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Backtracing persistent biomarker shifts to the age of onset: A novel procedure applied to men's and women's white blood cell counts in post-traumatic stress disorder

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ABSTRACT

Background: Traumatic experiences tend to be preserved in altered biomarker profiles. These profiles can be traced back from cross-sectional data regarding the age of exposure. Consequently, the change across developmental stages, e.g. from childhood to adulthood, can also be reconstructed. This study introduces a backtrace procedure that is illustrated using white blood cell (WBC) counts in full / partial post-traumatic stress disorder (PTSD). The procedure was applied separately on men's and women's data to provide a replication of the analysis based on different subsamples.

Methods: The analysis was carried out with data from the CoLaus|PsyCoLaus study (N = 5111, 2370 men and 2741 women, age range 35–88 years). It was restricted to traumatic experiences that occurred until the age of 35, i.e., the lower age limit of the sample. The WBC counts from up to two assessments were standardized, pooled and assigned to the reported age of trauma exposure. This resulted in age series for each marker, whereas the reference values were based on subjects who did not experience any trauma exposure. The backtrace procedure ascertained the peaks and troughs of the age series and determined the best-fitting critical age range surrounding each peak or trough based on the best p-value from simple t-tests.

Results: In CoLaus|PsyCoLaus, 750 participants reported trauma exposure until the age of 35, and 86 (out of 329) men and 187 (out of 421) women thereof were coded with a full or partial PTSD. Full / partial PTSD after trauma exposure in childhood was characterized by increased WBC counts (lymphocytes, eosinophils – in women also neutrophils). This pattern was partly retained during adolescence, in men due to eosinophils counts and in women due to lymphocyte counts. For exposure in young adulthood, the deviations were in the negative direction – in men with decreased basophils, in women with decreased lymphocytes and monocytes.

Conclusions: Summarizing, the backtrace approach revealed WBC profiles in PTSD that were specific to particular developmental age stages. The strongest persistent upregulation of the immune system related to trauma exposure was traceable to childhood / early adolescence both in men and in women. Further research will show which biomarkers are similarly suitable for backtracing as WBC counts. As in PTSD, the backtrace approach could also be applied to identifying persistent biomarker profiles in other mental disorders, as well as autoimmune and other chronic diseases.

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Introduction

Post-traumatic stress disorder (PTSD) is a mental disorder that can be triggered by exposure to a traumatic or stressful event. Biomarker research in PTSD has two typical methodological scenarios. One of them aims at timely measurement after exposure to a traumatic event, either supplemented or not by prospective measurements. The other scenario – delayed measurement – focusses on persistent shifts in biomarker levels, either within a chronic posttraumatic condition or based on the idea of "frozen markers". The latter assumes that shifted markers are detectable even after the remission of post-traumatic symptoms. This reasoning can be broadly extended to other mental disorders and their onset. However, methodological approaches that take advantage of the wealth of "frozen markers" data are needed in PTSD research as in other research domains. In the following, we present a novel approach, the backtrace procedure.

In PTSD, the "frozen markers" concept implies that traumatic experiences are preserved in altered biomarker profiles that could be reconstructed years or even decades after trauma-inducing exposure. A preliminary impression of heterogeneous "freezing" outcomes emerges from the study of Vidovic et al. [1], who examined a series of markers in combat veterans with PTSD 6 and 11.5 years after the traumatic experience. While prolactin and overall lymphocyte counts remained at increased levels at the second measurement, other markers (cortisol levels, natural killer cell cytotoxicity, glucocorticoid receptor expression) returned to levels similar to those measured in controls. In other studies, heart rate and blood pressure have been documented to remain shifted across time / age [2].

From a methodological perspective, the "frozen markers" concept opens up interesting perspectives for retrospective analyses based on cross-sectional data. First of all, it helps to overcome the typical limitation of longitudinal studies to short prospective observation periods and / or to specific age groups. In addition, the analysis of "frozen markers" in large cross-sectional databases allows the assessment of long-range changes between generations and, more importantly, age-of-onset-dependent processes. With the latter, the study of developmental stages [3] also becomes an attainable target.

In this study, a novel methodological procedure was developed to trace persistently shifted markers in cross-sectional data back to the age of onset. The backtrace procedure is illustrated by white blood cell (WBC) counts in full / partial PTSD. PTSD was chosen since, as Pitman et al. [4] pointed out, "PTSD is the only major mental disorder for which a cause is considered to be known". An unequivocal exogenous trigger (trauma) and relatively unambiguous information about the age of onset (age of trauma exposure) are crucial for demonstrating the procedure. Moreover, the procedure was applied separately on men's and women's data to provide a replication of the analysis based on different subsamples, which was preferred over a reliability procedure such as split-half. The database came from CoLaus|PsyCoLaus, a large epidemiological study in Switzerland.

Material and methods

The CoLaus|PsyCoLaus cohort

Data used for the current study were derived from the population-based longitudinal study CoLaus|PsyCoLaus [5,6]. The CoLaus|PsyCoLaus study was designed to explore the associations between mental disorders and cardiovascular diseases. The cohort was randomly selected from the 35- to 75-year-old residents of the city of Lausanne (Switzerland) from 2003 to 2006, according to the civil register. The initial cohort included 6734 people. Fig. 1 displays the overall workflow of the sampling process. The first follow-up (FU1) was carried out between 2009–2013 and the second follow-up (FU2) was conducted between 2014−2018.

At baseline, the psychiatric evaluation was restricted to the 35- to 66-year-old participants in the physical exam, resulting in a 67 % participation within this age range (N = 3719). From FU1 on, all individuals from the initial cohort were eligible for psychiatric evaluation. The cohort used in the present paper is comprised of the first assessment of all 5111 people who agreed to at least one psychiatric evaluation (3719 at baseline, 1155 at FU1, 237 at FU2).

Instruments

The French version [7] of the semi-structured Diagnostic Interview for Genetic Studies (DIGS) [8], was used for collecting diagnostic information on mental disorders. The assessments covered a broad spectrum of the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV Axis I criteria, as well as the course and chronology of comorbid features [7]. The French version of the DIGS revealed excellent inter-rater reliability in terms of kappa and Yule's Y coefficients for major mood and psychotic

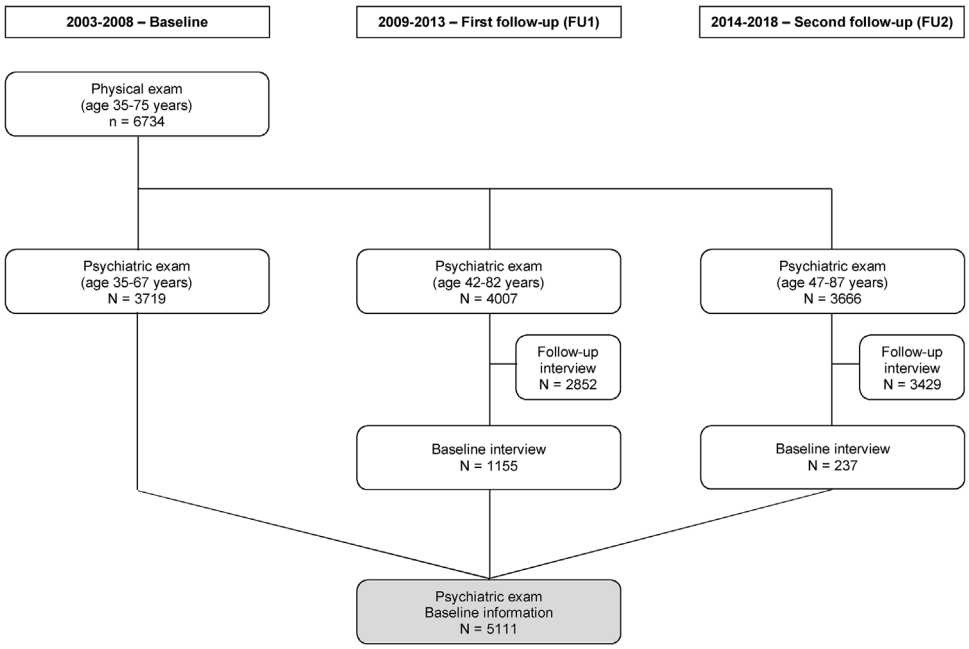

Fig. 1. The overall workflow of the CoLaus|PsyCoLaus sampling.

disorders as well as for substance use and antisocial personality disorders, whereas the 6-week test-retest reliability was slightly lower [7,9]. The DIGS was completed with the PTSD and the generalized anxiety disorder (GAD) sections of the French version [10] of the Schedule for Affective Disorders and Schizophrenia - Lifetime and Anxiety disorder version (SADS-LA) [11], and the brief phobia chapter of the DIGS was replaced by the corresponding, more extensive chapters of the SADS-LA which elicited detailed information relating to the DSM-IV criteria for agoraphobia with or without panic attacks, social and specific phobias. These anxiety disorders also revealed satisfactory test-retest reliability [10,12].

Information regarding the nature of potentially traumatic events as well as subsequent PTSD symptoms was extracted from the PTSD section of the interview. Five types of traumatic events were assessed based on the SADS-LA: 1) accident or severe catastrophe, 2) active combat or war, 3) witnessing trauma to others, and 4) violent crime, and 5) sexual trauma. Sexual trauma including rape, sexual abuse and exhibitionism was evaluated and coded separately. If a subject reported several events, he / she was asked to identify the most upsetting one and to indicate the age of first exposure to this event. Age of first sexual abuse was asked separately. All associations with single traumatic events are in relation to this specific event. The test-retest reliability for the PTSD diagnosis was estimated at Yule = 0.69 from a sample of 176 psychiatric patients [13].

In this analysis, PTSD was pooled with partial PTSD in order to achieve subsamples of reasonable size. Partial PTSD was defined according to Breslau et al. [14] by the presence of at least one symptom in each of the PTSD criteria B (re-experience), C (avoidance of stimuli), D (increased arousal) and the duration of at least one month.

Morning venous blood samples served to assess WBCs apart from other markers (inflammatory, cardio-metabolic; for more details see [5]). EDTA blood was used to assess WBC counts. WBC counts were obtained on a Sysmex XE-2100 and XE-5000 apparatus (Sysmex, Horgen, Switzerland) [15] using fluorescent flow cytometry with light scattering as a principle for differential and total leukocyte count. Neutrophils, lymphocytes, monocytes, eosinophils and basophils were computed, both as absolute values and as proportions of the total WBC count, and results were outputted directly from the apparatus.

WBCs were assessed twice, that is, at the follow-ups to CoLaus|PsyCoLaus. Neutrophils, lymphocytes, monocytes, eosinophils and basophils were computed, both as absolute values and as proportions of the total WBC count. In the analyses, we considered both parameters to see the full picture. Using only proportions or combined parameters such as the neutrophil-to-lymphocyte ratio [16] limits the range of relations that can be detected in the analysis (see, for example, the increased levels of neutrophils and lymphocytes in women as reported in the Results section).

All data preparation steps and all subsequent analyses were conducted separately for men and women. The Kolmogorov-Smirnov and the Shapiro-Wilk test served to check for the normal distribution of the WBC variables. If appropriate, the variables were smoothed, i.e., transformed by log or square root. Values were considered as outliers if above / below 3 standard deviations (SD) and were set to missing. In the next step, the variables were submitted to z-transformation. This enabled the averaging of the variables if data from two measurements were available. Finally, the variables were age-standardized using a linear or quadratic regression, if appropriate, in order to exclude bias related to different age patterns of WBC variables (referring to the age at measurement).

The analyses were limited to trauma exposures that occurred up to the age of 35. This is at the same time the youngest age of the participants at the baseline examination (see above).

The backtrace procedure to determine peaks and troughs and related critical age periods

The different analysis steps of the procedure are shown in a flow chart (Fig. 2). After pre-processing the data (step 1, see data preparation above), each WBC variable was first analyzed in the conventional way – *t*-test based on overall data – to provide a benchmark for the results from the backtrace procedure.

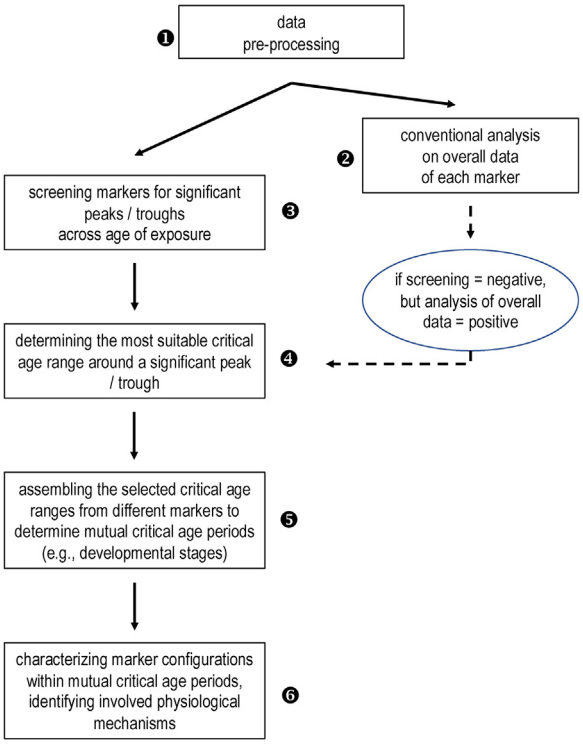

Fig. 2. Flow chart of the analysis steps.

The basic idea behind the procedure is, in brief, to trace the values for a marker back to the age of trauma exposure. Thus, instead of an overall mean as in step 2, we obtain a curve representing the fluctuations in the marker back to age of exposure. From this curve, we want to determine whether the fluctuations comprise periods of significantly increased (or decreased) marker values. Therefore, we first identify the peak and trough values of the curve, together with the age of exposure (step 3). If a peak or a trough significantly deviates from the reference value, we next take aim at the "critical" age range during which the deviation is in effect (step 4). A more detailed description of steps 3–4 follows below. The "critical" age ranges of several markers can be assembled in a descriptive graphic analysis (step 5) and can be used in any subsequent analyses (step 6).

In detail, steps 3 and 4 each comprise several intermediate steps. In the current application, the traced back WBC values were averaged in step 3 and displayed by age of exposure (based on yearly values). Thus, the resulting curve in fact represented a time series with age as the x-axis. Because of the strong fluctuations of the yearly values, the curve was smoothed by applying moving averages, i.e., by grouping the data into n-year age windows (also known as the sliding window approach). Peak and trough values were determined from the smoothed curves. They were compared with the reference value, which basically represents the overall mean level of the same marker in subjects who did not experience any trauma – here calculated after transformation and standardization (see above) and therefore close to 0.

A WBC variable was selected for further analysis in step 4 in two instances:

- if a peak or trough (or both) returned significant deviations from the reference value as indicated by t-tests;
- if the overall *t*-test in step 2 had yielded a significant result, for example due to a substantial shift of WBC levels without marked fluctuations across age.

In both instances, the peak (and / or trough) was chosen as the starting point for step 4 of the procedure.

The purpose of step 4 was to determine the best-fitting critical age range surrounding each peak or trough. That is, the step 3 analysis was extended by letting the age windows flexibly vary around a selected peak / trough. Therefore, instead of fixed intervals such as in the moving average approach, each possible age range around a selected peak (or trough) was now checked by applying t-tests. The best (lowest) p-value from these tests was used as a preliminary indicator of the most suitable critical age range. Exclusion criteria at that step were a small N (< 10) and a short age range (< 5 years), which are assumed to be indicative of outliers.

Steps 3 and 4 were repeated starting with different moving averages: with 3- and 5-year windows. This was necessary since different moving averages can return different peaks (or troughs). In cases of diverging results from different runs, again the one with the best p-value was chosen for further analysis. A more detailed description of the steps 3 and 4 of the backtrace procedure illustrated by an example can be found in the Appendix.

Statistical analysis and programming

In steps 2–4 of the procedure, we applied simple *t*-tests. The results based on the 0.01 p-value served as reference for interpretation. Results based on the 0.05 p-value were also documented and used in a supplementary way for pattern recognition purposes, for example, to visualize critical age periods (step 5). Due to the exploratory nature of this analysis, we explicitly refrained from performing adjustments for multiple testing in analyses of heterogeneous conditions, as in pattern recognition analyses such as LCA and in other exploratory analyses (see also [17]).

Programming and the analyses were carried out with Stata (Version 15); the basic preparation of the data, with SPSS Statistics (Version 23).

Ethics approval

The Institutional Ethics Committee of the University of Lausanne approved the CoLaus|PsyCoLaus study [5,6]. All participants signed a written informed consent form after receiving a detailed description of the goal, procedures and funding of the study.

Results

In CoLaus|PsyCoLaus, 960 (19.0 %) participants reported having experienced a trauma and specified one of the trauma subtypes. Of these, 425 (18.2 %) were male and 535 (19.9 %) were female. Furthermore, 329 men and 421 women were younger than or equal to 35 years at trauma exposure, and 86 men and 187 women thereof were coded with a partial (N = 47 and 87) or full PTSD (N = 39 and 100).

The descriptive parameters of each WBC count per interview in overall data are summarized in Table 1, and the averaged z-standardized values of persons with partial / full PTSD in Table 2. The measures were in the expected range, here exemplified by percentage values of WBC in men and women (Table 1): 54.4–56.9 % and 55.1–56.7 % in neutrophils, 29.8–32.2 % and 31.3–33.0 % in lymphocytes, 9.2 % and 8.2 % in monocytes, 3.1–3.2 % and 2.7 % in eosinophils, 0.6–0.8 % in basophils.

As Table 2 additionally shows, after pre-processing of the data, the comparisons with subjects without trauma exposure yielded significant *t*-test results in neutrophils (decreased levels of counts and proportions) counterbalanced by lymphocytes (increased proportions). In women, leukocyte together with neutrophil levels were increased, whereas monocyte proportions were decreased.

After the analyses were differentiated by age of trauma exposure with the backtrace procedure, distinctly more significant results emerged related to specific critical age ranges (Table 3). In some instances, non-significant associations from the analysis with overall data even switched to strongly significant ones. Moreover, in one instance (lymphocyte

Table 1
Descriptives of white blood cell counts in men and women, by measurement.

	1st follow-up measurement			2nd follow-up measurement			units	data transformation *
	N	mean	SE	N	mean	SE		
men**								
leukocytes	1349	6.43	0.0556	1692	6.20	0.0442	G/l	log
basophils	1347	0.034	0.0006	1675	0.046	0.0007	G/l	square root
basophils %	1347	0.0056	0.0001	1675	0.0076	0.0001	%	square root
eosinophils	1348	0.20	0.0034	1675	0.190	0.0030	G/l	square root
eosinophils %	1348	0.032	0.0005	1675	0.031	0.0004	%	square root
lymphocytes	1347	2.018	0.0195	1675	1.810	0.0200	G/l	square root
lymphocytes %	1347	0.322	0.0022	1675	0.298	0.0020	%	–
monocytes	1347	0.586	0.0053	1675	0.5603	0.0044	G/l	square root
monocytes %	1347	0.092	0.0007	1675	0.0917	0.0005	%	square root
neutrophils	1347	3.541	0.0377	1675	3.584	0.0335	G/l	square root
neutrophils %	1347	0.544	0.0024	1675	0.569	0.0022	%	–
women***								
leukocytes	1614	6.190	0.0518	2101	6.097	0.0495	G/l	log
basophils	1613	0.035	0.0005	2063	0.046	0.0007	G/l	square root
basophils %	1613	0.006	0.0001	2063	0.008	0.0001	%	square root
eosinophils	1613	0.166	0.0027	2062	0.164	0.0027	G/l	square root
eosinophils %	1613	0.027	0.0004	2062	0.027	0.0004	%	square root
lymphocytes	1611	1.983	0.0147	2062	1.875	0.0284	G/l	square root
lymphocytes %	1611	0.330	0.0019	2062	0.313	0.0018	%	–
monocytes	1611	0.496	0.0039	2062	0.491	0.0038	G/l	square root
monocytes %	1611	0.082	0.0004	2062	0.082	0.0004	%	square root
neutrophils	1611	3.452	0.0343	2062	3.493	0.0300	G/l	square root
neutrophils %	1611	0.551	0.0021	2062	0.567	0.0019	%	–

Notes:
* similarly applied to values from both measurements.
** n with missing WBC values: 1021–1023 and 678–695.
*** n with missing WBC values: 1127–1130 and 640–679.

Table 2
z-standardized white blood cell counts in men and women with partial / full PTSD; p-values refer to t-tests against subjects without trauma exposure.

	N	mean	SE	p-value
men*				
leukocytes	91	−.1178	.09073	.219
basophils	91	−.1332	.08322	.114
basophils %	91	−.0951	.08522	.258
eosinophils	91	.0876	.10167	.328
eosinophils %	91	.1319	.09974	.152
lymphocytes	91	.0983	.09302	.307
lymphocytes %	91	.2406	.09340	.010
monocytes	91	−.0783	.09553	.355
monocytes %	91	.0335	.09262	.776
neutrophils	91	−.2080	.07722	.023
neutrophils %	91	−.2602	.09375	.005
women**				
leukocytes	195	.2003	.06179	.000
basophils	194	.0694	.05906	.189
basophils %	193	.0044	.05630	.822
eosinophils	192	.0869	.06848	.140
eosinophils %	194	.0479	.06748	.443
lymphocytes	194	.0803	.05946	.114
lymphocytes %	193	−.0867	.06465	.215
monocytes	193	.0603	.06373	.323
monocytes %	191	−.1332	.05721	.029
neutrophils	193	.1840	.06340	.002
neutrophils %	193	.1190	.06299	.070

Notes:
* n with missing WBC values (no measurement at all): 19.
** n with missing WBC values (no measurement at all): 37–41.

Table 3
p-values of t-tests for overall and age-range specific white blood cell count data, tests against subjects without trauma exposure.

	overall	specific age ranges			
	p-value	p-value	above ref.	below ref.	n
men					
leukocytes	.219				
basophils [3]	.114	.011		21–33	29
basophils % [3]	.258	.014		22–33	27
eosinophils [3]	.328	.018	9–21		35
eosinophils % [35]	.152	.008	9–21		35
lymphocytes [35]	.307	.002	8–13		17
lymphocytes % [3<5]	.010	.003	8–13		17
monocytes	.355				
monocytes %	.776				
neutrophils [35]	.023	.042		13–35	56
neutrophils % [3<5]	.005	.003		8–13	17
women					
leukocytes [3]	.000	.000	4–14		74
basophils	.189				
basophils %	.822				
eosinophils [3]	.140	.010	6–27		110
eosinophils % [3]	.443	.007	21–27		25
lymphocytes [35]	.114	.000	4–21		104
		.024		22–35	48
lymphocytes % [35]	.215	.024		22–35	48
monocytes [35]	.323	.012		23–27	18
monocytes % [35]	.029	.005		19–28	39
neutrophils [35]	.002	.000	5–13		63
neutrophils % [35]	.070	.037	26–35		35

Notes:
3 selection of the critical age range based on 3-year moving average.
35 selection of the critical age range based on equal 3-year and 5-year moving average.
3 < 5 selection of the critical age range based on 5-year over 3-year moving average due to lower p-value.

counts in women) both positive and negative associations were apparent during subsequent critical age ranges of trauma exposure. To facilitate comparison of the results, the significant age of exposure snippets of all WBC variables were plotted in Fig. 3 (a: men and b: women).

In men, eosinophil and lymphocyte counts remained persistently increased for years or decades when the traumatic experience occurred in childhood, both in terms of absolute values and proportions. The neutrophil proportions counterbalanced these shifts. When the traumatic experience occurred in adolescence, eosinophil levels remained persistently high, counterbalanced by decreased neutrophil counts. In adulthood, the latter were accompanied by decreased basophil counts and proportions.

In women, all main WBC, i.e., lymphocytes, eosinophils and neutrophils – and thus the overall leukocyte counts – showed persistently increased levels for trauma in childhood. Lymphocytes and eosinophils exhibited increased levels for trauma in adolescence, the latter also for trauma in young adulthood. Here, in women's twenties, decreased levels of monocytes and lymphocytes (both in terms of absolute levels and proportions) were apparent. In their thirties, decreased levels of lymphocytes (proportions) were counterbalanced by neutrophils (proportions).

Discussion

This study examined WBC count levels related to age of exposure to trauma in PTSD with a novel procedure based on cross-sectional data. The results suggest that WBC counts are among those markers that become shifted due to trauma exposure and retain increased / decreased levels across the life-span. It has been shown that the total WBC count reflects the severity of PTSD over one or several years [18]. This study showed that shifted levels can be identified even decades later. In both men and women, three similar configurations become apparent through the backtrace procedure: a strong immune response to trauma exposure in childhood, an attenuated response in adolescence and a weaker, partly inverse response in adulthood.

In subjects who experienced traumatic events during childhood and early adolescence, the immune system response resulting in partial / full PTSD was characterized by persistently increased WBC counts: lymphocytes, eosinophils – in women also neutrophils. The latter detail is particularly revealing, since lymphocytes and neutrophils often show a complementary relation in terms of proportions (see also the configuration in men). It can be assumed that the trauma outcome is more severe if the levels of several WBC groups are increased. Parenthetically, the stronger (and longer) involvement of WBC in women adds a new interpretation for why women experience more severe outcomes than men after trauma exposure, even if the trauma type is the same [19]. Overall, the WBC response to traumatic events resembled that to serious infectious challenges [20,21].

In young adulthood, this strong response smoothed out and was replaced by suppressed WBC levels: neutrophils and basophils in men, lymphocytes and monocytes in women. This emerging pattern possibly reflects a response of the WBC to an upregulation of the hypothalamic–pituitary–adrenal axis that is similar to leukopenia in hypercortisolism [22]. This interpretation remains to be corroborated by further research.

In the PTSD research literature, the most frequently reported deviation of WBC counts relates to increased lymphocyte levels and sometimes neutrophil or total leukocyte levels [23,24]. The assessments mostly derive from studies on veterans [1,25,26]. They can be time-lagged by up to 20 years [27,28], thus providing a preliminary template for the backtrace approach. In contrast to lymphocytes, the relationship between trauma exposure and eosinophils [29] and related conditions such as seasonal allergies and atopic diseases [30,31] has gained less attention. Actually, studies in the aftermath of the 9/11 tragedy showed that PTSD predicts asthma incidence [32].

To summarize the PTSD-relevant results, this study showed that the WBC-related part of the immune response after trauma exposure must be more complex than earlier studies with limited samples have reported, more multifarious in women than in men, and stronger and more

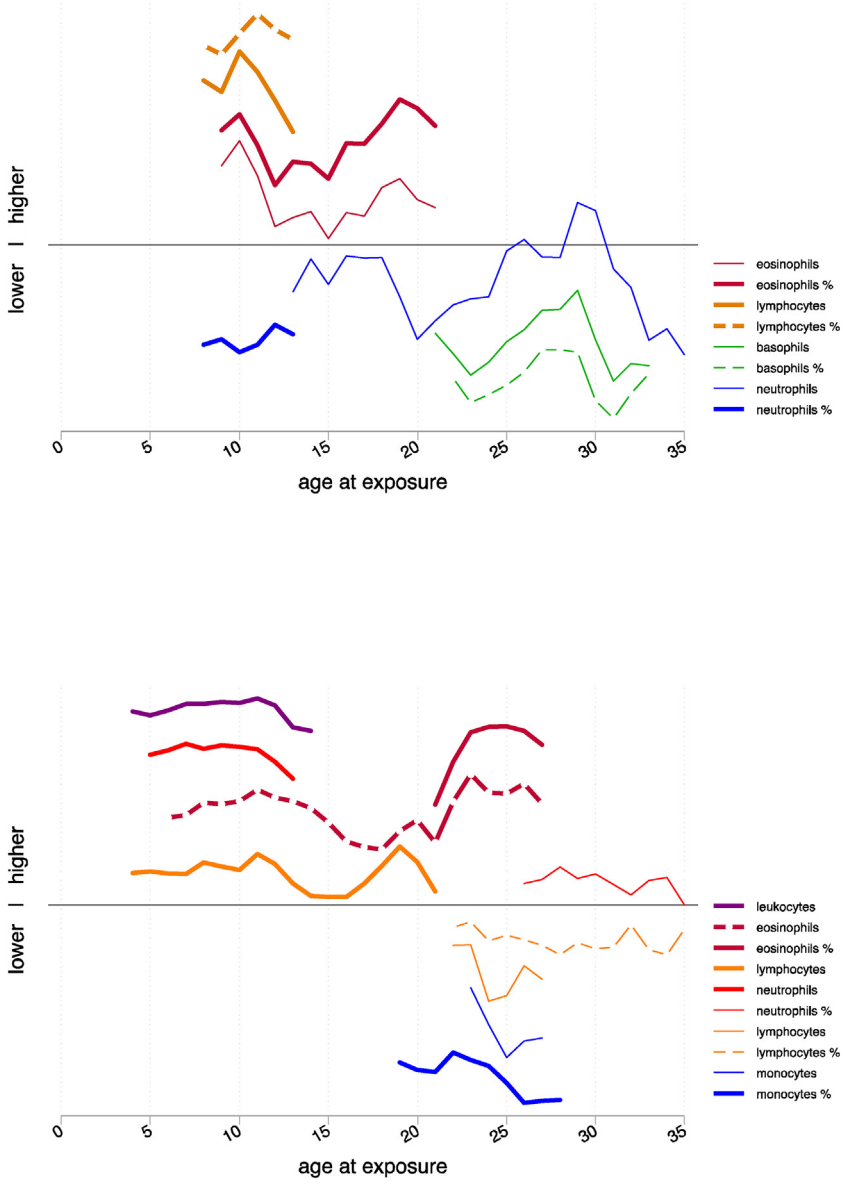

Fig. 3. Shifted white blood cell counts and proportions in partial / full PTSD across the age of trauma exposure in men (a) and women (b).
Notes: Bold lines denote 0.01- significance level, thin lines the 0.05 level. The y axis only contains the information as to whether an age snippet has a significantly lower or higher level than the reference value. The snippets, since derived from z-standardized values, were sorted out in order to facilitate the interpretation of the results. Their relative position above or below the reference value, respectively, is arbitrary.

persistent in younger developmental stages. In terms of WBC counts, PTSD in childhood and PTSD in adulthood represent different disorders despite being classified in the same way by symptoms, duration, burden, etc.

Interpretation variants for backtraced biomarkers

So far, we have adapted the most natural interpretation, namely that trauma experiences lead to physiological up- or downregulations [23]. Some of these changes might be transient and disappear (e.g., cortisol levels, natural killer cell cytotoxicity, glucocorticoid receptor expression [1]), while others such as the WBC counts in this study are presumed to "freeze", persist for a long time and also be measurable later in life. In the current context of this study, we refrain from specifying the causal implications: Do the up- or downregulations of WBC contribute to the development of severe symptoms and finally of PTSD? Or do they passively reflect more relevant up- or downregulations that were not investigated in the current analysis?

However, there are alternative interpretation options to be considered even on a formal methodological level. The first one suggests that the trauma experience interacts with a biomarker level at any specific stage of development by interrupting its successive change. This could result either in delaying developmental processes or simply in freezing current system states. In both instances, i.e., interrupting change or freezing, the marker levels, as measured years later, would systematically remain below or above the normal age-specific levels at the time of measurement. The latter notion might be combined with the hypothesis that more severe outcomes after trauma exposure reflect pre-existing high / low marker levels, e.g. a pre-existing pro-inflammatory state [33]. However, in view of marker shifts that also occur in less severe outcomes, this hypothesis holds little promise.

Another interpretation option brings secondary processes into focus. Here, the shifted marker levels are comprehensible as physiological

aftereffects of PTSD [34] or even as proxies for remission mechanisms. It is also imaginable that they increase / decrease in the course of time. Secondary processes can be expected to be more generalizing than processes directly related to trauma exposure. They can be assumed to consistently represent the severity of PTSD across different outcomes and to preferably cover extended age ranges. This cannot be definitively excluded in any biomarker series that is censored (limited) by the upper age limit in the analysis.

Studies on links between biomarkers and mental disorders have documented bidirectional relations between inflammatory markers and anxiety disorders [35] or between hypotension and affective disorders [36–38]. Thus, it seems wise to explore all options mentioned above in order to interpret the lasting marker shifts. Where developmental stages are reflected in the results through limited age ranges, attention is mainly pulled towards the first option (trauma exposure –> biomarker shifts –> PTSD). In censored markers, the third option (trauma exposure –> PTSD –> biomarker shifts) also deserves particular attention.

Methodological implications

The backtrace procedure allows the study of age-of-onset-dependent processes based on cross-sectional data. This opens new perspectives for large cross-sectional studies if, as is mostly the case, large longitudinal surveys covering long periods are lacking.

The particular advantage of the backtrace procedure is at the same time a major source of limitations. Markers that are only temporarily shifted [39] cannot be determined by this approach. Also, the categorization of markers into primary or secondary processes (see above) is not straightforward. Future research will show how chronic / recovered PTSD [40] is reflected in persistently shifted markers depending on onset across different developmental stages as well as which comorbidity patterns are linked to the different combinations.

The backtrace procedure is not limited to PTSD, but can be applied to other mental disorders as well as to somatic conditions such as chronic inflammatory, autoimmune and atopic diseases. PTSD was particularly suited for developing such a procedure, since it comes with an exogenous trigger (i.e., trauma exposure) and offers the full range of outcomes (no PTS symptoms, PTS symptoms, diagnosis). In most mental disorders and chronic inflammatory / autoimmune diseases, the onset triggers are not known, and the analysis will be limited to symptom and diagnosis level outcomes.

Apart from these practical issues there are more basic ones. The backtrace procedure is a tool for exploring heterogeneity as is latent class analysis and other pattern-recognition approaches typically implemented by person-centered models [41–44]. Although here the focus was solely on WBC, it has become clear that different mechanisms contribute to the disorder labeled as PTSD. Including further markers will extend the range of mechanisms involved even more. Furthermore, specific designs for heterogeneity-targeting research are still underdeveloped and underused.

Dealing with heterogeneity and complexity carries with it not only conceptual but also statistical challenges. Regarding inferential statistics, this study thwarted the currently popular notion that more rigid p-values would generally improve research quality [45]. The backtrace procedure suggested that even the "soft" 0.05-p-value norms turn out to be inferior when applied to a heterogeneous target such as PTSD. Many associations in PTSD that deserve a second glance became apparent only after a differentiation along developmental stages had been introduced. Rigidly introduced p-values provide no support in anticipating necessary differentiation steps in complex disorders.

Strengths and weaknesses of this study

The big sample of the CoLaus|PsyCoLaus survey and the wealth of data on somatic and psychiatric conditions, including biomarker data, is a rich source for pattern recognition analyses. Nevertheless, if the subgroups in the analyses became small, the CoLaus|PsyCoLaus sample turned out to be limited. This occurred despite using moving averages and grouping in order to smooth the data (see, for example, results related to different outcomes in adulthood). Clearly, the backtrace procedure relies on large case numbers since it differentiates the cases by (exposure or onset) age years. To reach satisfying case numbers for the present analysis, data from full and partial PTSD were pooled together. This might have smoothed the outcomes to some extent.

The PTSD questionnaire section in CoLaus|PsyCoLaus carries the limitation that it is focused on the most severe traumatic event. The only exception is sexual abuse, which was asked about separately. Therefore, how previous or subsequent traumatic events interfered with the results [46] could not be controlled for in this analysis. The PTSD questionnaire section also did not allow conclusions about trauma exposures in infancy (see for example [47]). Due to limited recall of events occurring before the age of three [48], events reported from this age period or "as early as I can remember" were randomly assigned to age 3–5 years. Based on the instrument, upon which the PTSD questionnaire section of CoLaus|PsyCoLaus was based (the SADS-LA), no more than five types of trauma exposure were included.

An important advantage of the CoLaus|PsyCoLaus study compared to most other studies is the multiple assessment of markers. The poor inter-correlations between neighbor measurements of the same marker illustrate an enormous amount of noise in the biomarker data. In this study with 5-year lags between measurements, they were in the range of 0.45−0.75 in WBC counts.

This study shares further common limitations of studies based on self-reporting data. Due to the recall bias known as a telescoping effect [49] – a remote onset age is typically pulled forward on the time scale by up to 3 years – the age of exposure and, accordingly, the developmental stages might occur slightly earlier than indicated. In addition, round numbers were more frequently reported than others.

Conclusions

Many biomarker shifts after trauma exposure such as those of WBC counts are retained across the life-span in persons with PTSD. Their profiles can be reconstructed by tracing back marker values to the age of exposure. Together with the marker profiles, different etiopathogenetic mechanisms become visible. In this study, WBC-related mechanisms in PTSD were shown to depend on developmental stage, thus contributing to the heterogeneity of trauma outcomes. The backtrace procedure presented in this study provides the key to a better understanding of this heterogeneity. It opens new perspectives for large cross-sectional studies if, as is mostly the case, longitudinal data covering long age ranges are not available. As in PTSD, the backtrace approach could also be applied to identifying persistent biomarker profiles in other mental disorders, as well as autoimmune and other chronic diseases.

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Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A

Procedure description: Details of the backtrace procedure, steps 3 and 4

In the following, steps 3 and 4 of the analysis flowchart (see Fig. 2 of the main text), which serve to determine critical age periods, are described in more detail and illustrated by an example.

Step three was based on an exploratory graphic display, shown in Fig. A1. The time series (red line, with *t*-test confidence intervals = green lines) represent the mean levels of a marker X at the age when a traumatic event was experienced. The reference value (blue line) represents the overall mean level of the same marker in subjects who did not experience any trauma; their marker level is constant.

The time series of marker X was smoothed by a moving average (MA) age period in order to avoid erratic curves and problems with small Ns when calculating the confidence intervals. The mean levels of marker X were calculated in this example for a 9-year MA (see issue 1 in the Fig. A1 ; the x-axis represents the age, i.e., the middle year of each successive 9-year age period; for example, the mean level of marker X at age 20 corresponds to the mean level of all subjects who experienced a traumatic event in the age period 16–24 years). As illustrated in this example, the mean levels of marker X are particularly low in subjects who experienced a traumatic event after age 22, as indicated by the upper confidence interval of the t-tests for the following age years, which fell below the mean of the marker in subjects who did not experience any trauma.

After visual inspection, a data-driven iterative procedure served to identify the peaks and lows in the data together with the best fitting critical age ranges surrounding each peak or low. The next analysis step started by determining the 'point of maximal divergence in each marker (see issue 2 in Fig. A1 ; in the schematic example the point of maximal divergence, i.e., the low, is at 30 years). This is the maximal difference

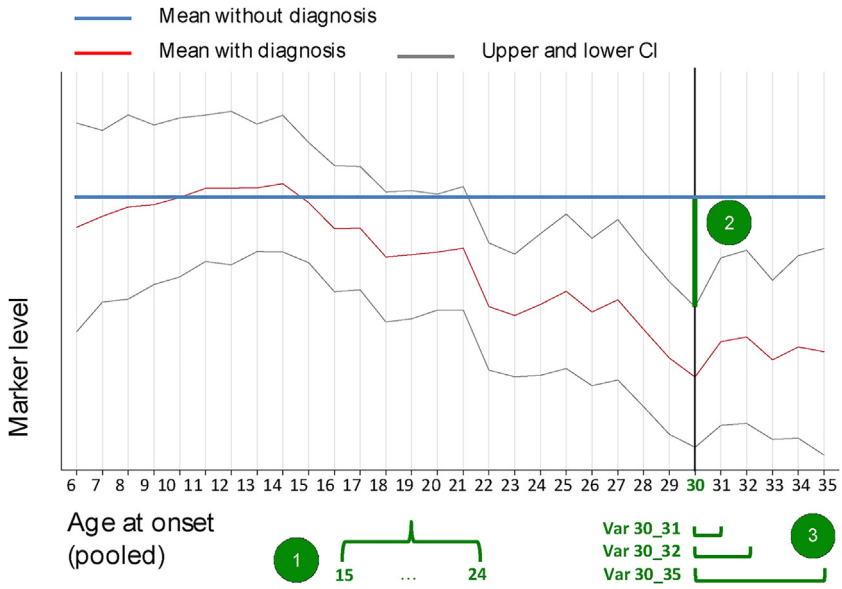

Fig. A1. Illustration of steps 3 and 4 of the backtrace procedure.

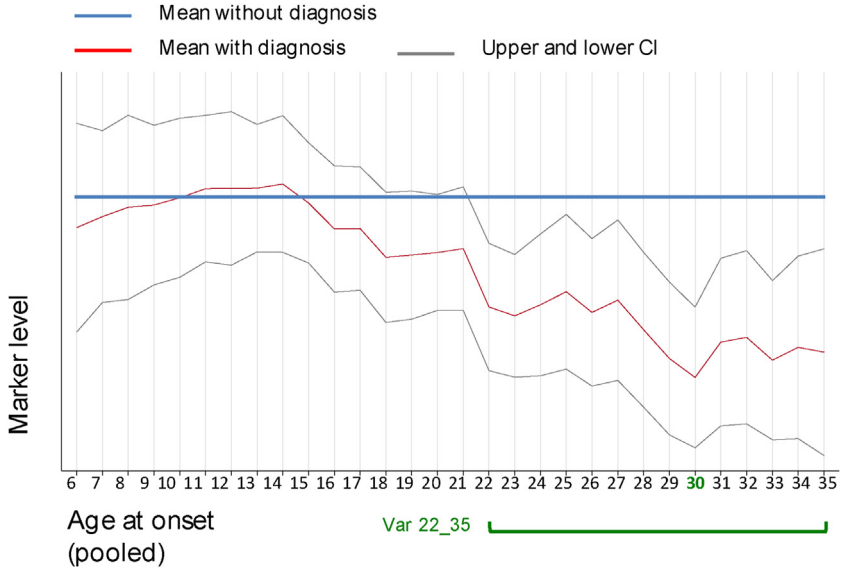

Fig. A2. The critical age period.

between the mean levels of a marker X by age and the reference value. For some markers, it was possible to identify both a low and a peak of maximal divergence. The 'point of maximal divergence' was not determined based on raw marker levels but on smoothed data in order to exclude outliers from the selection procedure. Smoothing was based on moving averages, e.g. 3- / 5- / 7-age year moving averages. It is possible to consider and include results from different moving averages in order to obtain the most comprehensive selection of markers.

Markers for which there was no significant difference between the two means at any age at onset, and which did not reveal a significant overall difference in their means, were excluded from the subsequent analysis steps. For those markers, it is assumed that differences in age at onset do not play a role. Exceptions were accepted if the overall test was significant (see step 2 in the analysis flowchart (Fig. 2 in the main text)).

In step 4 of the procedure, as depicted in the analysis flowchart, a set of period variables were created based on the point of maximal divergence, in order to represent all possible periods that include the point of maximal divergence (see issue 3 in Fig. A1). Up to 200 new variables were created per marker. To give an example, variable '30_31' includes the values of marker X of those participants who experienced a traumatic event within the period 30–31. It excludes the values of participants who were exposed to trauma outside this period; their values were set to missing. The same procedure was applied to all other possible periods, including the age of maximal divergence, i.e., 30 (for example 30_32, 26_34, 12_34 etc.).

For each period variable, a *t*-test was applied to compare the values against the reference value. The period variable with the lowest p-value was assumed to most likely indicate the "best" critical age period for marker X (see Fig. A2). Further criteria for the selection included a sufficient period width (at least the MA range) and a minimal N (N greater than or equal to 10).

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