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Monocyte count in schizophrenia and related disorders: a systematic review and meta-analysis

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Review Article

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Abstract

Objective: Increasing evidence suggests that immunological and inflammatory dysfunctions may play an important role in predisposition, onset, and progression of schizophrenia and related psychosis. The activation of cells of the mononuclear phagocyte system, especially microglia and monocytes, has been reported in schizophrenia. We carried out this systematic review and meta-analysis to investigate if there are significant differences in monocyte count comparing healthy controls with people suffering from schizophrenia and related disorders. *Methods:* We searched main electronic databases; nine records met all our criteria and were included in the meta-analysis. Meta-analyses based on random effects models have been carried out generating pooled standardised mean differences (SMDs) of monocyte count in peripheral blood between schizophrenia and related psychosis and healthy controls. Heterogeneity was estimated. Relevant sensitivity and subgroup analyses were conducted. *Results:* Patients showed higher monocyte count as compared with healthy control (SMD = 0.393; $p = 0.001$). Heterogeneity across studies was from moderate to high ($I^2 = 65.952\%$); sensitivity analysis leaving out two studies responsible for most of the heterogeneity showed a slightly higher SMD. Subgroup analyses confirmed this result, showing no significant differences in the effect size across different study characteristics. *Conclusions:* Monocyte count can be considered an indirect marker of microglia activation in the central nervous system. Thus, the observed higher monocyte count in patients could be considered as a possible peripheral marker of microglia's activation in schizophrenia disorder.

Summations

- Schizophrenia patients showed higher monocyte count as compared with healthy controls.
- Monocyte count should be a possible easy available peripheral marker of microglia's activation in a real-world setting.

Considerations

- The moderate to high statistical heterogeneity across studies that limits the generalisability of our conclusions.
- Considering the limited number of included studies, it was impossible to quantitatively assess the significance of publication bias.

Introduction

Schizophrenia is a heterogeneous psychiatric disorder with a broad spectrum of clinical and biological manifestations; it is recognised as a major mental illness with a prevalence of approximately 1% in the global population (Kessler *et al.*, 2005; Tomasik *et al.*, 2016). While its diagnostic and clinical features are well established, the pathogenesis remains elusive. Different theories have been investigated coming from biological, genetic, and psychosocial approaches (Haraldsson *et al.*, 2011; Kahn and Sommer, 2015).

Among the pathophysiological hypothesis, there is a growing interest in the association between psychosis and the activation of the inflammatory system (Khandaker and Dantzer, 2016; Miller and Goldsmith, 2017).

Various studies suggested an increase of cytokines; some of them appeared to be a state marker as they were increased in acutely relapsed schizophrenia and in first episode psychosis (FEP) and normalised with antipsychotic treatment [interleukin (IL)-1β, IL-6, and transforming

growth factor-β] and some other appeared to be a trait markers, as their levels remained elevated in acute exacerbations and following antipsychotic treatment [IL-12, interferon-γ, tumour necrosis factor-α (TNF-α), and soluble IL-2 receptor (Miller *et al.*, 2011; Guo *et al.*, 2015; Dasdemir *et al.*, 2016; Turhan *et al.*, 2016)]. Moreover, variants of cytokines receptor genes seem to be involved in the pathogenesis of more severe psychosis (Khandaker *et al.*, 2018). Different studies also reported an increase in gene expression and serum levels of acute phase proteins, such as haptoglobin, serum resistin, and c-reactive protein, among patients with schizophrenia or at high risk to develop it later in life (Yang *et al.*, 2006; Miller *et al.*, 2014; Klemettilä *et al.*, 2017; Gurung *et al.*, 2018). Furthermore, abnormal expression of Toll-like receptors has been found in FEP and in the earliest stage of schizophrenia (Kéri *et al.*, 2017). An increased prevalence of autoimmune diseases has been observed in both patients with schizophrenia and their first-degree relatives, suggesting that autoimmune mechanisms may underlie these conditions (Eaton *et al.*, 2006; Larsen *et al.*, 2018).

Monocytes are a subset of leukocyte, derived from haematopoietic stem cells and formed in the bone marrow that can differentiate into macrophages and myeloid lineage dendritic cells. Monocytes are involved in the innate immune response and play a major role in defending the host from invading pathogens and influencing the process of adaptive immunity. The brain hosts several types of monocyte-derived cells, including perivascular cells, meningeal macrophages, choroid plexus macrophages, and microglia (Prinz and Priller, 2014). Peripheral monocyte count is part of the complete blood count, and it is widely used in the clinical setting as a marker of inflammation. There is replicated evidence for increased levels of circulating monocytes in schizophrenia, with monocytosis being especially prevalent in FEP (Drexhage *et al.*, 2011), due to enhanced expression of immune genes and overproduction of monocytes/macrophage-related cytokines (Beumer *et al.*, 2012). Moreover, circulating monocytes can be considered an indirect marker of microglia activation in the central nervous system, and monocytosis seems to be linked with high levels of activated brain microglia (Beumer *et al.*, 2012; Müller *et al.*, 2012). Indeed, under pathological condition, the activation of microglia may be part of systemic activation of the mononuclear phagocyte system that induces activation of circulating monocytes (Beumer *et al.*, 2012; Prinz and Priller, 2014). Post-mortem studies, positron emission tomography (PET) studies and magnetic resonance imaging (MRI) studies founded altered function, reduced density, and increased levels of microglial activation across several brain regions of schizophrenic patients (Radewicz *et al.*, 2000; Laskaris *et al.*, 2016; Trépanier *et al.*, 2016; van Kesteren *et al.*, 2017; Plavén-Sigray *et al.*, 2018). Unfortunately, post-mortem, PET and MRI studies are expensive and hard to execute and they cannot be performed on large numbers of subjects. Thus, circulating monocyte count could represent an easy available indirect marker of the mononuclear phagocyte system activation.

While various meta-analyses and reviews about other inflammatory biomarkers in schizophrenia and related psychosis have already been published, there is a lack of systematic data analysing specifically the monocyte count. Considering that an adequate amount of evidence was collected, we carried out this systematic review and meta-analysis to investigate if there are significant differences in monocyte count in peripheral blood comparing healthy controls (HCs) with people suffering from schizophrenia and related disorders. We attempt to better understand the strengths and consistency of the relationship, taking into account the potential effect of relevant moderators and heterogeneity.

Materials and methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO - registration number: CRD42019121566) (https://www.crd.york.ac.UK/prospero/).

Search strategy

We conducted a systematic search for all possible eligible peer-reviewed articles through PubMed, ScienceDirect, and Cochrane Library electronic databases. The search was extended until January 2019, including only abstracts in English. The publication date was not restricted in our search. According to different bibliographic rules, we combined the following keywords to identify specific and relevant studies: (psychosis OR psychotic OR schizophren* OR schizoaffective) AND (monocyt*). We also screened reference lists from selected articles to identify additional studies that may have been missed.

Eligibility criteria

Inclusion criteria were as follows: (1) adult subjects (≥18 years) diagnosed with schizophrenia and related disorder (schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, schizotypal personality disorder, delusional disorder) according to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria; (2) pairwise comparison with a control group of healthy volunteers; and (3) studies assessing monocyte count in peripheral blood in human blood samples *in vivo*. We considered FEP any first episode of psychosis (DSM diagnosis of schizophrenia and related disorders) occurring between 14 and 40 years in the absence of any substance use disorders. We excluded duplicate publication and overlapping samples to reduce the risk of an inappropriate weighting of study results. We decided to exclude studies with incomplete data, such as conference abstracts and dissertations, and grey literature of uncertain scientific quality or that did not undergo a rigorous peer-review process (Sacks *et al.*, 1996). The decision of whether to include studies in the meta-analyses was based on the above criteria, and a consensus was reached among the authors on those decisions.

Selection of studies and data extraction

After removal of duplicates, two authors (M.G.M. and S.L.) independently completed the preliminary screening based on titles and abstracts and, according to inclusion criteria, evaluated full text for the final decision. Two authors (S.L. and I.T.) independently extracted the following main information from all included studies: first author, year of publication, country, stage of disorder, setting, index, and control sample sizes, mean age, men and women ratio, psychopharmacology treatment and monocyte count for index and control groups. When the necessary data were not available from the published paper, we contacted the authors and requested the necessary information in order to reduce the risk of selective reporting bias and to include unpublished findings. Whenever multiple reports pertained to the same groups of patients, we retained only the most comprehensive report for the meta-analytic calculations to avoid duplication of information. Disagreements in suitability for inclusion were resolved by discussion and consensus, involving the mediation of all co-authors.

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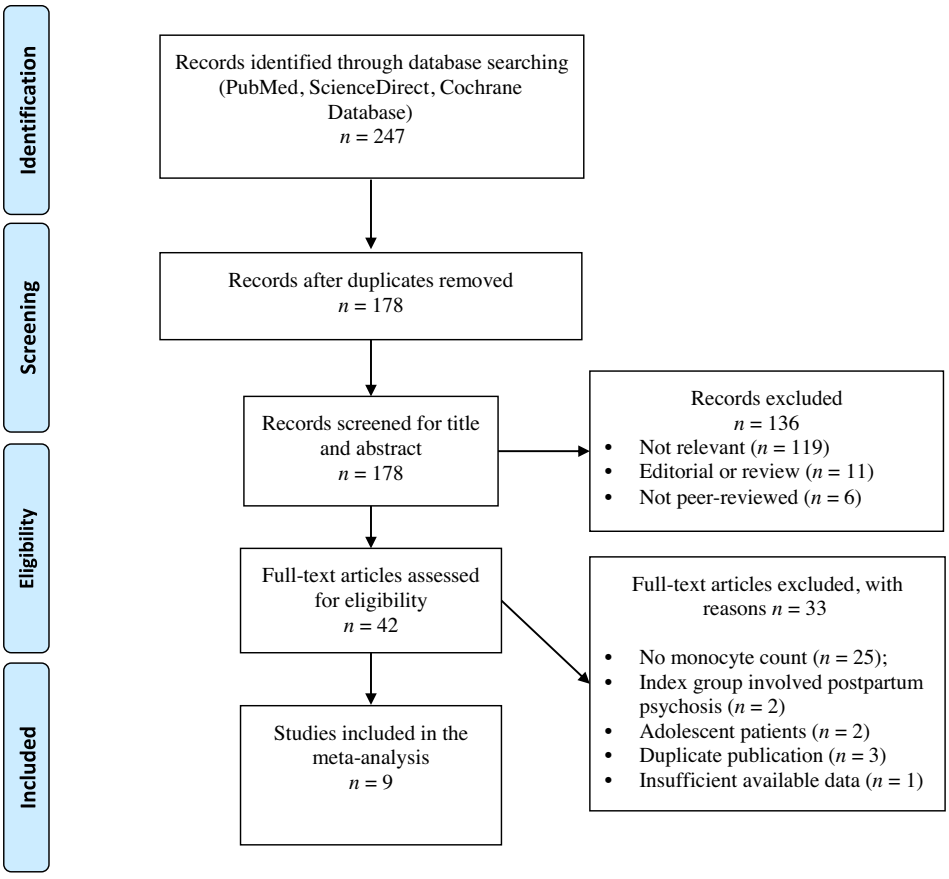

Fig. 1. Flow chart of studies selection process.

Quality assessment

Quality of eligible observational studies was assessed using the Newcastle Ottawa Scale (NOS) for case–control studies (Stang, 2010). Each study was evaluated based on eight items, categorised into three groups: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest for case–control studies. A higher score indicates higher methodological quality.

Data analysis

Meta-analyses of monocyte count were carried out generating pooled standardised mean differences (SMDs), with related 95% confidence intervals (CIs), between patients and HC. To address heterogeneity, meta-analyses were conducted according to the random effects model. Statistical significance was set at $p < 0.05$, and conventional forest plots were used to summarise results. Publication bias was explored using a visual examination of funnel plot. Besides, if at least 10 studies were included in the meta-analysis, Begg's test (Begg & Mazumdar, 1994) and Egger linear regression test were used to assess the symmetry of the effects and to statistically test for publication bias (Sterne *et al.*, 2001). Consistency across studies was measured using the I^2 statistics test (Higgins *et al.*, 2003), with values of 25%, 50%, and 75%, taken to indicate low, moderate, and high levels of heterogeneity, respectively.

We conducted sensitivity analyses removing studies with the strongest effect sizes and studies with the largest sample sizes as recommended by the Cochrane Handbook, section 9.7 (Higgins & Green, 2008). Moreover, for analyses showing significant associations including at least four studies and showing an I^2 higher than 25%, we performed a sequential and combinatorial algorithms' sensitivity analysis leaving out single studies up to *a priori* defined I^2 value of 25% (Patsopoulos *et al.*, 2008). In this approach, for a meta-analysis of n studies, we perform n new meta-analyses, where one study is excluded from the calculations each time. The study that is responsible for the largest decrease in I^2 is dropped and a new set of $n - 1$ studies is created. We continue by successively re-analysing reduced sets of studies and applying the same rule one step before I^2 decreases below the requested I^2 (Patsopoulos *et al.*, 2008). We also carried out subgroup analyses including analysis of statistical difference among subgroups in order to explore the heterogeneity of the effect according to a set of study characteristics such as stage of schizophrenia and related disorder (established disorder vs. FEP), setting (inpatients vs. outpatients), and country of origin (Europe vs. USA). Further, we performed meta-regression analyses (if the number of studies was at least 10) in order to investigate the possible effect of mean age and gender on monocyte count (Higgins & Green, 2008).

Comprehensive Meta-analysis Software version 3.0 (Biostat, Englewood, NJ) was employed in all analyses.

Results

Studies selection and characteristics

Our search generated 247 records. After removing duplicates, screening for title, abstract and full text, nine records met all our criteria and were included in our meta-analysis (Wilke *et al.*, 1996; Zorrilla *et al.*, 1996; Miller *et al.*, 2015; Pavlović *et al.*, 2016;

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Table 1. Characteristics of studies included in the meta-analysis

				Patients					Healthy controls			
Study	Country	Stage of disorder	Setting	*n*	Mean age	Males (*n*)	Treatment	Monocyte	*n*	Mean age	Males (*n*)	Monocyte
Garcia-Rizo *et al.* (2017)	Spain	FEP	Inpatients	75	27.95	51	Naïve	0.43	80	27.79	47	0.40
Miller *et al.* (2015)	USA	Established disorder	Inpatients and outpatients	108	41.8	59	Treated	0.41	44	37.3	19	0.40
Moody *et al.* (2018)	USA	FEP	Inpatients	25	26.1	13	Naïve	0.60	44	29.9	20	0.45
Orhan *et al.* (2018)	Sweden	FEP	Inpatients and outpatients	39	28.3	27	Naïve and treated	0.49	21	25.7	11	0.42
Özdin *et al.* (2017)	Turkey	Established disorder	Inpatients	163	34.51	103	Treated	0.4	157	33.92	85	0.4
Pavlović *et al.* (2016)	Bosnia and Herzegovina	Established disorder	Inpatients	100	n/a	n/a	n/a	0.62	100	n/a	n/a	0.42
Wilke *et al.* (1996)	Germany	Established disorder	Inpatients and outpatients	51	36.2	20	Naïve and treated	0.49	39	34.6	21	0.36
Yüksel *et al.* (2018)	Turkey	Established disorder	Inpatients	52	35.69	30	Naïve and treated	0.62	53	37.06	20	0.48
Zorrilla *et al.* (1996)	USA	Established disorder	n/a	92	30.5	54	Naïve and treated	0.38	94	29.1	52	0.31

FEP, first episode psychosis; n/a, not available.

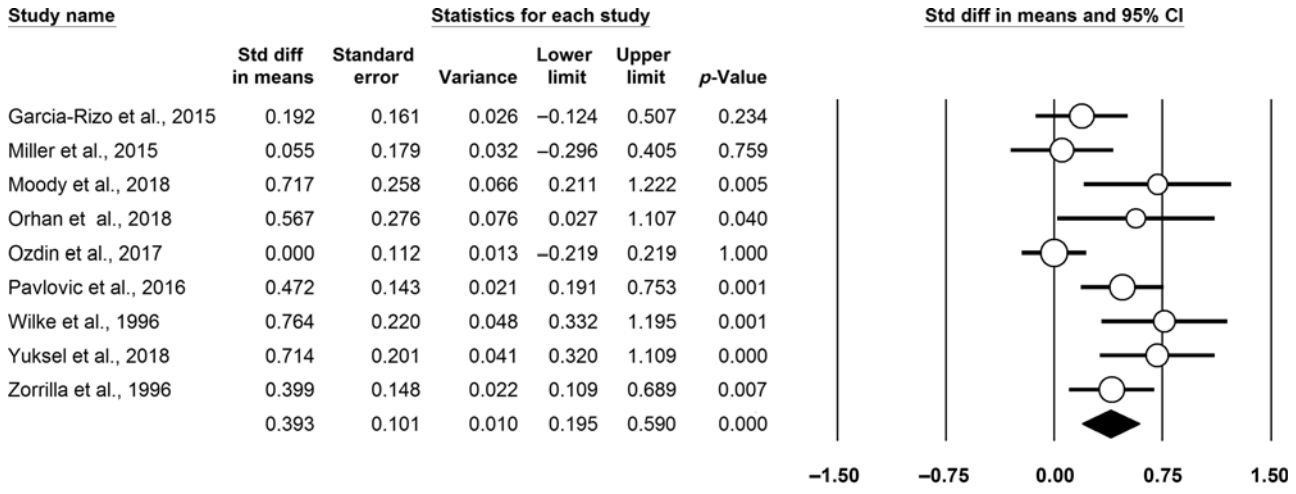

Fig. 2. Forest plot: differences in monocyte count between patients and healthy controls.

Garcia-Rizo *et al.*, 2017; Özdin *et al.*, 2017; Moody and Miller, 2018; Orhan *et al.*, 2018; Yüksel *et al.*, 2018) (Fig. 1).

Included studies were published between May 1996 (Wilke *et al.*, 1996) and July 2018 (Orhan *et al.*, 2018). Considering the stage of the disorder, three studies included FEP patients (Garcia-Rizo *et al.*, 2017; Moody and Miller, 2018; Orhan *et al.*, 2018), while the remaining six studies included subjects affected by established schizophrenia and related psychosis. Two studies included patients treated with psychotropic medications (Miller *et al.*, 2015; Özdin *et al.*, 2017), two included drug-naïve patients (Garcia-Rizo *et al.*, 2017; Moody and Miller, 2018), four included mixed samples of drug-treated and drug-free patients (Wilke *et al.*, 1996; Zorrilla *et al.*, 1996; Orhan *et al.*, 2018; Yüksel *et al.*, 2018), whereas for one study, this information was not available (Pavlović *et al.*, 2016). All the included studies showed high methodological quality, one study obtained six stars at NOS (Pavlović *et al.*, 2016), three studies obtained seven stars at NOS (Wilke *et al.*, 1996; Özdin *et al.*, 2017; Yüksel *et al.*, 2018), while the remaining four studies obtained eight stars at NOS.

Since the included studies were less than 10, we could not assess the risk of publication bias. Full details of the included studies are summarised in Table 1.

Meta-Analysis

Nine studies (Wilke *et al.*, 1996; Zorrilla *et al.*, 1996; Miller *et al.*, 2015; Pavlović *et al.*, 2016; Garcia-Rizo *et al.*, 2017; Özdin *et al.*, 2017; Moody and Miller, 2018; Orhan *et al.*, 2018; Yüksel *et al.*, 2018), based on nine different samples accounting for 1337 individuals, provided data suitable for monocyte count between patients ($n = 705$) and HC ($n = 632$).

Psychotic patients had higher monocyte count as compared with HC (SMD = 0.393; 95% CI: 0.195 to 0.590; $p = 0.001$) (Fig. 2). Heterogeneity across studies was from moderate to high

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Table 2. Monocytes count SMD by single study characteristics: subgroup analyses

	No. of studies	SMD (95% CI)	I^2 (%)	*p*	Test of difference between subgroups		
					Q-value	df (*Q*)	*p*-Values
Country							
Europe	6	0.417 (0.149–0.685)	73.179	0.000*	0.077	1	0.782
USA	3	0.357 (0.023–0.690)	58.609	0.001*			
Setting							
Inpatients	5	0.381 (0.094–0.669)	74.816	0.000*	0.047	1	0.977
Inpatients and outpatients	3	0.442 (−0.022–0.905)	70.590	0.002*			
Stage of disorder							
FEP	3	0.438 (0.098–0.778)	43.386	0.002*	0.082	1	0.775
Established disorder	6	0.376 (0.121–0.630)	74.523	0.000*			

SMD, standardised mean differences; FEP, first episode psychosis.
* Significantly different: $p < 0.05$; Statistical trend: $0.05 < p < 0.1$.

($I^2 = 65.952\%$). Sensitivity analyses removing the study with the strongest effect size (Wilke *et al.*, 1996) showed no difference in SMD and heterogeneity (SMD = 0.350; 95% CI: 0.152 to 0.547; $p = 0.001$; $I^2 = 63.484\%$), while sensitive analysis removing the study with the largest sample size (Özdin *et al.*, 2017) showed slightly higher SMD and moderate heterogeneity (SMD = 0.449; 95% CI: 0.274 to 0.624; $p = 0.000$; $I^2 = 43.697\%$). Sensitivity analysis, based on the sequential and combinatorial algorithms, leaving out two studies responsible for most of the heterogeneity (Miller *et al.*, 2015; Özdin *et al.*, 2017), showed a slightly higher SMD (SMD = 0.497; 95% CI: 0.341 to 0.652; $p = 0.000$; $I^2 = 19.553\%$). Subgroup analyses showed no significant differences in the effect size across different study characteristics (stage of disorder, setting, and country of origin) (Table 2). Visual examination of the funnel plot showed a slight asymmetry (Supplementary Fig. 1), considering that the studies were fewer than 10, it was impossible to quantitatively assess the significance of publication bias.

Discussion

Main findings

The present meta-analysis is the first to explore the monocyte count in peripheral blood in schizophrenia and related psychosis compared to HC. We included nine studies, all of them showed high methodological quality according to the NOS for case–control studies, reinforcing our results. We observed that people suffering from schizophrenia and related psychosis showed statistically significant higher monocyte count than HC. According to conventional cut-offs, the effect was small to medium. Heterogeneity was from moderate to high. Relevant sensitivity analysis removing the study with the largest sample sizes (Özdin *et al.*, 2017) and sequential and combinatorial sensitivity analysis leaving-out Miller *et al.* (2015) and Özdin *et al.* (2017) studies showed an effect size slightly higher than the overall meta-analysis. Subgroup analysis revealed no influence of different study characteristics on the effect size excluding that the observed heterogeneity should be explained by the explored covariates. Meta-regression exploring the effect of mean age and gender was not conducted because the number of included studies was fewer than 10. Visual examination of the funnel plot showed a slight asymmetry suggesting a possible presence of publication bias, considering the small number of included studies, we cannot conduct Begg's and Egger test to quantify the significance of publication bias.

Interpretation of findings

This meta-analysis, showing higher levels of monocytes in schizophrenia and related psychosis compared to HC, should be read in the context of activation of cells of the mononuclear phagocyte system, with a particular focus on circulating monocytes and their possible cross-talk with the microglia.

Monocytosis has been observed in schizophrenia both in treated and drug-naïve subjects, in FEP, and in children with psychosis (Zorrilla *et al.*, 1996; Drexhage *et al.*, 2011). Monocytosis is associated with worsening of psychotic symptoms, and it is modulated by antipsychotic treatment (Dimitrov, 2011; Miller & Goldsmith, 2017). Accumulation of monocytes and macrophages has also been found in the cerebrospinal fluid of patients with schizophrenia during acute psychotic episodes (Nikkilä *et al.*, 1999). In addition to peripheral monocytosis, enhanced expression of inflammatory genes in circulating monocytes has been observed in non-affective psychosis. In particular, schizophrenia patients showed an activated monocyte gene cluster including IL-1β, IL-6, TNF, Prostaglandin-endoperoxide synthase 2, Pentraxin-3, and various proinflammatory chemokines. Interestingly, the overexpression of these genes was particularly evident in active psychosis (Drexhage *et al.*, 2010). Moreover, increased levels of cytokines mainly produced by monocytes (such as IL-1β, IL-6, IL-12, and TNF) or cytokines having a primary effect on mononuclear phagocyte system (such as granulocyte-macrophage colony-stimulating factor, monocyte chemoattractant protein-1, macrophage inflammatory protein-1α and 1β) have been found in schizophrenia (Miller *et al.*, 2011; Frydecka *et al.*, 2018; Gallego *et al.*, 2018).

The mononuclear cells, in their brain (microglia), circulation (monocytes), and tissue (macrophages) components, have been considered as a key element in the two-hit pathogenesis model for psychosis (Bergink *et al.*, 2014). Gene–environment interactions (such as infection or stress) during foetal or early life in genetically susceptible individuals induce an aberrant pro-inflammatory differentiation of myeloid precursors to monocytes, macrophages, dendritic cells, and microglia. This inflammatory activation induces an abnormal growth, differentiation, and function of brain neuronal circuitry and leads to a "vulnerable brain"

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(first hit). The second hit takes place later, usually during adolescence, in the form of various exogenous or endogenous stimuli (microbes, stress, puberty, postpartum period), leading to a further and excessive microglia activation resulting in abnormalities of the neuronal circuitry in the brain and psychosis (Picker *et al.*, 2017). PET studies highlighted the microglial activation or dysfunction in schizophrenia patients, while neuroimaging investigation confirmed structural brain changes in both white and grey matter regions in patients with FEP and schizophrenia (Beumer *et al.*, 2012; Laskaris *et al.*, 2016; Plavén-Sigray *et al.*, 2018). In this context, the microglia activation seems to be caused or accompanied by monocyte activation reflected by the above-mentioned blood monocytosis, enhanced inflammatory gene expression in monocytes, and high serum levels monocyte/macrophage-related cytokines (Beumer *et al.*, 2012). This cross-talk between monocytes and microglia is mainly mediated by cytokines found to be increased in schizophrenia such as IL-1β, IL-6, IL-8 or TNF-α (Beumer *et al.*, 2012), suggesting a role of monocytes and microglia's interaction in the pathophysiology of psychosis (Miller *et al.*, 2011; Notter and Meyer, 2017). Moreover, a recent study that identified brain tissue macrophages proximal to neurons in schizophrenic patients in high inflammatory state speculates on the monocytes capacity for infiltrating brain tissue when high inflammatory status drives the inflammatory cascade by signalling to microglia (Cai *et al.*, 2018).

All these evidence highlight a possible role of the mononuclear phagocyte system in the pathophysiology of psychotic disorders. Considering the activation of the microglia as part of a systemic activation of the mononuclear phagocyte system and the proofs of cross-talking between microglia and monocytes when an inflammation occurs, we can speculate that the observed higher monocyte count in psychotic patients is a reflex of the high levels of activated brain microglia (Beumer *et al.*, 2012; Garcia-Rizo *et al.*, 2017). We suggest, therefore, monocyte count as a possible easy available peripheral marker of microglia's activation in a real-world setting. Monocyte count is inexpensive, often routinely available, and it can be calculated in large, already collected data sets. It is also characterised by minimal patient discomfort, making it easily replicable.

This result is consistent with the higher monocyte to lymphocyte ratio (MLR) observed in non-affective psychosis compared to HC found in our previous meta-analysis (Mazza *et al.*, 2019). Even if MLR, reflecting two immune pathways, is probably more predictive in evaluating inflammation than monocytes alone, we decided to deepen the investigation in the field with the present meta-analysis considering that by now there are only a few studies investigating MLR in psychosis.

Limitation

This meta-analysis should be considered in the context of the following limitations that may affect confidence on findings. First, although we tested effects of setting, stage of disorder, and country of origin, it should be considered that other covariates, such as lifestyle, smoking, BMI, and ethnicity, might influence this association. Moreover, the small number of studies including naïve ($n = 2$ studies) and treated ($n = 2$ studies) cohorts did not allow us to conduct a subgroup analysis investigating for the effect of the psychopharmacological treatment on the monocyte blood cell count. Second, we found a moderate to high statistical heterogeneity across studies that, even if explored using sensitivity and subgroups analysis, partially limits the generalisability of our conclusions. Third, considering the need for strict and rigorous diagnostic criteria according to American Psychiatric Association, we decided to exclude grey literature in order to reduce the risk of including low-quality studies not receiving peer-review process. However, the decision to exclude the grey literature should be considered as a possible limitation because it may provide data not found within published literature, providing an important forum for disseminating studies with null or negative results, thus excluding this source of literature could increase the publication bias (Paez, 2017). Fourth, since several studies have been excluded due to our restrictive inclusion criteria, we included a limited number of studies and it was impossible to quantitatively assess the significance of publication bias. Moreover, we have to consider that cross-sectional studies are difficult to publish if the results are negative. Fifth, considering that the number of included studies was fewer than 10, we did not conduct meta-regression analysis exploring the effect of age and gender. Finally, all included studies had relatively moderate sample sizes and modest effect size limiting the strengths of the overall estimated effect size. In sum, judgement about evidence from this meta-analysis should be considered modest so far.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/neu.2020.12

Author contributions. MGM, AR and MC designed the study and wrote the protocol. IT and SL collected the data. MGM and AR conducted the analysis and interpretation of data. MGM, AR, MC, and MC wrote the first draft of the manuscript. IT and SL revised the manuscript. All authors contributed to and have approved the final manuscript.

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Conflict of interest. None.

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