Peer victimization in adolescence alters gene expression and cytokine profiles

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ABSTRACT

Social adversity downregulates antiviral genes and upregulates inflammatory genes, altering cytokine levels. We investigated how peer victimization during adolescence affects gene expression, cytokine levels, and cellular dynamics in young adulthood. Using data from the Zurich Brain and Immune Gene Study (z-GIG, $n = 200$; 47% female), we assessed peer victimization between ages 11 and 20 and analyzed mRNA abundance and plasma cytokine profiles from 144 participants at age 21. Employing a counterfactual design with genetically-informed inverse-probability weighting, we adjusted for baseline confounders in individual and environmental characteristics, enhancing causal inferences regarding peer victimization and health outcomes. *In silico* deconvolution displayed that victims exhibited altered leukocyte composition, including reduced MΦ1- and elevated MΦ2-like monocytes, compared to non-victimized peers. They also had higher proportions of activated dendritic cells and regulatory T cells, along with changes in various immune cell ratios. Differential expression of genes was overrepresented in immunomodulatory Reactome pathways, such as *Immune system, Cytokine signaling in immune system, Interferon signaling*, and *Signaling by interleukins*. Exploratory analysis revealed additional downregulated Reactome pathways of interest. Victims showed elevated levels of pro-inflammatory cytokines, including CCL5, CCL11, and IL-16 compared with controls. Transcription factors STAT2 and IRF1 were identified as key drivers, with numerous matches in overrepresented Reactome pathways. Findings suggest that adolescent peer victimization can lead to changes in gene regulatory activity and cytokine levels, potentially altering the immune profile in young adulthood. These results underscore the importance of health policies aimed at preventing peer victimization, building resilience, and mitigating its long-term effects.

Keywords: peer victimization, gene expression, in silico deconvolution, leukocytes, cytokines, transcription factors, target genes, Reactome pathways, counterfactual

1. Introduction

Peer victimization (PV) among adolescents, characterized by sometimes-traumatic experiences of verbal and physical abuse as well as systematic social exclusion, not only defines a challenging youth experience but also may entail excessive stress and associated stress-related pathology, with effects similar to those observed in situations of forceful social subordination (Sapolsky, 2004). Such stress poses long-term consequences, including psychological distress like anxiety, depression, agoraphobia, externalizing problems, general 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., 2011, 2010), and may even lead to suicide (Cha et al., 2018; Koyanagi et al., 2019; Van Geel et al., 2022). Moreover, PV is linked to physical stress symptoms including headaches, skin problems, poor appetite, abdominal pain, vomiting, stiffness, backaches, dizziness, sleeping difficulties, and fatigue (Gini and Pozzoli, 2009, 2013; Hager and Leadbeater, 2016). Given the high global prevalence of PV, estimated at around 30% (Biswas et al., 2020), and its significant consequences, a deeper understanding of the complex molecular impacts of PV on the stress process may inform public health initiatives.

The occurrence of PV as a potent social stressor during adolescence introduces developmental considerations, as this period is marked by significant, possibly permanent, changes in the neuroendocrine, transcriptional, and immune systems that are critical for stress regulation (Casey et al., 2008; Rowson et al., 2019). These changes can in turn influence cytokine regulation (Chiang et al., 2012; Giletta et al., 2018; Polacchini et al., 2018), which feeds back into neuroendocrine

processes (Dantzer et al., 2008) and creates a "neuroimmune pipeline" that has implications for future health (Miller and Cole, 2012).

Biologically-informed PV research has focused on individual differences in the stress response, such as 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 and other epigenetic processes (e.g. Marzi et al., 2018). While one study investigated immunomodulatory gene expression in homophobic victimization (Li et al., 2020), no such analysis has been conducted for PV. Studying gene expression is crucial for understanding how PV affects health, however, because it reveals the underlying biological mechanisms that link stress to modulation of the immune system.

Furthermore, previous studies were limited by analyzing the biomolecular outcomes separately in different samples and by lacking longitudinal data on PV, but such studies can not address potentially influential, time-varying socio-environmental confounders (Zuber et al., 2023). Findings on the impact of PV may also be biased by common-method variance as many studies use both PV and health data from the same self-reported source (Gini and Pozzoli, 2013). Additionally, as PV studies are observational for ethical reasons, their inherent susceptibility to treatment selection bias should be acknowledged and addressed (Schoeler et al., 2018).

Social adversity is often associated with a characteristic transcriptomic profile with upregulated proinflammatory genes and downregulated antiviral genes, a pattern termed the "conserved transcriptional response to adversity" (CTRA; Cole, 2019). Chronic activation of the CTRA is associated with an increased risk of psychological symptoms such as depression and anxiety, inflammation-related diseases such as cardiovascular diseases, metabolic diseases, neoplastic diseases and cancer, and downregulated immune function such as viral infections and a reduced response to vaccines (Cole, 2019, 2013). Research into the CTRA profile and the regulation of inflammatory and interferon pathways, particularly for PV, remains nascent. Furthermore, Miller et al. (2009) revealed significant variations in transcription factor (TF) activity due to low SES—a social adversity with parallels to PV in terms of stress—with higher NF-κB and CREB activity, and lower GR (and consequently higher NF-κB:GR ratio) binding motif abundance. This finding warrants the inclusion of TF activity analysis in genomic studies of PV.

In the present study, twenty-one-year-olds who experienced PV between ages 11 and 20 were contrasted with unaffected controls on a series of biological profiles, using a longitudinal design for PV and the inclusion of time-varying confounders. First, *in silico* deconvolution was used to estimate the composition of leukocytes in the victims compared to the controls (Avila Cobos et al., 2020). Second, victims and controls were compared with respect to CTRA patterns and pre-selected functional Reactome pathways related to the immune system. Third, genome-wide functional enrichment was analyzed on an exploratory basis. Next, activity of TFs and their target genes were examined using TF binding sites of differentially expressed (DE) genes. Finally, 18 measures of proinflammatory and other cytokines were examined using a Multiplex immunoassay.

To address possible selection bias, a counterfactual approach was used throughout the analyses by applying genetically-informed inverse probability weighting (IPW) including pre-victimization characteristics and polygenic risk scores (PRS) for attention-deficit/hyperactivity disorder (ADHD), panic disorder (PD), generalized anxiety disorder (GAD), and major depressive disorder (MDD).

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 ($n \approx 1,500$) started in 2004 with Zurich elementary school children aged 7–9, notable for high ethnic heterogeneity ($>$ 60% of the 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. 500 eligible subjects were randomly drawn from 28 strata and 200 finally participated in z-GIG at age 21 (response rate 40%), of whom 186 consented to blood sampling. No systematic non-participation was identified. IPW addressed selection bias from sample stratification. 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. A total of 32.5 mL of peripheral blood was drawn by trained phlebotomists from the antecubital vein and stored in serum, EDTA and PAXgene RNA tubes. The serum and EDTA samples were immediately centrifuged at 2000 xg 10 min to extract serum and plasma, and all samples including PAXgene tubes were stored at $-80\,^{\circ}$C until analysis. mRNA from PAXgene tubes was extracted following the protocol previously described (Becker et al., 2022), converted to cDNA using Lexogen QuantSeq 3' mRNA FWD, and sequenced at a depth of 15M reads, 1x100bp, on a NovaSeq 6000. DNA was isolated from EDTA blood following the method previously described (Jagannath et al., 2020). 153 samples contained sufficient mRNA/DNA for high-throughput bulk analysis. Subsequently, a mRNA gene count matrix was generated using the nf-core/rnaseq pipeline. mRNA-seq data were aligned to the reference genome GRCh38 using STAR v2.7.6a, and Salmon (Patel et al., 2023). Adapter sequences and low-quality bases were trimmed using cutadapt v1.16. Quantification of gene expression levels was performed with featureCounts v2.0.1 from the subread package. Quality control (QC) metrics were compiled and visualized using MultiQC v1.9. DNA genotyping was performed using Illumina Infinium LCG Assay aligned with the reference genome GRCh38. mRNA and DNA were processed at LIFE & BRAIN Gmbh, Bonn, Germany. The resulting genotyping data was provided in PED file format and underwent QC measures including basic QC (maf > 0.01; info > 0.8), strand flipping, sex check, and clumping before analysis. Summary statistics used for the PRS, initially mapped on GRCh37, required a liftover process for alignment with GRCh38 used in our data. PRS calculations were carried out using PLINK 1.90b7 (Purcell et al., 2007), GNU awk 5.1.0, and the UCSC LiftOver Tool, based on recognized GWAS of European populations (ADHD: Demontis et al., 2023, 2023; GAD: Otowa et al., 2016, 2016; MDD: Wray et al., 2018; PD: Forstner et al., 2021).

For quantifying blood plasma cytokines in triplicates, Multiplex immunoassay with the Bio-Plex Human Cytokine Screening Panel, 48-Plex (BioRad, #12007283) was employed, according to the protocols of the manufacturer. Bio-Plex Manager version 6.1 (Bio-Rad Laboratories, 2023) was used for data analysis. Protein concentrations were calculated using the appropriate standard curves.

The experimenter and wet lab personnel were blinded to PV conditions, while only the data analyst was informed of the 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 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 (11.1%) individuals were identified in the analytic sample who accordingly were only exposed to SE but never exhibited DB, and a binary variable was created to represent this PV profile (Fig. S1A visualizes the derivation of the PV profile).

2.4. *Inverse probability weighting and time-varying confounders*

In our analyses, IPW (Hernán and Robins, 2020) was applied to adjust for biopsychosocial confounders resulting from both selection into treatment (PV) and selection into the stratified sample. This method creates a pseudo-population approximating a randomized

trial, thereby aiming to enhance causal inference. Three waves of pre-victimization variables (ages 7–9) from reports by the young person, teachers, and parents were used. The IPW also included PRS for psychiatric disorders to help mitigate genetic confounding (Vrijen et al., 2023). Specifically, we used a logit model on the confounders affecting both the treatment and the outcome (Rubin, 1997) to derive propensity scores of getting peer-victimized, and calculated weights w_i for estimating the average treatment effect on the treated (ATT),

$$w_i = D_i + (1 - D_i)(e_i/1 - e_i)$$

where D denotes the indicator of victim status and e is the propensity score (Morgan and Winship, 2015). While the use of IPW is generally recommended for observational studies, especially in the context of PV (Baldwin et al., 2023), Reifeis et al. (2020) recommend IPW specifically for genomic data analysis, highlighting its ability to produce consistent estimates. Baseline data for the logit model come from the first three z-proso waves (ages 7–9) and PRS for MDD, ADHD, PD, and GAD from summary statistics as referenced in 2.2. See Table S1 for a complete list of the confounding factors and rationale. To minimize extrapolation bias, we restricted ATT estimation to victims with propensity scores in the range of the control (common support) and excluded seven of the initial 23 victims 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 were used as sampling weights throughout the analyses.

2.5. *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 transcription factor analyses, and (3) cytokine dysregulation. Statistical analyses were performed using R 4.3.2 (R Development Core Team, 2023). A base model was defined with the PV dummy and adjustments for subjects involved in DB or both SE and DB. Victimization and perpetration related to sexual harassment, as well as victimization from sexual assault were adjusted for but not included in the initial PV profile due to their distinct causal mechanisms (Frøyland et al., 2023). Additionally, adjustments were made for time-varying confounders, including BMI (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). In the mRNA models, the time of blood draw was controlled for diurnal and annual variations by including sine and cosine terms corresponding to the day of the year (doy), calculated as $\sin(2\pi/365 \times \text{doy})$ and $\cos(2\pi/365 \times \text{doy})$; in cytokine models, the season of blood draw was controlled. Additionally, all models controlled for chronic and metabolic diseases, and long-term medication use (binary). In an extended model, genes *CD14, CD19, CD3D, CD4, CD8A, FCGR3A,* and *NCAM1* were included to control for confounding from individual differences in leukocyte composition (Cole et al., 2007; Fredrickson et al., 2013; Li et al., 2020).

2.5.1. *In silico deconvolution*

Potential differences in leukocyte composition between victims and controls were determined using an *in silico* cell-type deconvolution analysis with the LM22 basis matrix (Newman et al., 2015) and the FARDEEP algorithm (Avila Cobos et al., 2020; Hao et al., 2019).

2.5.2. *Gene expression analysis*

The mRNA expression matrix was normalized using the edgeR TMM normalization (Robinson et al., 2010), with a minimum count of 5 and a proportion of 5%, followed by log2-transformation. DE genes among victims were examined based on *a priori* hypotheses and genome-wide *exploration*. In the *a priori* analysis, the CTRA profile (Cole, 2019) was first examined, followed by enrichment analysis of DE genes using pre-selected Reactome pathways (v84; Gillespie et al., 2022). In the *exploratory* analysis, the entire Reactome database was queried using genome-wide DE genes.

2.5.2.1 *A priori analysis*

Following previous studies (Li et al., 2020; Ross et al., 2021), first, CTRA genes were analyzed as repeated measures, with sign-inverted counts for genes expected to be downregulated due to stress, in a complex survey design (Lumley, 2023) using IPW and subject-specific intercepts. Next, a genome-wide DE analysis was performed using limma (Gordon K. Smyth et al., 2022) with IPW applied. Empirical sandwich estimators were calculated to account for the variance of the pseudo-population due to IPW using geex (v1.1.1; Reifeis and Hudgens, 2022; Reifeis et al., 2020; Saul and Hudgens, 2020). Fisher's exact tests for overrepresentation were conducted in key immunoregulatory Reactome pathways relevant to our study, including *Immune*

System (R-HSA-168256), *Cytokine Signaling in Immune system* (R-HSA-1280215), *Interferon Signaling* (R-HSA-913531), *Signaling by Interleukins* (R-HSA-449147) and *TNFR2 non-canonical NF-κB pathway* (R-HSA-5668541). These pathways were pre-selected to ensure a balanced representation of antiviral and pro-inflammatory processes. P value adjustments for multiple comparisons were conducted using the Benjamini and Hochberg (1995) method, to control the type I error rate for our targeted hypotheses.

2.5.2.2 *Exploratory analysis*

In the exploratory phase of the DE gene analysis, overrepresentation was assessed by querying the entire Reactome database with the genome-wide DE genes, considering all 2,570 existing Reactome pathways for p value adjustment.

2.5.3. *Cytokine analysis*

To identify the final proteins synthesized by the cells, log2-transformed quantities of cytokines (CCL4, CCL5, CCL11, CCL27, CSF1, CXCL9, CXCL10, IL-9, IL-16, LTA, PDGFB, SCF, SDF-1α, SCGFβ, SF, and TNF), which showed signals using multiplexing assays, were analyzed using the same models with IPW. P values were adjusted for multiple cytokine comparisons.

2.5.4. *Transcription factor activity analysis*

The activity of TFs was inferred from the motifs of DE genes using the TRANSFAC database (Matys et al., 2003). The Harmonizome database (Rouillard et al., 2016) was then queried for transcription factor target genes (TFTG), and the previously identified Reactome pathways and their genes were matched to the TFTG.

3. Results

3.1. *IPW performance*

The maximum absolute standardized difference between treated and control obtained for IPW covariates was 0.163 (Fig. S1B shows the balance after weighting), demonstrating a satisfactory balance for our sample size (Austin, 2009). Difference between the mean of the estimated weights and the estimated expected value of the weights was -0.007, indicating high agreement (Reifeis and Hudgens, 2022).

3.2. *In silico deconvolution*

In silico cell-type deconvolution revealed several differences in the leukocyte profile associated with PV. LM22 includes expression data from cells that are not present in peripheral blood but whose precursors are. For instance, monocytes in peripheral blood, before migrating to tissues and differentiating into M0 macrophages (MΦ0), exhibit precursor characteristics that determine whether MΦ0 will polarize into M1 or M2 macrophages (MΦ1, MΦ2) (Boyette et al., 2017). Consequently, we interpreted macrophage signals as stemming from monocytes. Deconvolution estimated higher proportions of activated dendritic cells (DCs+), regulatory T cells (Tregs), and MΦ2-like monocytes as well as lower proportions of MΦ0-like monocytes, MΦ1-like monocytes, eosinophils, and follicular-like T helper cells (Tfh) in victims compared to control (Fig. 1A). The following β coefficients reflect the relative abundance of the respective cell type. Several ratios of certain cell types were lower in victims: MΦ1:MΦ2 ratio ($\beta = -0.116$; 95% CI=[-0.207, -0.025]; $p_{\text{adj.}} = 0.0143$), CD8+ T cells to Tregs ratio ($\beta = -0.371$; 95% CI=[-0.634, -0.107]; $p_{\text{adj.}} = 0.0113$), and (B memory, CD8+ T, CD4+ T cells):Tregs ratio ($\beta = -0.500$; 95% CI=[-0.857, -0.144]; $p_{\text{adj.}} = 0.0113$) (Fig. 1B). MΦ2 contribute to conditions such as autoimmune reactions, asthma, and various allergic and skin disorders (Martinez et al., 2009), and indeed we observed increased risk among victims of reporting asthma ($\beta = 0.142$; 95% CI=[0.009, 0.275]; $p = 0.0359$) and a trend for reporting allergy that just missed statistical significance ($\beta = 0.085$; 95% CI=[-0.008, 0.177]; $p = 0.0722$) based on a linear probability model.

3.3. *Differential gene expression*

In the CTRA analysis, the base model showed an average log2FC of 0.244 (95% CI=[0.082, 0.406]; $p = 0.0035$), corresponding to a fold change of about 1.18 (Fig. 1C). Controlling for leukocyte-coding genes, the extended model revealed a slightly higher log2FC of 0.317 (95% CI=[0.126, 0.508]; $p = 0.0014$), corresponding to a fold change of 1.24.

In the genome-wide DE analysis, 984 upregulated and 1,014 downregulated genes (FC $\notin (0.8, 1.2)$, $p_{\text{adj.}} < .05$) were identified using p value adjustment for the entire genome (Fig. 1D). We further analyzed the results both under *a priori* assumptions and *exploratively*, as follows:

First, by focusing on testing hypotheses related to the CTRA alone, we confirmed our repeated measures findings, also revealing the up- and downregulation of specific CTRA genes, including 13 of 61 (37.7%) DE genes; 2 of 25 (8%) genes typically upregulated under stress were upregulated, and 19 of 36 (52.7%) typically downregulated genes were downregulated. Altogether, this pattern emphasizes the pronounced downregulation of the antiviral component of the CTRA.

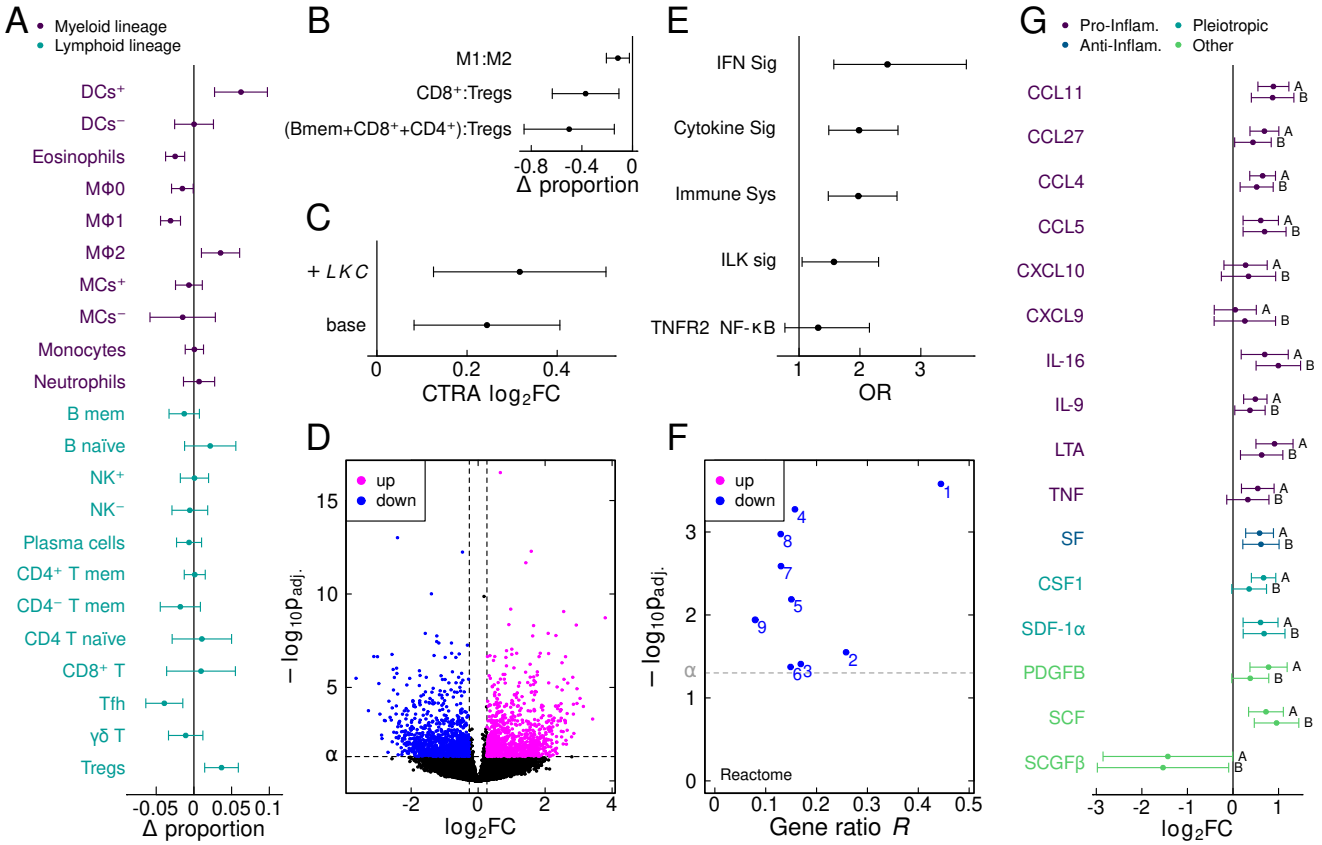

Figure 1: Leukocytes and gene expression. ***(A)*** Changes in relative leukocyte abundance in victims compared to controls with 95% CIs. DC=dendritic cells, MΦ=monocyte/macrophages, MC=mast cells, NK=natural killer cells, Tfh=follicular-like T helper cells, $\gamma\delta$ T=gamma delta T cells, Tregs=T regulatory cells. ***(B)*** Ratios of specific cell types in the deconvolution analysis with 95% CIs. ***(C)*** Upregulation of CTRA from victims vs. unaffected control. base=base model, *+LKC*=leukocyte coding genes added in model. ***(D)*** Volcano plot of differential expressed genes from genome-wide analysis. ***(E)*** Odds ratios for Reactome pathway enrichment from Fisher tests of pre-selected pathways. IFN Sig=Interferon Signaling, Cytokine Sig=Cytokine signaling in Immune system, ILK=Signaling by interleukins, TFNR2 NF-κB=TNFR2 non-canonical NF-κB pathway. ***(F)*** Queried Reactome pathways from genome-wide analysis, up: N/A, down: 1=Formation of ATP by chemiosmotic coupling, 2=Cristae formation, 3=Interferon alpha/beta signaling, 4=Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins., 5=SRP-dependent cotranslational protein targeting to membrane, 6=Eukaryotic Translation Termination, 7=The citric acid (TCA) cycle and respiratory electron transport, 8=Interferon Signaling, 9=Cytokine Signaling in Immune system. ***(G)*** Comparison of cytokine levels in victims vs. controls with 95% CIs. A=base model, B=leukocyte coding mRNA genes included in model.

Next, Fisher's exact tests indicated overrepresentation of DE genes in four pre-selected Reactome pathways: *Immune system* (OR = 1.974; 95% CI=[1.474, 2.615]; $p_{\text{adj.}} = 0.0002$) with 47 DE genes (6 upregulated (e.g. *HGF*; log2FC = 1.436; $p_{\text{adj.}} = 0.0377$) and 41 downregulated (e.g. *IFI27*; log2FC = −2.130; $p_{\text{adj.}} < 0.0001$), *Cytokine signaling in immune system* (OR = 1.985; 95% CI=[1.483, 2.631]; $p_{\text{adj.}} = 0.0002$) with the same 47 DE genes as in *Immune system*, *Interferon signaling* (OR = 2.452; 95% CI=[1.565, 3.753]; $p_{\text{adj.}} = 0.0010$) with 22 DE genes (one upregulated (*IRF6*; log2FC = 1.309; $p_{\text{adj.}} = 0.0191$) and 21 downregulated (e.g. *IFI27*), and *Signaling by interleukins* (OR = 1.573; 95% CI=[1.044, 2.312]; $p_{\text{adj.}} = 0.0431$) with 24 DE genes (5 upregulated (e.g. *HGF*) and 19 downregulated (e.g. *FASLG*; log2FC = −1.937; $p_{\text{adj.}} = 0.0015$). *TNFR2 non-canonical NF-κB pathway* missed statistical significance as a pathway (OR = 1.314; 95% CI=[0.762, 2.162]; $p_{\text{adj.}} = 0.2127$), but still included 14 DE genes (six upregulated (e.g. *LTA*; log2FC = 1.442; $p_{\text{adj.}} = 0.0006$) and eight downregulated (e.g. *FASLG*). (Fig. 1E) visualizes the ORs; the pathway hierarchy is also shown in Fig. 2 (showing results of the complete Reactome query); DE gene data can be accessed in the Supplement).

Finally, the *exploratory* genome-wide functional enrichment analysis across the entire Reactome database identified an overrepresentation of downregulated genes in nine top-level Reactome pathways: *Metabolism, Organelle biogenesis and maintenance, Immune system,*

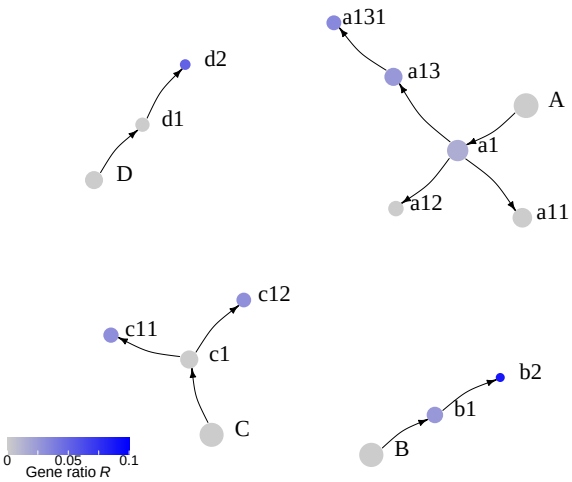

Figure 2: Hierarchy of queried Reactome pathways. The figure displays the hierarchical organization of pathways from the Reactome query with overrepresentation in downregulated genes (the query did not show any upregulation), as also visualized in the Reactome pathway browser. Node sizes represent relative term sizes, colors the gene ratio R. A=*Immune system*, a1=*Cytokine Signaling in Immune system*, a11=S*ignaling by Interleukins*, a12=*TNFR2 non-canonical NF-κB pathway*, a13=*Interferon signaling*, a131=*Interferon alpha/beta signaling*, B=*Metabolism*, b1=*The citric acid (TCA) cycle and respiratory electron transport*, b3=*Formation of ATP by chemiosmotic coupling*, C=*Metabolism of proteins,* c1=*Translation*, c11=*SRP-dependent cotranslational protein targeting to membrane,* c12=*Eukaryotic Translation Termination*, D=*Organelle biogenesis and maintenance,* b1=*Mitochondrial biogenesis*, b2=*Cristae formation*. The Gene ratio indicates the proportion of DE genes within a specific pathway that are present in the query set.

and *Metabolism of proteins*. A gene-set ratio (recall, R), representing the proportion of DE genes within a specific pathway present in the query set, along with p values were obtained. Fig. 2 shows a selective excerpt from the Reactome browser, focusing on the key pathways analyzed in this study. In the identified pathways, R ranged from 0.079 to 0.444 (Table 1; Fig. 1F). Notably, the preselected pathways, *Interferon signaling* and *Cytokine signaling in Immune system*, also survived adjustment for multiple across the entire Reactome database.

3.4. *Cytokines*

In both the base and the extended models we observed cytokine differences between victims and controls, primarily characterized by pro-inflammatory cytokine activity in victims. For instance in the base model: CCL11 (log2FC $= 0.887$; 95% CI=[0.542, 1.231]; $p_{\text{adj.}} < 0.0001$); CCL4 (log2FC $= 0.650$; 95% CI=[0.364, 0.936]; $p_{\text{adj.}} = 0.0001$); LTA (log2FC $= 0.911$; 95% CI=[0.498, 1.323]; $p_{\text{adj.}} = 0.0001$), albeit with notable anti-inflammatory signals from SF (log2FC $= 0.583$; 95% CI=[0.274, 0.892]; $p_{\text{adj.}} = 0.0007$) as well as elevation in pleiotropic cytokines (multi-functional, both pro- and anti-inflammatory), e.g. CSF1 (log2FC $= 0.671$; 95% CI=[0.400, 0.942]; $p_{\text{adj.}} < 0.0001$). Growth factors were generally increased in victims, e.g. PDGFB (log2FC $= 0.780$; 95% CI=[0.366, 1.194]; $p_{\text{adj.}} = 0.0007$). The range in log2FC corresponds to a median fold change of 1.12. In the extended model, this profile remained largely unchanged, with an average absolute change in log2FC of 0.175 (SD $= 0.110$), albeit with an increase in BIC (mean $= +17.6, \text{SD} = 13.6$). Fig. 1G visualizes cytokine results, complete cytokine level estimates are presented in supplemental Table S2 and Table S3.

3.5. *Transcription factors*

Initially 380 active TFs were inferred (270 upregulated and 110 downregulated; FC $\notin (0.8, 1.2), p_{\text{adj.}} < .05$. Among the many TFs with negligible motif overlap (ratio R representing DE genes in the pathway with binding motifs matching the respective TFs) three downregulated and one upregulated TF clearly stood out (Fig. 3A). Using one standard deviation as a threshold, these outliers were separated from the presumed noise, revealing upregulation of ZNF559 ($R = 0.225$; $p_{\text{adj.}} = 0.0304$), and downregulation of STAT2 ($R = 0.545$; $p_{\text{adj.}} = 0.0047$), IRF8 ($R = 0.138$; $p_{\text{adj.}} = 0.0199$), and IRF1 ($R = 0.082$; $p_{\text{adj.}} = 0.0089$). Additionally, TF NF-κB showed notable upregulation, just missing statistical significance ($R = 0.054$; $p_{\text{adj.}} = 0.0541$). All four TFs had matches with TFTG in Reactome pathways that are part of the *Cytokine signaling in immune system* sub-pathway in the *Immune system* top-level pathway (Fig. 2), with STAT2 and IRF1 contributing the most TFTG (Fig. 3B). There was minimal evidence that TF downregulation resulted from DE genes coding for these TFs (Fig. 3C). In summary, the data showed marked changes in specific TFs, with notable downregulation of STAT2, IRF8, and IRF1, and upregulation of ZNF559. Among these, STAT2 and IRF8 had the most matches in TFTGs of Reactome query pathways.

4. Discussion

PV is a common problem with documented, potentially serious consequences for mental and physical health (Lereya et al., 2015). Additionally, PV can induce severe social stress during critical periods of immune system development (Rowson et al., 2019), potentially influencing gene expression, TF activity, leukocyte composition, and cytokine levels. We examined these outcomes in young adulthood, drawing on extensive lon-

Table 1: Overrepresentation analysis of Reactome pathways for differentially expressed genes.

Category	Pathway Name	Reactome ID	R	$p_{\text{adj.}}$
Upregulated genes:				
-	-	-	-	
Downregulated genes:				
Metabolism	Formation of ATP by chemiosmotic coupling	R-HSA-163210	0.440	0.0003
	Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins	R-HSA-163200	0.157	0.0005
	The citric acid (TCA) cycle and respiratory electron transport	R-HSA-1428517	0.130	0.0026
Organelle biogenesis and maintenance	Cristae formation	R-HSA-8949613	0.258	0.0282
Immune system	Interferon alpha/beta signaling	R-HSA-909733	0.169	0.0390
	Interferon Signaling	R-HSA-913531	0.130	0.0011
	Cytokine Signaling in Immune system	R-HSA-1280215	0.079	0.0115
Protein metabolism	SRP-dependent cotranslational protein targeting to membrane	R-HSA-1799339	0.150	0.0065
	Eukaryotic Translation Termination	R-HSA-72764	0.149	0.0424

The table lists pathways that are significantly up- or downregulated. For each pathway, the associated Reactome pathway ID, the gene ratio (R), and the adjusted p value are provided.

gitudinal data that describe PV histories and used data from targets, teachers, parents, and genomic sources to estimate inverse probability weights and adjust for time-varying confounding. PV profiles were carefully derived, focusing on "pure victims" (i.e., individuals who were victimized but never perpetrated).

In silico cell-type deconvolution showed that adolescent PV was associated with increased proportions of DC+ and a shift towards higher MΦ2-like monocyte- and lower MΦ1-like monocyte polarization, consistent with findings by Cole et al. (2011), who noted that dendritic cells and monocytes are transcriptionally sensitive to the social environment. Recall, our analysis detected this pattern in macrophage-like monocytes; we hypothesize that true MΦs likely reside in tissues, which were beyond the scope of our measurements. The pattern aligns with existing literature suggesting that a downregulation of STAT/IRF signaling contributes to diminished MΦ1 while an upregulation of NF-κB signaling favors MΦ2 (Sica and Mantovani, 2012). MΦ1 are typically associated with pro-inflammatory responses, whereas MΦ2 play roles in anti-inflammatory processes and regeneration. However, MΦ2 also contribute to adverse health conditions including autoimmune reactions, asthma, and various allergic and skin disorders (Martinez et al., 2009). In fact, we found evidence for increased risk of asthma and allergy among victims. We also noted frequent reports of skin problems (results not shown). Genes in the TCA cycle were downregulated, which could explain the skewing towards MΦ2 (Bei et al., 2023). Munshi et al. (2020) proposed that social stress impacts the differentiation and proliferation of immune cells; the current findings document similar effects associated with PV.

We also observed an increased number of Tregs, which specialize in suppressing autoimmune reactions. This increase in Tregs may also dampen immune responses to external antigens (Sakaguchi et al., 2008), suggesting a role for Tregs in the immune suppression associated with PV. In a study with cancer patients, Haruna et al. (2022) found that Tregs suppress cytotoxic CD8+ T cells, thereby inhibiting immune responses. Consequently, the decreased CD8+ T cells:Tregs ratio we observed suggests active immune suppression, pointing to a potential mechanism. The decrease in eosinophils and Tfh underscores the general immunosuppressive tendency and predisposition to autoimmune diseases, indicating a multi-layered immunophenotype.

The analysis showed enriched CTRA gene expression among victims. This pattern is consistent with the

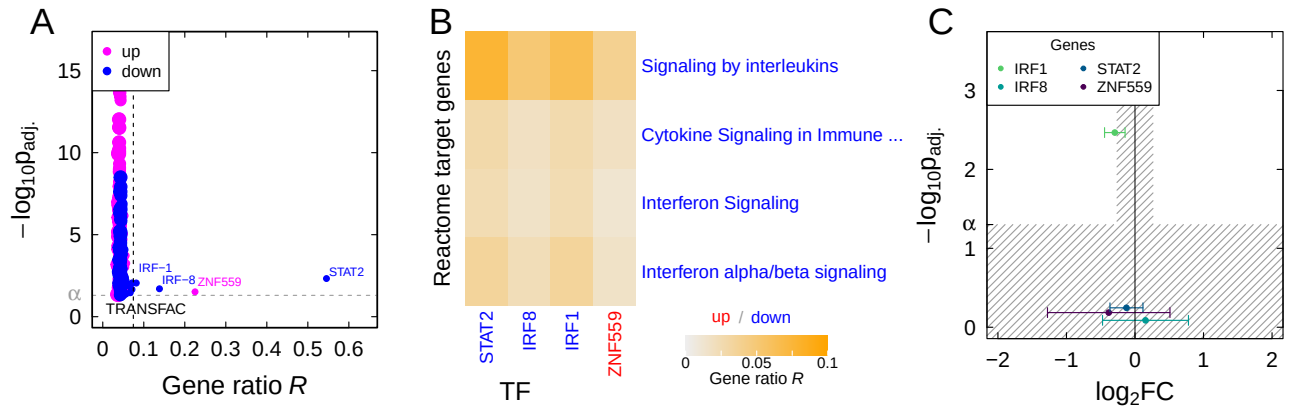

Figure 3: Transcription factors (TF). ***(A)*** TF yield of Reactome query. Vertical dashed line denotes 1 SD above mean *R*. ***(B)*** TFs with TFTG matches in Reactome query pathways. Only pathways with matches are shown. Magenta intensity indicates gene ratio R in the pathways. Red characters denote upregulation, blue downregulation. ***(C)*** TF coding genes. Differential expression of genes coding for TFs. This figure demonstrates that there is hardly any evidence for the enrichment of TFs being due to the differential expression of genes coding for these TFs.

literature that found the CTRA associated with various social adversities, such as 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; S.-H. Lee et al., 2023; Moieni et al., 2015; Snodgrass et al., 2022, 2018, 2019), psychological stress and anxiety (Chiang et al., 2019; Wingo and Gibson, 2015), and racial and sexual discrimination (M. J. Lee et al., 2021; Li et al., 2020; Thames et al., 2019).

The observed enrichment in pre-selected Reactome pathways *Immune System, Cytokine Signaling in Immune system, Signaling by Interleukins*, and *Interferon Signaling* suggests potential long-term effects on physical health, potentially leading to increased susceptibility to infections and other immune-related diseases. The queried overrepresentation of downregulated genes in *Interferon alpha/beta signaling, Interferon Signaling*, and their parent *Cytokine Signaling in Immune system* further supports these findings. In our *a priori* analysis, the *Signaling by Interleukins* pathway demonstrated marked differential expression, supporting our hypothesis that PV induces stress and activates pro-inflammatory mechanisms. This pathway exhibited significant dysregulation with a combination of upregulated and downregulated genes, emphasizing its role in stress-induced inflammatory responses. However, in a separate *exploratory* analysis of over 2,500 other pathways from the entire Reactome database, the pathway did not retain statistical significance. This observation illustrates the limitations of multiple hypothesis testing, where significant findings in specific pathways may be obscured by adjustments for multiple comparisons (see Perneger, 1998). Nonetheless, the consistent differential expression of 24 genes within this pathway remains a critical and relevant discovery, independent of the broader context.

Reactome pathways related to metabolism *(Respiratory electron transport, ATP synthesis by chemiosmotic coupling, Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins*, and *The citric acid (TCA) cycle and respiratory electron transport*) as well as to organelle biogenesis and maintenance (*Cristae formation*, invaginations of the inner mitochondrial membrane that increase surface area for energy production) are central to cellular respiration and energy production in the mitochondria (Hirschenson et al., 2022). The overrepresentation of downregulated genes observed in these pathways points to mitochondrial dysfunction, which can contribute substantially to the aging process and is considered one of the "hallmarks of aging" (López-Otín et al., 2023). It can affect cellular energy availability and promote metabolic symptoms such as fatigue, muscle weakness, unexpected weight gain or loss, changes in skin color, abdominal pain, nausea or vomiting, decreased appetite, developmental problems or metabolic diseases such as diabetes and cognitive decline (Parikh, 2010). These symptoms align closely with those reported by victims (Gini and Pozzoli, 2009, 2013; Hager and Leadbeater, 2016).

The observed overrepresentation of downregulated genes in pathways related to the metabolism of pro-

teins (*SRP-dependent cotranslational protein targeting to membrane, and Eukaryotic Translation Termination*) can lead to translational read-through and thus to misfolded proteins (Karijolich and Yu, 2014), which can accumulate in cells and tissues, leading to cellular stress, dysfunction, and death. They can disrupt normal cellular processes, trigger inflammatory responses, and impair the function of organs and systems contributing to cognitive decline and dementia (Karanth et al., 2020) and the progression of neurodegenerative diseases such as Huntington's, Alzheimer's, and Parkinson's (Ciechanover and Kwon, 2015; Lin and Beal, 2006).

The observed upregulation of NF-κB may trigger the expression of pro-inflammatory processes (Liu et al., 2017; Sakowicz, 2022). This is mostly in line with (Miller et al., 2009), although there was no evidence for enrichment of CREB or GR. In sum, the *a priori* Reactome analysis confirmed overrepresentation in expected immunomodulatory pathways; additionally, *exploratory* analysis suggested the involvement of novel pathways related to metabolism, protein metabolism, and organelle maintenance.

The elevated plasma cytokine levels observed among victims are consistent with mRNA transcription leading to active protein translation. This aligns with studies showing increased cytokine levels in response to psychosocial stress, with potential long-term health effects (Marsland et al., 2017). The elevation of proinflammatory cytokines may contribute to disease symptoms reported in adolescents exposed to PV, including depressive symptoms, fatigue, social withdrawal, and metabolic syndrome (Slavich and Irwin, 2014). Interestingly, the proinflammatory elevation occurred despite evidence of downregulated genes in cytokine signaling pathways. One possible explanation is the presence of firmly established cell dynamics operating independently of current gene expression, highlighting the complexity of the observed immunophenotype.

The TF/TFTG analyses identified four central TFs: STAT2, IRF1, IRF8, and ZFN559. In particular, downregulated TFs STAT2 and IRF1 were associated with TFTG in the downregulated *Signaling by interleukins* and *Interferon signaling* pathways. TF activity was not directly related to the differential expression of the genes encoding them, suggesting that other factors such as miRNA regulation, protein-protein interactions, or post-transcriptional modifications may have influenced their depletion (Arimoto et al., 2018). STAT2 and IRF1 are members of the JAK1/JAK2-STAT1/STAT2/STAT3-IRF1 axis, critical for interferon response genes (Garcia-Diaz et al., 2017). The observed downregulation of STAT2/IRF1 aligns with the observed downregulation of gene expression in the Reactome pathways in victims and may have implications for the modulation of immune, inflammatory, and innate antiviral responses.

We observed stronger evidence of suppressed antiviral functions than of increased inflammation. One possible explanation for this difference may be that victims developed psychological coping strategies or biological mechanisms that mitigate inflammation (i.e., a physiological adaptation) indicative of immune tolerance or exhaustion and uniquely associated with the chronic stress of longstanding PV (Schietinger and Greenberg, 2014). The characteristics of the PV profile suggest a chronic PV phenotype: initial acute phases might have occurred earlier, allowing the molecular system ample time to adapt, leading to a state of altered or dysregulated response rather than an initial response phase. Cells protect themselves from prolonged inflammation through intracellular communication and can automatically reduce inflammation if the inflammatory response persists, such as through the downregulation of the HPA axis (Brendgen et al., 2023; Miller et al., 2011). An alternative explanation is that chronic inflammation levels are generally low in young adulthood and so less prone than the innate antiviral response to stress-related upregulation during this developmental period.

5. Limitations and future work

Data originate from a specialized sample in Zurich, a city known for its high living standards. Thus, results may not be fully generalizable. However, PV still predicted indicators of distress even within this privileged sample. Although the sample size was suitable for analyzing gene signatures and pathways, future work should investigate larger sample sizes to look more closely at smaller gene sets or individual genes (Cole et al., 2003).

Since no self-reported measures of participants' appraisal of their experienced social adversity were available, participants were classified as 'victims' using external criteria by subtracting DB from SE. However, appraisals are stronger predictors of biological impacts than external assessments (Kemeny, 2003; M. J. Lee et al., 2021; Zych et al., 2020b), suggesting our results may underestimate associations involving PV.

The detailed PV profile and IPW addressed typical confounding in observational studies on PV. However, despite a thorough literature review, the propen-

sity score model may still be misspecified, potentially compromising causal inferences. Tools like WGCNA (Langfelder and Horvath, 2008) and MOFA (Pierre-Jean et al., 2020) were inapplicable due to lack of IPW support. Future updates should include options for sample-weighted data, often necessary in observational studies.

Even though we examined a decade-long time series of PV, the limited sample size required using a binary treatment dummy. This prevented analysis of different patterns like early vs. late or chronic vs. acute victimization. Future research should explore these patterns to understand their distinct impacts. Additionally, longitudinal mRNA data and examination of tissue samples, beyond peripheral blood, would provide deeper, possibly causal insights into the molecular changes associated with PV.

6. Conclusions

The present study explored the relationship between a decade of peer victimization (PV) in adolescence and subsequent immune system gene expression, cytokine levels, and cellular dynamics in young adulthood. Utilizing a counterfactual design, we examined mRNA abundance levels, cellular dynamics, and cytokine profiles from peripheral blood. Among victims, results revealed reduced antiviral and increased inflammatory molecular responses, aligning with existing literature on social adversity. Notably, among victims a pro-inflammatory and auto-immune disease-promoting profile was observed as well as signs of mitochondrial dysfunction and a pro-inflammatory cytokine pattern compared to controls. Findings identify key transcription factors that potentially drive the observed gene expression changes, suggesting roles for miRNA activity, protein-protein interactions, and post-transcriptional modification. The results underscore that young adults who experienced PV in adolescence exhibit marked differences in immune system gene regulation, which may negatively impact their future health.

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Conflict of interest

None.

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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Appendix

Table S1: Confounding factors affecting the causal pathway from PV to health-related outcomes, identified through expert knowledge. Variables include predictors of both exposure and outcome (Rubin, 1997) and incorporate interactions and higher order terms (SES^2 and age^2) to account for non-linear influences.

Confounder	Source
ADHD-score, conflict resolution, corporal punishment, isolated in class, locus of control, teacher rated bullying	K. Holt and L. Espelage, 2007; Lereya et al., 2015; Zych et al., 2020a
Adverse family incidents, broken family, conflictual family	Forster et al., 2020; Lereya et al., 2013
Age	Eastman et al., 2018
Aggression, anxiety*	Espelage et al., 2001; Schoeler et al., 2018
Birth complications	DiLalla et al., 2021
Birth rank	Dantchev and Wolke, 2019
Coparenting†	Martínez et al., 2019
Depression*	Penner-Goeke et al., 2023; Rose et al., 2016
Facial emotion recognition‡	Dede et al., 2021
Healthy leisure activities§, body weight (at baseline)	Puhl et al., 2011
Hostile attribution	Perhamus et al., 2022
Immigration, German language native	Qin et al., 2008
Negative behavior in childhood§, self-control	Cook et al., 2010; Jennings et al., 2011; Robson et al., 2020; Zych et al., 2020a
Number of siblings	Karišik, 2019; Wu et al., 2023
Sex	Casper and Card, 2017; Schoeler et al., 2018; White and Kaffman, 2020
Socio-economic status (SES)¶	Delprato et al., 2017; Shanahan et al., 2022; Tippett and Wolke, 2014; Wong and Schonlau, 2013
Violent peers	Duffy and Nesdale, 2009

*For anxiety and depression, PRS were used, in addition to a score for anxiety. †Coparenting score was derived from the extent to which father and mother agreed in their responses to survey questions on parenting. ‡For facial emotion recognition accuracy a score was created out of correct answers to Assessing Children's Emotional Skills (ACES; Schultz et al., 2004) instrument used in z-proso. §Healthy leisure and negative behavior scores were created from a score of corresponding z-proso questions. ¶Socio-economic status (SES) was created from parents' income, education and job prestige (ISEI). References of other scales and instruments used in z-proso can be found in the handbook (z-proso Project Team, 2024).

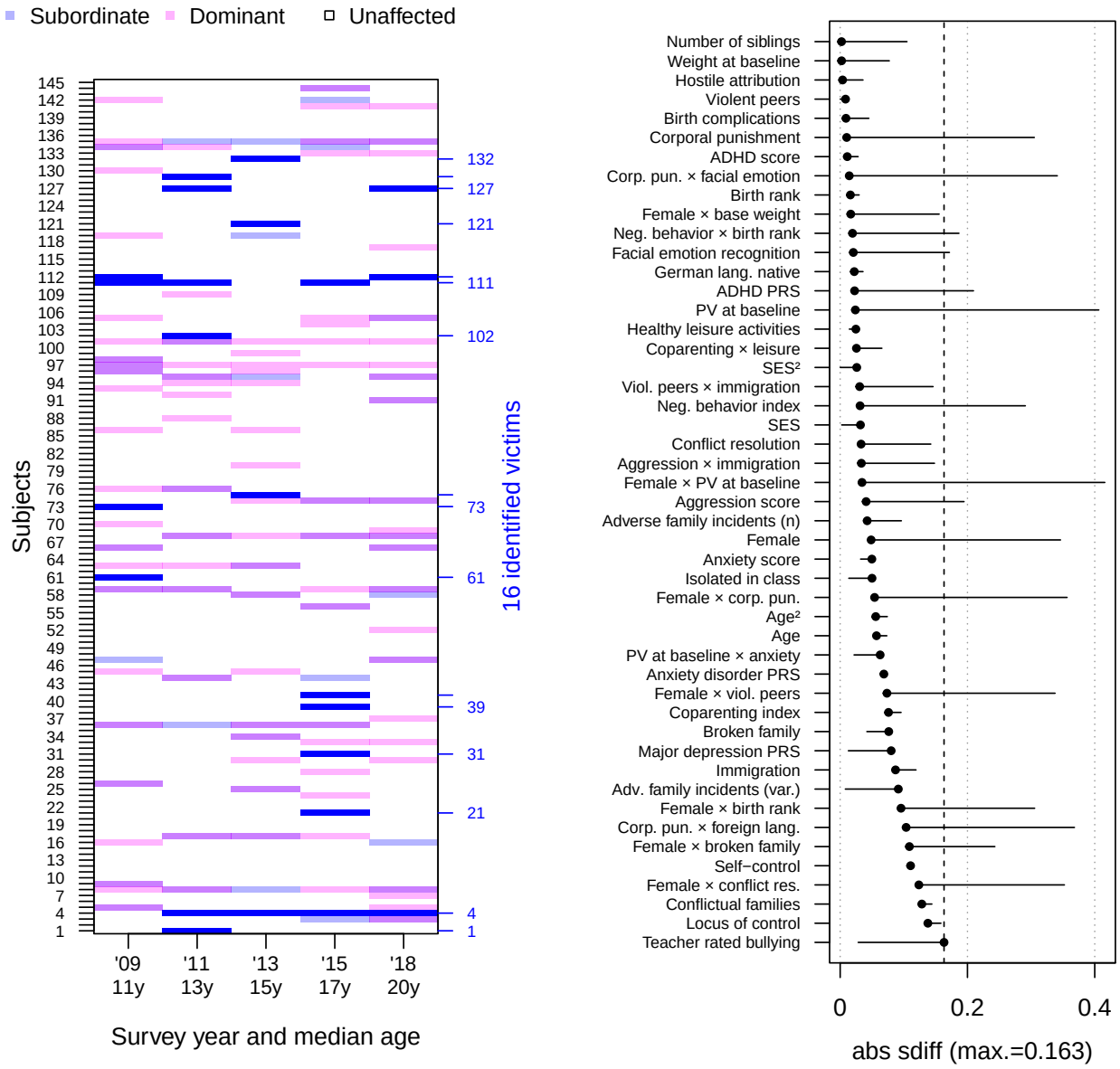

Figure S1: Peer victimization. (A) Prevalence of social peer adversity. The figure shows subordinate experiences and dominant behavior above 90% quantiles for each survey year. As the highest deciles, subjects above these thresholds are considered to be severely affected from the respective phenomenon. 16 individuals (7 male and 9 female) subjected to only subordinate experiences are identified as peer-victimized at the time of our study at around age 22. (B) Balancing after IP-weighting. The lollipop-plot shows absolute standardized differences between treated (PV) and control after IPW.

Table S2: Cytokines A—concentration profiles base model.

	β	SE	t	p	$p_{\text{adj.}}$	2.5%	97.5%
Pro-inflammatory:							
CCL4	0.650	0.144	4.512	<0.0001	0.0001	0.364	0.936
CCL5	0.609	0.198	3.077	0.0028	0.0045	0.216	1.002
CCL11	0.887	0.173	5.117	<0.0001	<0.0001	0.542	1.231
CCL27	0.689	0.161	4.267	<0.0001	0.0002	0.368	1.010
CXCL9	0.050	0.235	0.213	0.8319	0.8388	−0.418	0.518
CXCL10	0.276	0.242	1.139	0.2576	0.2898	−0.205	0.757
IL-9	0.490	0.131	3.745	0.0003	0.0007	0.230	0.750
IL-16	0.696	0.263	2.645	0.0096	0.0124	0.173	1.219
LTA	0.911	0.208	4.387	<0.0001	0.0001	0.498	1.323
TNF	0.544	0.183	2.978	0.0037	0.0056	0.181	0.907
Anti-inflammatory:							
SF	0.583	0.156	3.748	0.0003	0.0007	0.274	0.892
Pleiotropic:							
CSF1	0.671	0.136	4.918	<0.0001	<0.0001	0.400	0.942
SDF-1α	0.604	0.195	3.093	0.0026	0.0045	0.216	0.992
Other:							
PDGFB	0.780	0.208	3.745	0.0003	0.0007	0.366	1.194
SCF	0.724	0.195	3.718	0.0003	0.0007	0.337	1.110
SCGFβ	−1.429	0.726	−1.969	0.0520	0.0624	−2.871	0.013

Comparative analysis of cytokine levels to characterize the immune patterns in the investigated biological samples.

Table S3: Cytokines B—concentration profiles LKC controlled model.

	β	SE	t	p	$p_{\text{adj.}}$	2.5%	97.5%
Pro-inflammatory:							
CCL4	0.519	0.185	2.810	0.0063	0.0161	0.151	0.888
CCL5	0.693	0.241	2.880	0.0051	0.0152	0.215	1.171
CCL11	0.870	0.238	3.650	0.0005	0.0027	0.396	1.343
CCL27	0.438	0.205	2.140	0.0354	0.0637	0.031	0.845
CXCL9	0.260	0.344	0.757	0.4510	0.4780	−0.424	0.944
CXCL10	0.341	0.304	1.120	0.2660	0.2990	−0.264	0.945
IL-9	0.372	0.170	2.190	0.0311	0.0623	0.035	0.710
IL-16	0.995	0.249	3.990	0.0001	0.0022	0.500	1.490
LTA	0.629	0.237	2.650	0.0096	0.0216	0.157	1.101
TNF	0.326	0.236	1.380	0.1710	0.2060	−0.144	0.796
Anti-inflammatory:							
SF	0.613	0.203	3.120	0.0033	0.0150	0.210	1.017
Pleiotropic:							
CSF	0.354	0.195	1.820	0.0724	0.1000	−0.033	0.742
SDF-1α	0.682	0.234	2.920	0.0046	0.0152	0.217	1.148
Other:							
PDGFB	0.379	0.207	1.830	0.0714	0.1000	−0.034	0.791
SCF	0.956	0.249	3.840	0.0002	0.0022	0.460	1.451
SCGFβ	−1.540	0.735	−2.090	0.0398	0.0651	−2.998	−0.073

Comparative analysis of cytokine levels to characterize the immune patterns in the investigated biological samples. With included leukocyte coding genes in the model.