 (16.0%) typically stress-upregulated genes were upregulated, 18 of 36 (50.0%) typically stress-downregulated genes were downregulated, and four did not follow the expected pattern (Supplementary Fig. S4). This profile suggests a skew in victims toward the typical stress-downregulated antiviral component of the CTRA.

Next, odds ratios (ORs) of Fisher's exact tests revealed a significant overrepresentation of DE genes in several preselected Reactome pathways among victims, compared to controls. Notably, two prominent

subpathways were identified within the *Immune system*: (1) one encompassing *Cytokine signaling in Immune system* (OR = 1.768; 95% CI = [1.252, 1.475]; $p = 0.0110$) and *Interferon Signaling* (OR = 2.427; 95% CI = [1.451, 3.907]; $p = 0.0110$), and culminating in *Interferon alpha/beta signaling* (OR = 2.305; 95% CI = [1.223, 4.090]; $p = 0.0243$) and *Interferon gamma signaling* (OR = 2.182; 95% CI = [1.259, 3.611]; $p = 0.0188$) activity. *Interferon alpha/beta signaling* included 11 DE genes, all downregulated, such as *IFI27* (log2FC = −2.142; $p = 0.0010$). *Interferon gamma signaling* included 14 DE genes: one upregulated (*ICAM1*, log2FC = 0.516; $p = 0.0243$) and 13 downregulated (e.g., *TRIM10*; log2FC = −1.098; $p = 0.0233$); (2) the other subpathway culminated in *TNFs bind their physiological receptors* (OR = 3.199; 95% CI = [1.128, 7.883]; $p = 0.0333$), which included 5 DE genes: two upregulated (e.g., *TNFRSF9;* log2FC = 1.327; $p = 0.0049$) and three downregulated (e.g., *FASLG;* log2FC = −2.324; $p = 0.0008$). Two top-level pathways also showed significant overrepresentation of DE genes: *Metabolism* (OR = 1.328; 95% CI = [1.148, 1.531]; $p = 0.0077$) and *Signal transduction* (OR = 1.236; 95% CI = [1.076, 1.416]; $p = 0.0135$). *Metabolism* included 174 DE genes, 88 upregulated (e.g., *TPH1;* log2FC = 2.652; $p = 0.0010$) and 86 downregulated (e.g., *FHL2;* log2FC = 2.916; $p = 0.0073$). *Signal transduction* included 191 DE genes, 123 upregulated (e.g., *FPR3;* log2FC = 3.314; $p = 0.0001$), and 68 downregulated (e.g., *H2BC7;* log2FC = −2.780; $p < 0.0001$). While *Signaling by Interleukins* did not reach statistical significance (OR = 1.320; 95% CI = [0.977, 1.759]; $p = 0.0789$), the pathway included 40 DE genes, 19 upregulated (e.g., *S100B;* log2FC = 2.865; $p = 0.0459$) and 21 downregulated (e.g., *FASLG*). Fig. 1D presents the ORs summarized in Table 2, with the *a priori* pathways included in the combined pathway hierarchy illustrated in Fig. 2. Complete DE gene summary statistics are available on-line.

The exploratory Reactome-wide query confirmed and extended *a priori* findings. For each pathway, the gene-set ratio (also referred to as "recall", R), representing the proportion of DE genes within the pathway present in the query set, along with FDR-adjusted p values, were derived. This analysis identified an overrepresentation of upregulated genes in pathways associated with *Chromatin organization* (R-HSA-4839726) and *Immune System* (R-HSA-168256), while downregulated genes were overrepresented in Metabolism (R-HSA-1430728), *Immune System* (R-HSA-168256), *Disease* (R-HSA-1643685), and *Metabolism of proteins* (R-HSA-392499) in victims, compared to controls (Table 3; Fig. 1F). Top-level *Immune System* was not significant in the Reactome-wide query; however, its significance in the *a priori* tests suggests statistical dilution due to its large gene set. These results indicated that the *a priori* cytokine- and interferon-related pathways were downregulated. In contrast, another pathway within the *Immune System—Neutrophil degranulation* (R-HSA-6798695)—was upregulated. Two new pathways were identified within *Metabolism*: one culminating in *Interconversion of Nucleotide Di- and Triphosphates* (R-HSA-499943) and another in *Selenoamino acid metabolism* (R-HSA-2408522), both of which showed an overrepresentation of downregulated genes. Additionally, the top-level pathway *Chromatin Organization* (R-HSA-4839726) and its subpathway *Chromatin Modifying Enzymes* (R-HSA-3247509) exhibited an overrepresentation of upregulated genes. Although the top-level pathways—*Metabolism of proteins* and *Disease*—were not significant, *SRP-dependent cotranslational protein targeting to membrane* (R-HSA-1799339) and *Influenza Infection* (R-HSA-168256) demonstrated significant downregulation, suggesting that statistical dilution of large gene sets may have obscured significance at the top level.

Table 2
Overrepresentation analysis of *a priori* Reactome pathways for differentially expressed genes.

	OR	lower	upper	p	p_{adj}
Immune system	1.768	1.246	2.462	0.0040	0.0110
_Cytokine signaling in Immune system (R-HSA-1280215)	1.778	1.252	2.475	0.0037	0.0110
__Interferon signaling (R-HSA-913531)	2.427	1.451	3.907	0.0026	0.0110
____Interferon alpha/beta signaling (R-HSA-909733)	2.305	1.223	4.090	0.0155	0.0243
____Interferon gamma signaling (R-HSA-877300)	2.181	1.259	3.611	0.0102	0.0188
__Signaling by interleukins (R-HSA-449147)	1.320	0.977	1.757	0.0646	0.0789
__TNFR2 non-canonical NF-kB pathway (R-HSA-5668541)	1.496	0.808	2.594	0.1435	0.1578
____TNFs bind their physiological receptors (R-HSA-5669034)	3.199	1.128	7.883	0.0333	0.0458
Metabolism (R-HSA-1430728)	1.328	1.148	1.531	0.0007	0.0077
Hemostasis (R-HSA-109582)	1.185	0.894	1.550	0.1626	0.1626
Signal transduction (R-HSA-162582)	1.236	1.075	1.416	0.0061	0.0135

Note: The table lists pathways with their odds ratios (OR), lower and upper confidence intervals, and adjusted p values (p_{adj}). Indentation reflects the hierarchical structure of Reactome pathways.

Among these findings, two key components of interferon-related signaling showed significance in the DE gene analysis, including *STAT1* (downregulated; log2FC = −0.486; $p = 0.0008$) and *SOCS4* (upregulated; log2FC = 1.223; $p = 0.0026$), while *JAK1* was not significant (log2FC = 0.125; $p = 0.2790$). Furthermore, the glucocorticoid receptor gene *NR3C1* (log2FC = 0.280; $p = 0.0414$) and *NFKB1*, which encodes NF-κB (log2FC = 0.214; $p = 0.0230$), were upregulated. Fig. 2 presents a targeted excerpt from the Reactome browser, highlighting key pathways and sub-pathways and their placement within the broader Reactome hierarchy. Notably, *a priori* pathways and sub-pathways within *Immune System* and *Metabolism*—where CTRA genes are known to be active—were also identified in the exploratory Reactome query after correction for multiple testing across more than 2,500 pathways.

3.4. Transcription factors

A total of 108 active TFs were inferred, including 93 associated with upregulated DE genes and 15 with downregulated DE genes in victims, compared to controls (Fig. 3A). Recall (R)—defined here as the proportion of DE genes with TF binding sites matching their respective TFs—was used to evaluate motif overlap. To identify a subset of the most relevant TFs, the mean plus one standard deviation was applied as a reference threshold, selecting three TFs associated with downregulated genes: IRF2 (R = 0.088; $p = 0.0144$), IRF8 (R = 0.114; $p = 0.0028$), and STAT2 (R = 0.364; $p = 0.0166$). To avoid overlooking potentially meaningful signals, two additional TFs below the threshold were included: IRF4 (R = 0.055; $p = 0.0144$), associated with upregulated genes and included due to its membership in the IRF family, and NF-κB (R = 0.040; $p = 0.0435$), associated with downregulated genes and included because its encoding gene, *NFKB1*, was differentially expressed ($\log_2$FC = 1.160; $p = 0.0230$) and represented the only DE TFTG within the CTRA gene set, despite modest fold change.

All five TFs had matches with TFTGs in Reactome pathways of the exploratory analysis, with STAT2 and IRF2 regulating the largest number of targets (Fig. 3B). Upregulated *Chromatin organization* and downregulated *Interferon signaling* pathways emerged as most strongly regulated by the selected TFs. No substantial evidence indicated that TF activity was regulated by the expression of their encoding genes (Fig. 3C). This conclusion is supported by non-significant p values for *IRF2* (log2FC = 0.071; $p = 0.7232$), *IRF4* (log2FC = −0.799; $p = 0.5141$), *IRF8* (log2FC = −0.818; $p = 0.2740$), and *STAT2* (log2FC = 0.959; $p = 0.8330$), as well as the relatively small fold change for *NFKB1* despite statistical significance.

3.5. Cytokines

Among pro-inflammatory cytokines, elevations in the extended model included TNF (log2FC = 0.571; 95 % CI = [0.186, 0.957]; $p = 0.0130$) and CCL4 (log2FC = 0.132; 95 % CI = [0.049, 0.214];

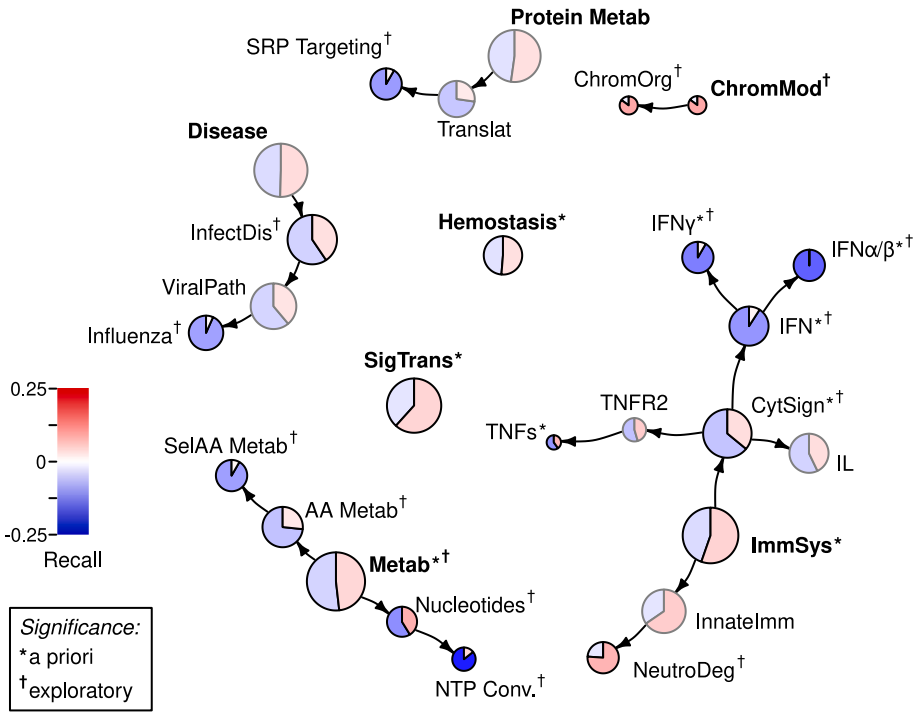

Fig. 2. Hierarchy of analyzed Reactome pathways. $^{*,\dagger}p < 0.05$. The figure displays the hierarchical organization of pathways with overrepresentation in up- and downregulated genes, as visualized in the Reactome pathway browser. Node sizes correspond to relative term sizes, and colors indicate the gene ratio ("recall" R), representing the proportion of DE genes in a pathway that are present in the query set. Red shades indicate upregulated pathways, while blue shades denote downregulated pathways. The figure integrates results from both *a priori* and exploratory Reactome analyses. Abbreviations are detailed in the caption of Fig. 1. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

$p = 0.0087$), while reductions were observed for CXCL10 (log2FC = −1.108; 95 % CI = [−1.424, −0.791]; $p < 0.0001$) and CXCL9 (log2FC = −1.096; 95 % CI = [−1.532, −0.659]; $p < 0.0001$). CCL5 was also reduced but did not reach statistical significance (log2FC = −0.350; 95 % CI = [−0.692, −0.009]; $p = 0.1185$). Similarly, CSF1 was reduced without statistical significance (log2FC = −0.240; 95 % CI = [−0.581, −0.101]; $p = 0.2941$). Among growth factors, CLEC11A was significantly reduced (log2FC = −3.116; 95 % CI = [−4.416, −1.816]; $p < 0.0001$) while PDGFB showed a tendency to be elevated (log2FC = 0.286; 95 % CI = [−0.090, 0.663]; $p < 0.2687$) but was not statistically significant.

4. Discussion

PV is a common problem with documented, potentially serious consequences for mental and physical health (Lereya et al., 2015). Additionally, PV induces significant social stress during critical periods of immune system development (Rowson et al., 2019), potentially affecting molecular mechanisms including leukocyte composition, gene expression, TF activity, and cytokine levels. Leveraging longitudinal data, this study investigated the biological consequences of adolescent PV in young adulthood. PV profiles were carefully derived from prospective self-reports, focusing on "pure victims"—individuals who experienced victimization but did not perpetrate it. Reports from the young person, parents, and teachers along with genomic data were used to implement a counterfactual design with IPW accounting for baseline and time-varying confounders across all analyses.

Adolescent PV was associated with shifts in leukocyte composition, characterized by reduced M1-like monocytes, a lower M1-like:M2-like monocyte ratio, and a trend toward increased DC^{+} proportions compared to non-PV controls, consistent with prior research noting that dendritic cells and monocytes are transcriptionally sensitive to the social environment (Cole et al., 2011). The implicated skew toward an M2 phenotype reflects suppressed pro-inflammatory responses, aligning with downregulated *Interferon alpha/beta* (IFN-α/β) *signaling* and *Interferon gamma* (IFN-γ) *signaling* pathways (Mosser and Edwards, 2008; Sica and Mantovani, 2012). Notably, this pattern was observed in monocytic precursors, suggesting that actual macrophages likely reside in tissues beyond the scope of peripheral blood measurements. While M2 cells contribute to tissue repair and anti-inflammatory processes, they are also associated with increased autoimmune risk (Martinez et al., 2009) consistent with the elevated rates of asthma, allergies, and skin problems observed in victims. Additionally, M2-like skewing suggests a transition from an acute to a chronic immunoregulatory state (Sica and Mantovani, 2012).

PV-induced immune dysregulation was further evidenced by an elevated neutrophil:monocyte ratio and upregulated expression of *NR3C1* compared to non-PV controls, suggesting altered glucocorticoid sensitivity as previously reported (Cole, 2008). Reduced $CD8^{+}$ T cells: Tregs ratios, reflecting Treg-mediated inhibition of cytotoxic $CD8^{+}$ T cells compared to controls, suggests immune suppression and potential exhaustion (Haruna et al., 2022; Schietinger and Greenberg, 2014). Reduced eosinophils and follicular-like Th levels, potentially reflecting a tendency toward lower CCL5, a known eosinophil chemoattractant (Kameyoshi et al., 1992), further support an immunosuppressive profile and autoimmune predisposition. These findings align with stress-induced leukocyte modulation models (Cole, 2008; Dhabhar, 2009; Munshi et al., 2020).

The upregulation of the CTRA profile observed in victims compared to non-PV controls is consistent with stress-induced observations in other social adversities, including low socioeconomic status (Knight et al., 2016; Levine et al., 2017; Powell et al., 2013; Shanahan et al., 2022), low social connection and loneliness (Chun et al., 2017; Cole et al., 2015a, 2015b; Kim et al., 2021; Korytář et al., 2016; Lee et al., 2023; Moieni et al., 2015; Snodgrass et al., 2018, 2019, 2022), psychological stress and anxiety (Chiang et al., 2019; Wingo and Gibson, 2015), and racial and sexual discrimination (Lee et al., 2021; Li et al., 2020; Thames et al., 2019).

Table 3
Overrepresentation analysis of *exploratory* Reactome pathways for differentially expressed genes.

Pathway Name	Pathway ID	Top Pathway	*R*	p_{adj}
Upregulated genes:				
Neutrophil degranulation	R-HSA-6798695	Immune System (R-HSA-168256)	0.074	0.0399
Chromatin organization	R-HSA-4839726	Chromatin organization (R-HSA-4839726)	0.085	0.0399
_Chromatin modifying enzymes	R-HSA-3247509	Chromatin organization (R-HSA-4839726)	0.085	0.0399
Downregulated genes:				
Cytokine Signaling in Immune system	R-HSA-1280215	Immune System (R-HSA-168256)	0.057	0.0009
_Interferon Signaling	R-HSA-913531	Immune System (R-HSA-168256)	0.104	0.0002
__Interferon alpha/beta signaling	R-HSA-909733	Immune System (R-HSA-168256)	0.155	0.0009
__Interferon gamma signaling	R-HSA-877300	Immune System (R-HSA-168256)	0.126	0.0039
Metabolism	R-HSA-1430728	Metabolism (R-HSA-1430728)	0.041	0.0014
_Metabolism of nucleotides	R-HSA-15869	Metabolism (R-HSA-1430728)	0.110	0.0197
__Interconversion of nucleotide di- and triphosphates	R-HSA-499943	Metabolism (R-HSA-1430728)	0.222	0.0097
_Metabolism of amino acids and derivatives	R-HSA-71291	Metabolism (R-HSA-1430728)	0.059	0.0342
__Selenoamino acid metabolism	R-HSA-2408522	Metabolism (R-HSA-1430728)	0.094	0.0299
SRP-dependent cotranslational protein targeting to membrane	R-HSA-1799339	Metabolism of proteins (R-HSA-392499)	0.097	0.0245
Infectious disease	R-HSA-5663205	Disease (R-HSA-1643685)	0.044	0.0472
_Influenza Infection	R-HSA-168255	Disease (R-HSA-1643685)	0.092	0.0093

Note: The table lists pathways that are significantly up- or downregulated. For each pathway, the associated top-level Reactome pathway, Reactome pathway ID, the gene ratio (R), and the adjusted p value (p_{adj}) are provided. Indentation reflects the hierarchical structure of Reactome pathways.

Reactome analyses highlighted immune, metabolic, and chromatin organization pathways in victims, suggesting potential long-term effects on immune function and physical health. *Immune System* pathways included downregulated IFN-α/β and IFN-γ signaling, consistent with reduced antiviral responses and the observed M2-like skew (Mosser and Edwards, 2008; Sica and Mantovani, 2012). Downregulated *Metabolism* pathways suggested mitochondrial dysfunction (Blanco and Kaplan, 2023; Hirschenson et al., 2022)—a "hallmark of aging" (López-Otín et al., 2023)—potentially linked to cellular energy deficits, fatigue, and metabolic symptoms reported by victims (Gini and Pozzoli, 2009; Hager and Leadbeater, 2016; Hirschenson et al., 2022), as well as increased type-2 diabetes risk (Haythorne et al., 2019; Prashanth et al., 2021). Upregulated *Chromatin organization* pathways, associated with transcriptional regulation changes and epigenetic DNA modifications, may amplify stress responsiveness and hint at potential cancer risks (MacAlpine and Almouzni, 2013; Zhao et al., 2021).

PV was also associated with disruptions in *Metabolism of proteins*, with downregulated *SRP-dependent cotranslational protein targeting to membrane* suggesting translational read-through and misfolded protein accumulation (Karijolich and Yu, 2014), potentially leading to cellular stress, dysfunction, and death, thereby contributing to inflammation and neurodegenerative diseases such as dementia, Alzheimer's, Parkinson's, and Huntington's disease (Ciechanover and Kwon, 2015; Karanth et al., 2020).

Downregulation in *Disease* pathways, particularly *Infectious disease* and *Influenza infection*, further supports a pattern of immune dysregulation resembling expression profiles observed in these conditions; NF-κB, essential for cytokine production and pathogen clearance, is often hijacked by viruses like influenza to suppress host immunity (Gaur et al., 2011)—although its precise role in the current profile remains unclear, its involvement cannot be excluded. Dysregulation of enriched *Hemostasis* pathways may exacerbate inflammation and increase the risk of thrombosis or clotting complications (Margetic, 2012), while impaired *Signal Transduction* pathways, as supported by downregulated *STAT1* and non-significant changes in *JAK1*, may also contribute to immune dysregulation, autoimmunity, and cancer susceptibility (Liongue et al., 2023; Samra et al., 2024). Together, these findings suggest that PV-induced stress may contribute to disruptions across immune, metabolic, and regulatory pathways.

Key TFs, including STAT1, IRF2, and NF-κB, exhibited activity differences in victims compared to non-PV controls, with regulation independent of encoding gene expression, suggesting involvement of miRNA regulation, protein–protein interactions, or post-transcriptional modifications (Arimoto et al., 2018). STAT2 and IRF2 emerged as key

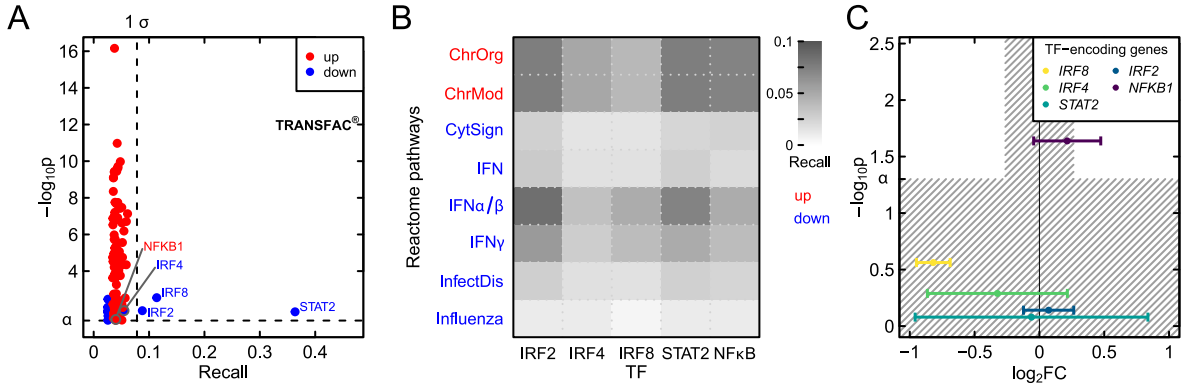

Fig. 3. Transcription factors (TFs). ***(A)*** TF yield of TRANSFAC® query, up = TFs associated with upregulated DE genes, down = TFs associated with downregulated DE genes. The vertical dashed line denoting 1 SD above the mean gene ratio (R), defined as the proportion of DE genes with TF binding sites matching their respective TFs. ***(B)*** TFs with TFTG matches in Reactome query pathways. Only pathways with reasonable matches (R > 0.01) are shown. Gray intensity indicates gene ratio ("recall" R) within the pathways, defined as the proportion of DE genes in a pathway relative to its total genes, with red representing upregulated and blue representing downregulated pathways. ***(C)*** Coefficient plot of TF-encoding genes, highlighting limited correspondence between TF activity and differential expression of their encoding genes, suggesting alternative regulatory mechanisms beyond transcriptional control. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Interferon signaling regulators, with STAT2 likely inhibiting IFN-γ signaling and IRF2 likely inhibiting IFN-α/β signaling (Arimoto et al., 2018; Hida et al., 2000; Negishi et al., 2018; Oshima et al., 2004). The suppression of IFN-γ signaling may further contribute to the M2-like immune skew and its associated autoimmune implications (Elser et al., 2002). STAT2 and IRF2 were also implicated as potential promoters in the upregulated *Chromatin organization* pathways, suggesting a role in driving transcriptional changes and possibly facilitating epigenetic DNA modifications. NF-κB was retained despite low motif overlap due to gene-level upregulation and its relevance to the CTRA; its known regulation of CCL4 and TNF—both elevated in our data—supports biological plausibility, though its contribution should be interpreted cautiously given the modest motif-based signal (Liu et al., 2017; Miller et al., 2009). By contrast, IRF8 and IRF4 appeared to play minimal roles in the identified pathways, with their regulatory activity restricted to a subset of TFTGs.

Altered plasma cytokine levels in victims compared to non-PV controls corroborated the observed immune dysregulation, with elevated TNF and CCL4 linked to PV-associated symptoms such as fatigue, anxiety, depressive symptoms, and metabolic syndrome (Munshi et al., 2020; Slavich and Irwin, 2014). In contrast, reduced CXCL10 and CXCL9 levels reflected diminished IFN-γ signaling and impaired M1 activity (Mosser and Edwards, 2008; Samra et al., 2024), consistent with recent findings showing that suppression of STAT1–CXCL9/CXCL10 signaling weakens T-cell recruitment and immune activation (Liu et al., 2024). Lower CLEC11A levels, critical for hematopoietic progenitor cell development (Hiraoka et al., 1997; Ito et al., 2003) and β-cell function (Shi et al., 2023), may exacerbate immune dysregulation and aligns with risks of type-2 diabetes linked to mitochondrial dysfunction. Finally, an upward trend in PDGFB—vital for tissue repair, cell proliferation, and vascular development (Vanlandewijck et al., 2015)—may signify an adaptive response to stress-induced tissue damage.

Changes in leukocyte composition in victims likely contributed to altered cytokine levels, as, for instance, macrophages and dendritic cells are primary producers of pro-inflammatory cytokines (Yoshimura et al., 2021), though reverse causal mechanisms should also be considered. Persistent cytokine alterations, evident after leukocyte composition adjustments, suggest the involvement of additional mechanisms. For instance, the downregulated pathway *TNFs bind their physiological receptors* implies impaired receptor-ligand interactions, potentially disrupting inflammatory signaling. Alternatively, *STAT1* downregulation alongside unchanged *JAK1* expression suggests disrupted negative cytokine regulation mediated by the JAK1–STAT1 pathway (Yasukawa et al., 2000), associated with autoimmune and inflammatory diseases, interferon resistance, and impaired cytokine balance—patterns potentially shaped by prolonged stress exposure. A similar mechanism was recently described in tuberculosis, where impaired STAT1 signaling suppressed CXCL9 and CXCL10 expression and delayed immune activation (Liu et al., 2024), further supporting the link between *STAT1* dysfunction and weakened chemokine-mediated immune responses. Together, these findings highlight a PV-induced cytokine imbalance, contributing to suppressed antiviral responses, immune dysregulation, and increased risk of autoimmune conditions (Marsland et al., 2017).

Stronger evidence of suppressed antiviral functions than heightened inflammation was observed in victims compared to non-PV controls. This distinction may reflect immune tolerance or exhaustion potentially associated with the chronic stress of longstanding PV (Haruna et al., 2022; Schietinger and Greenberg, 2014). The PV profile, marked by impaired immune response, persistent dysregulation, and M2-like skew (Sica and Mantovani, 2012), as well as autoimmune tendencies, suggests a chronic PV phenotype: Initial acute phases of stress might have occurred earlier, potentially leading to an adapted or dysregulated immune state rather than an initial inflammatory response. An alternative explanation is that chronic inflammation levels may generally be low in young adulthood and so less prone than the innate antiviral response to stress-related upregulation during this developmental period. Notably, the observed combination of immune suppression and autoimmune tendencies may point to a biologically distinct PV profile—though this possibility remains speculative and should be examined in future comparative research.

5. Limitations and future work

The detailed PV model and IPW addressed common confounding factors in PV studies; nonetheless, the propensity score model, while addressing major confounders, may not fully account for unmeasured variables, potentially limiting causal inferences. Reverse causation—-where innate traits influence both PV exposure and biological outcomes—remains a theoretical possibility; however, no evidence from this study supports this hypothesis. Future studies should employ larger sample sizes to enable the exploration of nuanced patterns, such as early vs. late or chronic vs. acute victimization. Moreover, incorporating longitudinal mRNA data and tissue samples beyond peripheral blood will provide deeper insights into the molecular mechanisms underlying these processes. Participants were classified as *victims* based on external criteria, as self-reported appraisals of social adversity were not available. However, appraisals are stronger predictors of biological impacts than external assessments (Kemeny, 2003; Lee et al., 2021; Zych et al., 2020). This limitation suggests that our findings may underestimate the associations involving PV, underscoring the need for appraisal measures in future studies. The data, derived from a specialized sample in Zurich, a city with high living standards, may limit the generalizability of the findings; nonetheless, PV predicted indicators of distress even within this privileged context, demonstrating the value of this sample for understanding the effects of social adversity. While the sample size was suitable for analyzing gene signatures and pathways, larger samples are needed to investigate smaller gene sets or individual genes in greater detail (Cole et al., 2003). Analytical tools such as WGCNA (Langfelder and Horvath, 2008) and MOFA (Pierre-Jean et al., 2020) were not used due to their lack of support for IPW; future updates should address this need.

6. Conclusions

This study examined the impact of a decade of PV during adolescence on gene expression, leukocyte composition, and cytokine profiles in young adulthood. Using a counterfactual design, we observed suppressed antiviral responses, heightened inflammatory markers, and a profile indicating potential autoimmune risk in victims—findings consistent with prior research on social adversity. Dysregulated immune and metabolic pathways were associated with these changes and were regulated by key TFs, including STAT2 and IRF2; NF-κB was also implicated, though with more limited motif overlap. These TFs showed activity independent of their encoding genes, suggesting regulatory mechanisms beyond transcriptional control. Cytokine alterations further highlighted immune dysregulation associated with PV. Together, these findings shed light on the broad systemic effects of PV on immune function and its potential long-term health risks in young adulthood. Prevention and resilience-building strategies should prioritize early identification and support for at-risk adolescents, addressing not only the psychological toll but also the biological embedding of PV.

CRediT authorship contribution statement

Jens Heumann: Conceptualization, Data curation, Formal analysis, Project administration, Software, Visualization, Writing – original draft, Writing – review & editing. **Steve W. Cole:** Supervision, Validation, Writing – review & editing. **Manuel Eisner:** Conceptualization, Supervision, Writing – review & editing. **Denis Ribeaud:** Conceptualization, Supervision, Writing – review & editing. **Edna Grünblatt:** Conceptualization, Investigation, Resources, Supervision, Writing – review & editing. **Michael J. Shanahan:** Conceptualization, Funding acquisition,

Methodology, Resources, Supervision, Writing – review & editing.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2025.101025.

Data availability

Summary statistics from the differential gene expression analysis are publicly available at https://doi.org/10.5281/zenodo.13788820 ().

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