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Cytokine changes in clinical high risk for psychosis population following antipsychotic medication

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Serum cytokine alterations are associated with the usage of antipsychotic medications (AP). However, few studies have been designed to longitudinally measure cytokine changes during AP exposure in individuals at clinical high risk (CHR) for psychosis. This study aimed to assess changes in levels of cytokines after initiating AP in the prodromal phase. This longitudinal study involved individuals with CHR who completed the 1-year follow-up reassessment. Individuals with CHR were grouped into those treated with AP (AP + group) and those without (AP- group). Levels of vascular endothelial growth factor (VEGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, 2, 6, 8, and 10 were measured at baseline and 1 year after completion of the clinical assessment. This study included 88 CHR individuals (median age, 18 years and 40.9% [n = 36] women; AP- group: n = 28, AP + group: n = 60). The baseline serum levels of IL-6 were higher in the AP- group than in the AP + group ($z = -2.577$, $p = 0.010$). Self-controlled comparisons showed that VEGF ($z = 3.826$, $p < 0.001$), TNF-α ($z = 2.642$, $p = 0.008$), IL-8 ($z = 2.300$, $p = 0.021$), and GM-CSF ($z = 2.346$, $p = 0.019$) levels were significantly increased in the AP- group. In the AP + group, IL-6 ($z = 3.512$, $p < 0.001$) was significantly increased, IL-1β ($z = 2.563$, $p = 0.010$), and GM-CSF ($z = 2.095$, $p = 0.036$) were significantly decreased. Repeated-measures analysis of variance revealed a significant group × visit effect on VEGF ($F = 20.348$, $p < 0.001$), GM-CSF ($F = 7.042$, $p = 0.013$), and IL-1β($F = 4.670$, $p = 0.040$). The findings revealed significant differences in trajectories between individuals with CHR who were and were not taking AP. There is an association between AP use in CHR individuals and differences in inflammatory and neurotrophic factor trajectories.

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INTRODUCTION

Antipsychotic medications (AP) represent frontline treatment options for patients with psychosis, effectively managing clinical symptoms, particularly severe hallucinations and delusions during acute phases. The impact of AP on cytokines in patients with first-episode and stabilized schizophrenia (SZ) has been extensively studied [1, 2]. Different antipsychotic drugs may yield varying effects on cytokines. For instance, Patlola et al. [3] conducted a systematic review on the effects of risperidone on cytokines in first-episode versus chronic patients with psychosis. They found a significant reduction in pro-inflammatory cytokines following risperidone treatment, with noteworthy changes in interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels observed mainly in chronic patients rather than first-episode psychosis (FEP) patients. However, their study revealed significant effects of disease duration. This suggests that investigating the impact of AP on cytokines in patients with post-onset psychosis may be confounded by the influence of the psychotic states on cytokine levels. Immune system dysfunction is considered a significant characteristic in psychosis, marked by substantial alterations in specific peripheral cytokine concentrations [4, 5]. A recent systematic review and network meta-analysis [6] found consistent elevation in concentrations of IL-1β, IL-1 receptor antagonist (IL-1RA), soluble interleukin-2 receptor (sIL-2R), IL-6, IL-8, IL-10, TNF-α, and C-reactive protein in individuals with acute and chronic psychosis compared to healthy controls. Hence, it remains unclear whether changes in cytokine levels are primarily influenced by the psychosis itself or by the AP exposure.

Therefore, it is conceivable that the influence of AP on cytokine levels during the clinical high risk (CHR) stage, prior to the onset of full psychosis, may be somewhat less confounded by the effects of the disease itself. However, our previous research suggests that the use of AP during the CHR stage may have more drawbacks than benefits [7, 8], with greater advantages observed in initiating AP treatment during the first episode rather than during the CHR stage [9]. In our previous investigation [7], we found that nearly 80% of individuals classified as CHR in our cohort received AP treatment. Consequently, observing the effects of AP on cytokine

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levels in CHR individuals in real-world settings to better understand the impact of AP on cytokines remains uncertain, since whether the effects of AP on cytokine levels in CHR individuals are similar to those observed in patients with psychosis remains unanswered.

This study utilized a longitudinally constructed real-world CHR cohort to compare the changes in cytokine levels between CHR individuals using and not using AP at baseline and 1-year follow-up, aiming to investigate the impact of AP on cytokines. The research hypothesis posits that AP usage would alter the trajectory of cytokine changes in CHR individuals, leading to a decrease in inflammatory factor levels (anti-inflammatory effects of AP [3]) and an increase in neurotrophic factor levels (neuroprotective effects of AP [10]). To achieve this, a combination of cross-sectional and longitudinal designs was employed to examine the dynamic alterations in cytokine levels, encompassing peripheral concentrations of vascular endothelial growth factor (VEGF), TNF-α, IL-8, IL-6, IL-1β, IL-10, and granulocyte-macrophage colony-stimulating factor (GM-CSF).

MATERIALS AND METHODS

Participants and setting

The present study is a component of the ShangHai At Risk for Psychosis-extended (SHARP-extended) program, which involved 131 help-seeking first-visit participants recruited consecutively from the Shanghai Mental Health Center (SMHC) between January 1, 2020, and August 8, 2023. This research focused on individuals at CHR for psychosis and was conducted at a single site, the SMHC in China. 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 2013. All procedures involving human subjects/patients were approved by the Internal Review Board of the SMHC (Approval No. 2017-36 R). INFORMED consent was obtained from all participants during the recruitment stage. For participants under the age of 18, written parental INFORMED consent was obtained, and adolescents provided verbal assent. The research was conducted in accordance with the Declaration of Helsinki.

The SMHC serves as China's largest outpatient facility for medication management and psychotherapy, catering to patients from various regions across the country. In this study, a total of 394 individuals meeting the criteria for CHR were identified through face-to-face interviews utilizing the Structured Interview for Prodromal Syndromes (SIPS) [11, 12]. Eligible participants ranged from 13 to 45 years of age at baseline—chosen because the CHR state predominantly affects adolescents and young adults, with psychosis transition likelihood decreasing significantly after 45 years—and had received a minimum of 6 years of primary education. Exclusion criteria encompassed individuals with severe somatic diseases (diseases that may affect immune function, interfere with cytokine detection or pose risks to follow-up safety, including but not limited to uncontrolled diabetes, active autoimmune diseases, malignant tumors) such as cancer, as well as those with mental retardation, developmental disorders, or substance abuse. Notably, during recruitment and follow-up assessments, we confirmed no participants had a history of smoking; combined with the young age of the cohort (median 18 years) and strict exclusion of severe somatic diseases, this ensured no participants had significant medical comorbidities that could influence cytokine levels. Due to study design constraints, body mass index data were not collected.

Out of the 131 individuals identified with CHR, 88 participants (67.2%) completed 1-year face-to-face reassessments using the SIPS along with blood sample recollection. Thirty-three individuals did not complete the 1-year follow-up assessments, and ten were lost to follow-up. Comprehensive details regarding the study procedures, settings, and measurement implementation can be found elsewhere [13–16]. A notable aspect of our sample was the psychotropic naivety of all participants upon study entry. They underwent clinical assessment without prior treatment for any psychiatric disorder.

Criteria and assessments

We employed the SIPS to identify individuals meeting criteria for CHR, based on one of the following prodromal syndrome criteria: (1) Brief Intermittent Psychotic Syndrome, (2) Attenuated Positive Symptom Syndrome, or (3) Genetic Risk and Deterioration Syndrome. The SIPS comprises 19 items designed to assess four symptom domains: positive symptoms, negative symptoms, disorganized symptoms, and general symptoms. Additionally, the Global Assessment of Functioning (GAF) scale was utilized to evaluate the patients' overall psychological, social, and occupational functioning during the SIPS interview. In our previous studies, [14, 15] the Chinese version [16] of SIPS, which was developed by the SHARP team, also demonstrated good inter-rater reliability (intraclass correlation coefficient $r = 0{\cdot}96$, $p < 0{\cdot}01$ for the SIPS total score) and validity (26·4% converted to psychosis in the following 2 years) in China. The first author is SIPS certified through Yale University-sponsored SIPS training.

Psychosis conversion, the primary outcome of this study, was assessed using the Presence of Psychotic Symptoms (POPS) criteria [17] derived from the SIPS. Conversion was specifically defined by the presence of a positive symptom rated at level "6," indicating severe and psychotic, which is either dangerous, disorganized, or occurs for at least an hour a day on average over four days a week, totaling at least 16 h overall.

Antipsychotic exposure and groups

The current study is a naturalistic follow-up investigation [7, 18, 19], involving no additional intervention or financial compensation. The assumption of AP usage was documented by researchers during follow-up assessments, corroborated by family members, and verified through clinician reports and medical records. Information regarding medication usage was systematically recorded, including the types of antipsychotics, drug response, and duration of reduction or withdrawal. Specifically, individuals with CHR who had received AP treatment for at least 2 weeks [20, 21], with a minimum equivalent dose of 5 mg of olanzapine [22], were classified into the AP + group. Specifically, individuals with CHR in the AP + group had taken APs with an olanzapine-equivalent mean dose of 10.7 mg (standard deviation [SD] = 5.6 mg) for a mean duration of 45.7 weeks (SD = 12.7 weeks). During the 1-year follow-up, individuals with CHR were prescribed various types of AP, including aripiprazole (n = 20), olanzapine (n = 18), risperidone (n = 8), amisulpride (n = 4), paliperidone (n = 2), quetiapine (n = 2) and multiple APs (n = 6). To explore whether different AP types affect cytokine changes, we conducted subgroup analyses focusing on the three most commonly used APs (aripiprazole, olanzapine, risperidone) due to limited sample sizes in other AP subgroups. Using Kruskal-Wallis H tests, we compared baseline-to-1-year changes in key cytokines among the three subgroups. No significant differences in the magnitude of cytokine changes were observed across the three AP types (all $p > 0.05$). A small group of participants took psychoactive medication other than antipsychotic (27 individuals took antidepressants, with a fluoxetine-equivalent [23] dose of 29.7 mg [SD = 13.1], and the mean administration duration was 21.7 [SD = 12.9] weeks). To rule out potential confounding of antidepressant use on cytokine changes, we conducted a sensitivity analysis: subgroup analyses of baseline-to-1-year cytokine changes were performed within the AP- and AP + groups, stratified by antidepressant use (yes/no). Results showed no significant differences in the direction or magnitude of cytokine changes between subgroups with and without antidepressants (all $p > 0.05$), indicating antidepressant use did not substantially confound the observed cytokine trajectories.

Measurement of cytokine levels

Venous blood samples were obtained both at baseline and during the 1-year follow-up period [24, 25]. Collection was conducted in the morning after participants had fasted for a minimum of 3 h. Ten mL of peripheral venous blood were drawn into anticoagulant-free tubes. After 1 h at room temperature, the samples underwent centrifugation at 1,710 g for 20 min at 4 °C to separate the serum. The serum was then stored at −80 °C until analysis. Analysis was performed using enzyme-linked immunosorbent assay with the Human HS Cytokine Premixed Kit (Catalog#: FCSTM09-10, USA) following the manufacturer's instructions. Duplicate measurements were taken for each sample. The concentrations of VEGF, TNF-α, IL-8, IL-6, IL-1β, IL-10, and GM-CSF were expressed as pictograms of protein per milliliter of serum (pg/mL). Calibration of all data was conducted using standard curves generated for each cytokine.

Statistical analysis

CHR individuals were categorized based on their antipsychotic assumption during the follow-up period into two groups: AP- and AP + . Quantitative variables were presented as mean (standard deviation) for normally

Table 1. Demographic clinical and cytokine variables at baseline, comparison between AP- and AP + groups.

Variables	AP-	AP +	Comparison	
			$t/Z/\chi^2$	*P* value
Cases(n)	28	60	-	-
Age(years)[mean(S.D.)]	18.9(4.5)	18.2(4.5)	$t = 0.889$	0.377
Male[n(%)]	12(42.9)	40(66.7)	$\chi^2 = 4.477$	0.034
Female[n(%)]	16(57.1)	20(33.3)		
Education(years)[mean(S.D.)]	10.8(2.9)	10.3(3.0)	0.712	0.479
Family history(none)[n(%)]	20(71.4)	48(80.0)	$\chi^2 = 0.948$	0.623
Family history(low-risk),[n(%)]	4(14.3)	5(8.3)		
Family history(High-risk),[n(%)]	4(14.3)	7(11.7)		
GAF [Mean(S.D.)]	56.0(7.5)	52.5(9.1)	$t = 1.732$	0.087
SIPS-P [Mean(S.D.)]	10.5(3.4)	10.4(4.1)	$t = 0.035$	0.972
SIPS-N [Mean(S.D.)]	12.5(6.2)	13.3(6.8)	$t = -0.505$	0.615
SIPS-D [Mean(S.D.)]	6.6(2.7)	7.6(3.8)	$t = -1.281$	0.204
SIPS-G [Mean(S.D.)]	9.3(3.2)	8.8(2.8)	$t = 0.642$	0.523
SIPS-Total [Mean(S.D.)]	38.8(10.9)	40.1(11,9)	$t = -0.502$	0.617
VEGF [Median(IQR)] [Mean(S.D.)]	57.0(34.1–106.7) 75.9(55.7)	70.0(41.8–108.2) 80.9(51.0)	$Z = -0.672$	0.502
TNF-α [Median(IQR)] [Mean(S.D.)]	10.2(7.8–11.4) 9.7(2.5)	10.0(8.2–12.5) 10.3(2.9)	$Z =$ -0.932	0.351
IL-8 [Median(IQR)] [Mean(S.D.)]	6.7(5.2–10.6) 8.8(6.6)	8.8(5.9–10.9) 9.4(5.2)	$Z = -1.380$	0.168
IL-6 [Median(IQR)] [Mean(S.D.)]	1.3(0.8–1.6) 1.3(0.8) 0.9(0.5)	0.9(0.6–1.2) 0.9(0.5)	$Z = -2.577$	0.010
IL-1β [Median(IQR)] [Mean(S.D.)]	0.3(0.1–0.5) 0.4(0.4)	0.4(0.2–0.5) 0.4(0.3)	$Z = -1.425$	0.154
IL-10 [Median(IQR)] [Mean(S.D.)]	0.3(0.1–0.8) 0.4(0.5)	0.2(0.1–0.6) 0.3(0.5)	$Z = -0.534$	0.593
GM-CSF [Median(IQR)] [Mean(S.D.)]	2.4(1.8–3.3) 2.6(1.1)	2.6(1.9–3.1) 2.7(1.0)	$Z = -0.349$	0.727

SIPS structured interview for prodromal syndromes, *SIPS-P* positive symptoms, *SIPS-N* negative symptoms, *SIPS-D* disorganization symptoms, *SIPS-G* general symptoms, SIPS-Total, Total score of SIPS, *GAF* global assessment of functioning, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *IL-10* interleukin (IL)-10, *IL-1β* interleukin (IL)-1beta, *IL-6* interleukin (IL)-6, *IL-8* interleukin (IL)-8, *TNF-α* tumor necrosis factor-α, *VEGF* vascular endothelial growth factor, Low-risk family history, having any family members with mental disorders or a first-degree relative with non-psychotic disorders; High-risk family history, having at least one first-degree relative with psychosis, *IQR* interquartile range, t/χ^2: *t* for independent t test, *Z* for Mann-Whitney test, χ^2 for kappa test.

Table 2. Clinical and cytokine variables at 1-year follow-up, comparison between AP- and AP + groups.

Variables	AP-	AP +	Comparison	
			$t/Z/\chi^2$	*P* value
Converters(n(%))	5(17.9)	16(26.7)	$\chi^2 = 0.815$	0.367
GAF-v2 [Mean(S.D.)]	71.1(9.3)	68.1(10.1)	$t = 1.354$	0.179
SIPS-P-v2 [Mean(S.D.)]	3.7(2.7)	4.7(4.6)	$t = -0.995$	0.322
SIPS-N-v2 [Mean(S.D.)]	7.6(6.3)	11.0(7.0)	$t = -2.123$	0.037
SIPS-D-v2 [Mean(S.D.)]	2.8(3.1)	4.7(4.1)	$t = -2.105$	0.038
SIPS-G-v2 [Mean(S.D.)]	6.0(3.1)	6.0(3.3)	$t = -0.094$	0.925
SIPS-Total-v2 [Mean(S.D.)]	20.1(13.2)	26.3(16,3)	$t = -1.745$	0.085
VEGF-v2 [Median(IQR)] [Mean(S.D.)]	89.6(57.7–134.4) 105.4(73.0)	73.3(35.2–100.3) 79.4(51.9)	$Z = -1.822$	0.068
TNF-α-v2 [Median(IQR)] [Mean(S.D.)]	10.8(9.7–12.3) 10.7(2.2)	10.4(9.1–12.4) 10.7(2.9)	$Z = -0.381$	0.703
IL-8-v2 [Median(IQR)] [Mean(S.D.)]	9.0(6.6–13.3) 11.1(5.8)	8.6(6.0–11.9) 9.4(4.8)	$Z = -1.111$	0.267
IL-6-v2 [Median(IQR)] [Mean(S.D.)]	1.0(0.7–1.4) 1.2(0.7)	1.0(0.7–1.4) 1.2(0.6)	$Z = -0.036$	0.971
IL-1β-v2 [Median(IQR)] [Mean(S.D.)]	0.4(0.3–0.6) 0.5(0.3)	0.3(0.2–0.4) 0.3(0.2)	$Z = -1.967$	0.049
IL-10-v2 [Median(IQR)] [Mean(S.D.)]	0.3(0.1–0.7) 0.4(0.5)	0.3(0.1–0.5) 0.3(0.3)	$Z = -0.725$	0.468
GM-CSF-v2 [Median(IQR)] [Mean(S.D.)]	2.8(1.9–3.5) 2.9(1.2)	2.5(1.9–3.0) 2.5(0.9)	$Z =$ -1.411	0.158

SIPS structured interview for prodromal syndromes, *SIPS-P* positive symptoms, *SIPS-N* negative symptoms, *SIPS-D* disorganization symptoms, *SIPS-G* general symptoms, *SIPS-Total* total score of SIPS, *GAF* global assessment of functioning; *GM-CSF* granulocyte-macrophage colony-stimulating factor, *IL-10* interleukin (IL)-10, *IL-1β* interleukin (IL)-1beta, *IL-6* interleukin (IL)-6, *IL-8* interleukin (IL)-8, *TNF-α* tumor necrosis factor-α, *VEGF* vascular endothelial growth factor, *IQR* interquartile range, t/χ^2: *t* for independent t test, *Z* for Mann-Whithey test, χ^2 for kappa test.

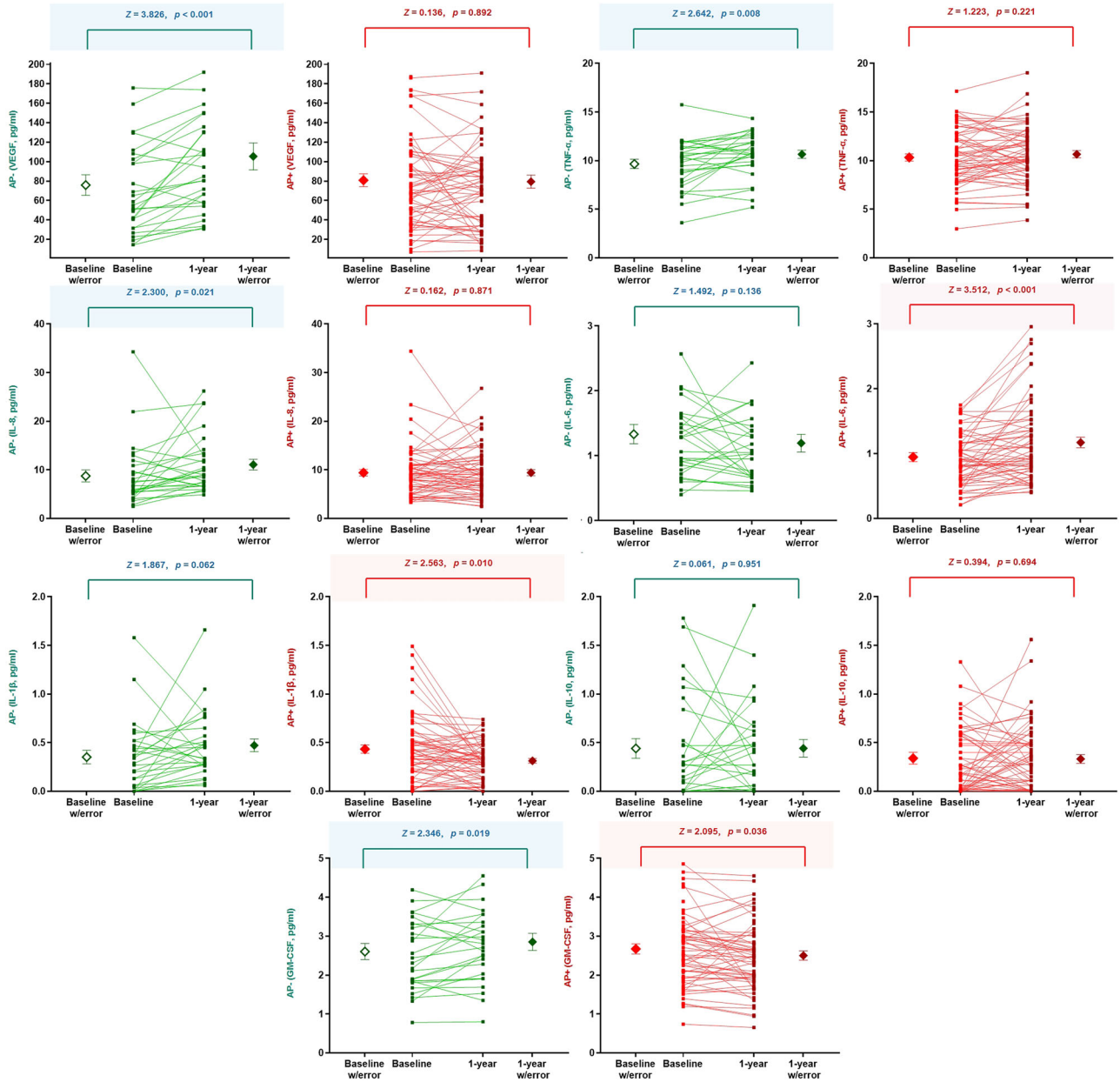

Fig. 1 Self-controlled comparisons for serum levels of cytokine factors between baseline and follow-up, stratified by AP- and AP + group. GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-10, interleukin (IL)-10; IL-1β, interleukin (IL)-1beta; IL-6, interleukin (IL)-6; IL-8, interleukin (IL)-8; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; The paired Wilcoxon test was used for self-controlled analysis. The level of statistical significance was set at a two-tailed *p* value of 0.05. Effect sizes (r values) were calculated as ($r = z/\sqrt{n}$ (n = 28 for AP- group, n = 60 for AP + group); r ≥ 0.5 indicates large effect, 0.3 ≤ r < 0.5 indicates medium effect, 0.1 ≤ r < 0.3 indicates small effect.

distributed data and median (interquartile range) for non-normally distributed data. Qualitative variables were expressed as frequencies (%). The normality of inflammatory variables' distribution was assessed using the Kolmogorov-Smirnov test, revealing non-normal distribution for all cytokine variables. Group comparisons were conducted using χ^2 tests for categorical variables and independent t-tests or Mann-Whitney tests for continuous variables. Changes in cytokine levels between baseline and 1-year follow-up were compared using the paired sample Wilcoxon signed rank test for non-normally distributed continuous variables; effect sizes for significant changes were calculated as r values using the formula $r = z/\sqrt{n}$ (z = Wilcoxon z-statistic, n = sample size per group). Trajectories of cytokine levels between the AP- and AP + groups were evaluated using repeated-measures analysis of variance (RMANOVA). RMANOVA with a factorial design (2 visits × 2 groups) was employed to assess significant interactions between visit (baseline and 1-year) and group (AP- and AP +) regarding their effects on cytokine levels. Effect size was evaluated using η^2, with values of 0.01 indicating a small effect, 0.06 indicating a medium effect, and 0.14 indicating a large effect. To account for the potential influence of psychosis conversion on cytokine trajectories, we further adjusted the RMANOVA model by including conversion status (converter/non-converter) as a covariate.

To enhance the readability and logical flow of the results section in this document, the following presentation structure was implemented: (1) First, report baseline demographic and clinical characteristics and their group comparisons to establish cohort comparability; (2) second, describe changes in clinical characteristics at the 1-year follow-up to track temporal shifts in the cohort's clinical profile; (3) third, present within-group changes in cytokine levels (via Wilcoxon signed-rank tests) to highlight subgroup-specific temporal trends; (4) finally, report RANOVA results (main effects of group and time, visit × group interactions) and corresponding post-hoc analyses to synthesize longitudinal group differences in cytokine trajectories.

RESULTS

Baseline demographic, clinical and cytokine characteristics

The baseline characteristics of the AP- and AP + groups are summarized in Table 1. Most variables showed no statistically significant differences. However, the AP + group had more males ($\chi^2 = 4.477$, $p = 0.034$) than the AP- group. Additionally, the level of IL-6 ($z = -2.577$, $p = 0.010$) was higher in the AP- group than in the AP + group.

Follow-up clinical and cytokine characteristics

The 1-year follow-up characteristics of the AP- and AP + groups are summarized in Table 2. The AP + group exhibited a higher severity level of negative symptoms ($t = -2.123$, $p = 0.037$) and disorganization symptoms ($t = -2.105$, $p = 0.038$) compared to the AP- group.

Self-controlled comparisons of cytokine levels

The paired sample Wilcoxon tests (Fig. 1) showed that VEGF ($z = 3.826$, $p < 0.001$, $r = 0.408$), TNF-α ($z = 2.642$, $p = 0.008$, $r = 0.282$), IL-8 ($z = 2.300$, $p = 0.021$, $r = 0.245$), and GM-CSF ($z = 2.346$, $p = 0.019$, $r = 0.250$) levels were significantly increased in the AP- group. In the AP + group, IL-6 ($z = 3.512$, $p < 0.001$, $r = 0.449$) was significantly increased, IL-1β ($z = 2.563$, $p = 0.010$, $r = 0.327$) and GM-CSF ($z = 2.095$, $p = 0.036$, $r = 0.267$) were significantly decreased.

Changes of clinical and cytokine factors

After a 1-year follow-up, data analyzed using the RMANOVA model (Table 3) revealed a significant group × visit effect on VEGF ($F = 20.348$, $df = 1$, $p < 0.001$), GM-CSF ($F = 7.042$, $df = 1$, $p = 0.013$), and IL-1β ($F = 4.670$, $df = 1$, $p = 0.040$). No significant group effect was observed for both clinical and cytokine variables. However, a significant visit effect was noted on all clinical variables, VEGF ($F = 4.902$, $df = 1$, $p = 0.035$), and TNF-α ($F = 5.412$, $df = 1$, $p = 0.028$).

To interpret the significant time × group interactions, post-hoc pairwise comparisons were conducted to assess within-group changes from baseline to follow-up. For VEGF, levels increased significantly in the AP- group, whereas no significant change was observed in the AP + group. This indicates that AP use may mitigate the natural upward trend of VEGF in non-AP users. For IL-1β, the AP- group showed no significant change, while the AP + group exhibited a significant decrease. This suggests that AP use is associated with reduced IL-1β levels over time. For GM-CSF, the AP- group had a significant increase in levels, whereas the AP + group had a significant decrease. This demonstrates opposing trajectory patterns based on AP use (Fig. 2).

When including conversion status as a covariate in the RMANOVA model, the core group × visit interactions reflecting AP effects remained robust, confirming AP use drives cytokine trajectory differences independent of psychosis conversion. For conversion status-related effects, there were no significant between-subject differences in baseline cytokine levels by conversion status (all $p > 0.05$); among within-subject time × conversion status interactions, only IL-10 showed significance ($F = 4.107$, $p = 0.046$), while all other cytokines had no significant conversion-related time-dependent changes (all $p > 0.05$). Notably, IL-10 had no significant AP-related trajectory differences in the original model, so its conversion-related interaction does not affect core conclusions about AP.

DISCUSSION

This study aimed to investigate the association between AP use and cytokine profiles in the CHR state. To the best of our knowledge, this is the first study to examine the impact of AP on cytokines in CHR individuals. The findings revealed comparable baseline characteristics between the AP- and AP + groups, with the only notable differences being a higher proportion of males and lower levels of IL-6 observed in the AP + group. No significant differences were observed in other variables. Dynamic changes in cytokine levels during the follow-up period showed significant increases in VEGF, TNF-α, IL-8, and GM-CSF levels in the AP- group, while IL-6 levels significantly increased and IL-1β and GM-CSF levels decreased in the AP + group. Consistent with our hypothesis, there was an association between AP use and differences in the trajectory of cytokine changes. Moreover, significant differences were observed in the change trajectories of VEGF, IL-1β, and GM-CSF between the two groups, with increases in the AP- group and decreases in the AP + group.

In our study sample of CHR individuals, we observed a more pronounced effect of AP on VEGF levels. Specifically, in the AP- group, VEGF levels significantly increased after 1 year, whereas the

Table 3. Changes of clinical and cytokine factors analysis by RMANOVA, comparisons between AP- and AP + groups.

Variables	Visit × Group			Group			Visit		
	F	*p*	η^2	*F*	*p*	η^2	*F*	*p*	η^2
SIPS-P	2.224	0.147	0.076	1.264	0.271	0.045	**56.026**	**<0.001**	**0.675**
SIPS-N	1.235	0.276	0.044	0.525	0.475	0.019	**16.728**	**<0.001**	**0.383**
SIPS-D	1.399	0.247	0.049	3.149	0.087	0.104	**33.146**	**<0.001**	**0.551**
SIPS-G	0.006	0.940	0	0.397	0.534	0.014	**24.973**	**<0.001**	**0.481**
SIPS-Total	1.941	0.175	0.067	1.061	0.312	0.038	**51.425**	**<0.001**	**0.656**
GAF	0.866	0.360	0.031	1.106	0.302	0.039	**135.426**	**<0.001**	**0.834**
VEGF	**20.348**	**<0.001**	**0.430**	0.043	0.838	0.002	**4.902**	**0.035**	**0.154**
TNF-α	1.906	0.179	0.066	3.179	0.086	0.105	**5.412**	**0.028**	**0.167**
IL-8	2.118	0.157	0.073	0.543	0.468	0.020	1.967	0.172	0.068
IL-6	2.357	0.136	0.080	0.599	0.446	0.022	1.252	0.273	0.044
IL-1β	**4.670**	**0.040**	**0.147**	0.349	0.560	0.013	0.087	0.771	0.003
IL-10	0.066	0.799	0.002	0.226	0.638	0.008	0.060	0.808	0.002
GM-CSF	**7.042**	**0.013**	**0.207**	0.002	0.969	0	0.221	0.642	0.008

SIPS structured interview for prodromal syndromes, *SIPS-P* positive symptoms, *SIPS-N* negative symptoms, *SIPS-D* disorganization symptoms, *SIPS-G* general symptoms, SIPS-Total, Total score of SIPS, *GAF* global assessment of functioning, *GM-CSF* granulocyte-macrophage colony-stimulating factor, *IL-10* interleukin (IL)-10, *IL-1β* interleukin (IL)-1beta, *IL-6* interleukin (IL)-6, IL-8, interleukin (IL)-8, *TNF-α* tumor necrosis factor-α, *VEGF* vascular endothelial growth factor, *RMANOVA*, repeated measures analysis of variance. The effect size *(η^2) = 0.01(small), $\eta^2 = 0.06$(medium), $\eta^2 = 0.14$ (large)*. Bold indicates significant values.

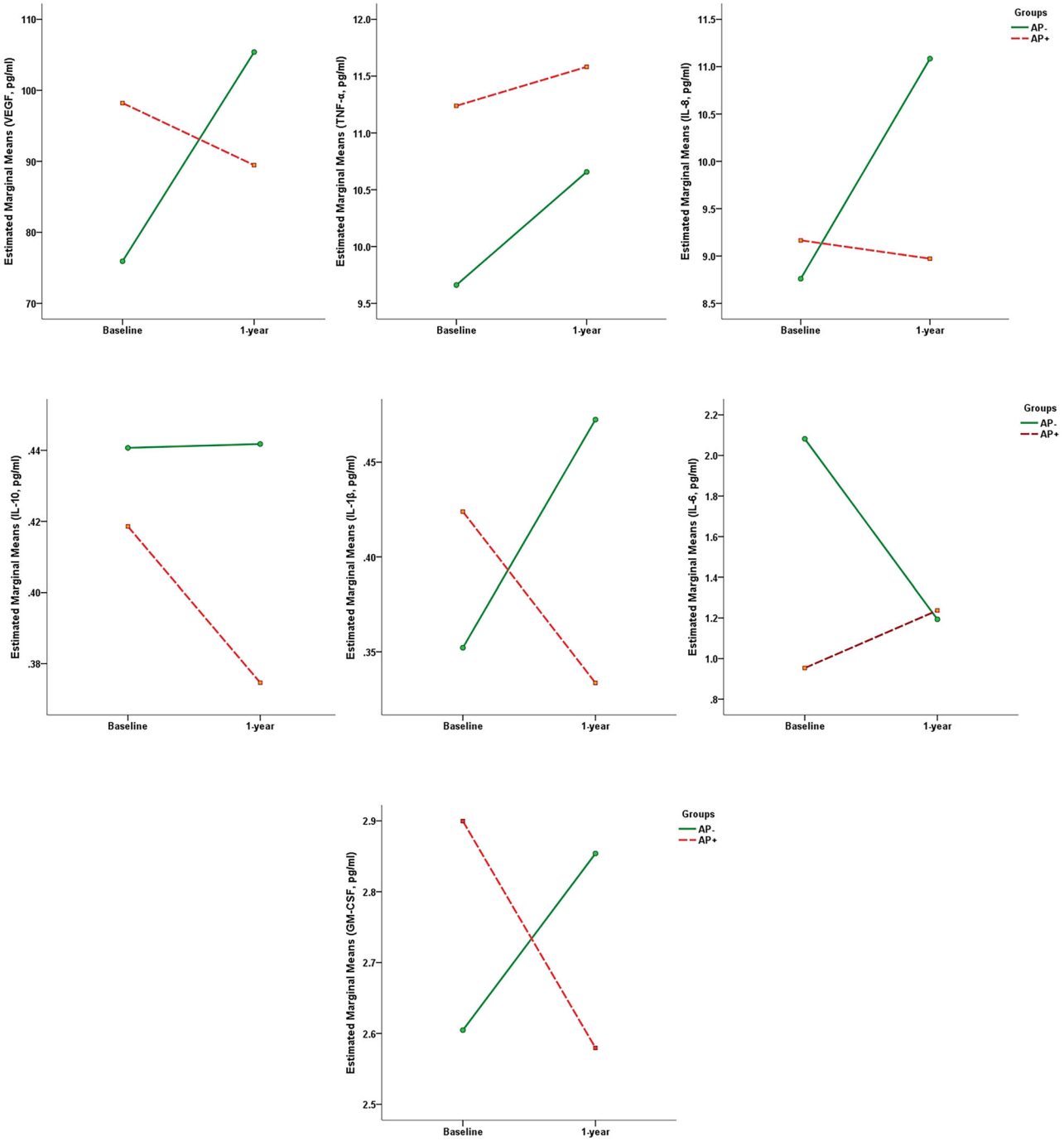

Fig. 2 Mean score trajectories for cytokine factors based on the RMANOVA. GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-10, interleukin (IL)-10; IL-1β, interleukin (IL)-1beta; IL-6, interleukin (IL)-6; IL-8, interleukin (IL)-8; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; RMANOVA, repeated measures analysis of variance.

changes in VEGF levels were minimal in the AP + group. Additionally, there were significant differences in the trajectory of VEGF changes between the two groups. This finding is inconsistent with previous research in patients with SZ [26]. A major topic in the literature regarding the role of VEGF in SZ revolves around whether the VEGF molecular pathway is involved in the mechanism of action of AP. Several studies [27, 28] have reported higher serum VEGF levels in patients with SZ treated with AP compared to controls. This evidence suggests that AP therapy may exert its action by directly and/or indirectly increasing serum VEGF levels, possibly by inducing VEGF gene expression in brain areas critical to the pathophysiology of SZ [29, 30]. The discrepancy in research conclusions may primarily relate to the stage of psychosis. CHR represents the prodromal phase of the illness, whereas SZ represents the later stage. In the CHR stage, baseline VEGF levels may not be abnormal [31], leading to minimal changes with AP use. Conversely, in the AP- group, the significant increase in VEGF levels suggests that individuals in the CHR stage may possess self-regulatory mechanisms under conditions of stress and inflammation imbalance [24]. This notion is supported by Ye et al. [32, 33], who found no baseline VEGF abnormalities in CHR individuals and reported a trend of VEGF

elevation in unmedicated CHR participants over follow-up—consistent with our observation of significant VEGF increase in the AP- group and minimal changes in the AP + group.

In terms of inflammatory factors, we observed an overall increase in cytokine levels among individuals with CHR, regardless of whether they were in the AP + or AP- group. Particularly noteworthy were the elevated levels of TNF-α in the AP- group and IL-6 in the AP + group. The only exception was a decrease in IL-1β levels in the AP + group, while the AP- group showed a trend towards an increase ($p = 0.06$), with significant differences observed in the trajectory of changes between the two groups. Numerous studies [34], including meta-analyses [35], have reported elevated levels of IL-6 in various phases of SZ, with the majority of patients receiving AP treatment [36]. For instance, Hartwig et al. [37] identified increased levels of soluble IL-6 receptors in a clinical two-sample Mendelian randomization study, suggesting a compensatory response to elevated IL-6 levels in SZ. Similarly, multiple studies have reported elevated levels of TNF-α and IL-8, other pro-inflammatory cytokines, in SZ [38, 39] and CHR populations [32].

The IL-1 family, including IL-1β, represents major pro-inflammatory cytokines. While many studies have reported elevated IL-1β levels in SZ [40], particularly among those receiving atypical APs, findings regarding IL-1β in SZ have not been consistent. For example, a meta-analysis by Potvin et al. [41] in 2008 found no significant alterations in IL-1β levels in both in vivo and in vitro studies. Interestingly, a study [42] observed decreased levels of IL-1β in first-episode drug-naïve patients with a disease duration of less than 2 years, suggesting that the trajectory of IL-1β changes may differ among early-stage patients. Furthermore, GM-CSF is recognized as a crucial hematopoietic growth factor and immune modulator, exerting profound effects on the functional activities of various circulating leukocytes [43]. In this study, GM-CSF levels increased in the AP- group while decreased in the AP + group, indicating differential trajectories of change. This observation suggests that AP may have indirect anti-inflammatory effects. However, the results of this study also imply that the effects of AP on inflammatory factors in CHR individuals are complex, potentially characterized by a pattern of changes rather than being solely determined by a few factors.

Despite its novelty, the present study has several limitations: (1) The CHR cohort was followed up naturally, and the types, doses, and durations of AP use could not be controlled. Although all patients were prescribed atypical AP, it remains unknown whether different types of AP have different effects on cytokines, posing a confounding factor. As a naturalistic real-world study, we were unable to randomize participants to AP + or AP- groups, and AP use was non-random (potentially tied to clinical judgment of illness severity or transition risk). While Table 1 shows no significant baseline differences between groups in SIPS subscales (SIPS-P, SIPS-N, SIPS-D, SIPS-G) or total score (all $p > 0.05$)—suggesting baseline illness severity may have limited impact—this non-random assignment still introduces the possibility of unmeasured confounding (e.g., uncaptured clinical factors influencing AP prescription). Additionally, we categorized participants into AP + or AP- based on overall 1-year exposure, without collecting granular data on short-term AP use fluctuations or within-participant switches between AP + and AP- status. This binary grouping cannot capture the nuanced impact of dynamic AP exposure patterns on cytokine changes. (2) The sample included in the analysis had a poor sex balance, with males being more likely to use AP than females. This disparity might reduce statistical power and bias the results. Supplementary analysis showed only baseline IL-1β in the AP- group was higher in males than females ($z = -1.974$, $p = 0.048$); no other gender-related cytokine differences existed in either the AP- or AP + group, so this single difference did not confound core AP-related cytokine trajectory comparisons. (3) Due to limited resources, only VEGF, a neurotrophic factor-related cytokine, was included in the study, and the trajectories of change for other factors are unknown. Our focus on VEGF alone means conclusions about neurotrophic factor trajectories should be interpreted with caution, as we cannot rule out that other neurotrophic factors may exhibit different change patterns in response to AP. (4) The CHR status was followed up for only 1 year, and some individuals with CHR may transition to psychosis beyond this timeframe. Although the study primarily focused on the CHR state, there may be differences in conversion rates between the AP + and AP- groups in the future [44], particularly within 2 to 3 years, leading to mismatch between the two groups.

CONCLUSIONS

This study investigated the effects of AP on both inflammatory and neurotrophic factor responses in individuals with CHR status, representing the first examination of its kind in this population. The findings revealed significant differences in trajectories between individuals who were and were not taking AP, indicating that VEGF, IL-1β, and GM-CSF decreased in CHR individuals using AP, while they increased in those without AP usage. These results suggest that AP usage may influence both inflammatory and neurotrophic factor trajectories in CHR individuals. Future directions to build on this work include collecting granular short-term AP use data for shorter observation window analyses, enrolling larger cohorts to enable within-participant pre/post AP comparisons, expanding measured cytokines, and conducting longer follow-up to link AP-related cytokine changes to long-term outcomes like psychosis conversion.

DATA AVAILABILITY

The dataset(s) generated during the current study are not publically available due to ethical restrictions but are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Dr. THZ, YYW, LHX, and JJW. conceptualized the study, wrote the first draft of manuscript and conducted the statistical analyses. QH, HRC, ZHY, and YYW. interviewed participants and collected and organized the primary data. MLJ, HCL, JHZ, JG, YYT, LYZ, and XCT. managed the literature searches, statistical analyses and edited the manuscript. CBL, THZ and JJW. designed the study and provided supervision in the implementation of the study. All authors have approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Research Ethics Committee of the Shanghai Mental Health Center granted ethical approval for the study (2017-36 R). INFORMED consent was obtained from all participants during the recruitment stage. For participants under the age of 18, written parental INFORMED consent was obtained, and adolescents provided verbal assent. The research was conducted in accordance with the Declaration of Helsinki.

ADDITIONAL INFORMATION

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