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Altered peripheral blood compounds in drug-naïve first-episode patients with either schizophrenia or major depressive disorder: a meta-analysis

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ABSTRACT

Importance: Schizophrenia and major depressive disorder (MDD) are associated with increased risks of immunologic disease and metabolic syndrome. It is unclear to what extent growth, immune or glucose dysregulations are similarly present in these disorders without the influence of treatment or chronicity.
Objective: To conduct a meta-analysis investigating whether there are altered peripheral growth, immune or glucose metabolism compounds in drug-naïve first-episode patients with schizophrenia or MDD compared with controls.
Data sources and study selection: Case-control studies reporting compound measures in drug-naïve first-episode patients with schizophrenia or MDD compared with controls in the Embase, PubMed and PsycINFO databases.
Data extraction and synthesis: Two independent authors extracted data for a random-effects meta-analysis.
Main outcomes and measures: Peripheral growth, immune or glucose metabolism compounds in schizophrenia or MDD compared with controls. Standardized mean differences were quantified with Hedges' *g (g)*.
Results: 74 studies were retrieved comprising 3453 drug-naïve first-episode schizophrenia patients and 4152 controls, and 29 studies were retrieved comprising 1095 drug-naïve first-episode MDD patients and 1399 controls. *Growth factors:* brain-derived neurotrophic factor (BDNF) (g = -0.77, P < .001) and nerve growth factor (NGF) (g = -2.51, P = .03) were decreased in schizophrenia. For MDD, we observed a trend toward decreased BDNF (g = −0.47, P = .19) and NGF (g = −0.33, P = .08) levels, and elevated vascular endothelial growth factor levels (g = 0.40, P = .03). *Immune factors:* interleukin (IL)-6 (g = 0.95, P < .001), IL-8 (g = 0.59, P = .001) and tumor necrosis factor alpha (TNFα) (g = 0.48, P = .002) were elevated in schizophrenia. For C-reactive protein (CRP) (g = 0.57, P = .09), IL-4 (g = 0.44, P = .10) and interferon gamma (g = 0.33, P = .11) we observed a trend toward elevated levels in schizophrenia. In MDD, IL-6 (g = 0.62, P = .007), TNFα (g = 1.21, P < .001), CRP (g = 0.53, P < .001), IL-1β (g = 1.52, P = .009) and IL-2 (g = 4.41, P = .04) were elevated, whereas IL-8 (g = −0.84, P = .01) was decreased. The fasting *glucose metabolism* factors glucose (g = 0.24, P = .003) and insulin (g = 0.38, P = .003) were elevated in schizophrenia.
Conclusions and relevance: Both schizophrenia and MDD show alterations in growth and immune factors from disease onset. An altered glucose metabolism seems to be present from onset in schizophrenia. These findings support efforts for further research into transdiagnostic preventive strategies and augmentation therapy for those with immune or metabolic dysfunctions.

1. Introduction

Traditionally, schizophrenia and major depressive disorder (MDD) are seen as separate disorders based on their distinct clinical presentation. In clinical practice, however, overlapping symptoms are noticeable such as psychotic symptoms, apathy and cognitive

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dysfunction (Hill et al., 2009). Moreover, genetic and environmental risk factors point towards shared vulnerability between both disorders. A large genome-wide study showed that single-nucleotide polymorphisms are shared between major psychiatric disorders including schizophrenia and MDD (Lee et al., 2013). Environmental risk factors for development of psychopathology such as the experience of stress, urbanicity or low socioeconomic status increase risk for all psychiatric diagnoses (Buckholtz and Meyer-Lindenberg, 2012).

Impairment of neuroplasticity and vascularization in the brain are thought to underlie schizophrenia and MDD (Rao et al., 2017; Birkenhager et al., 2012; Xie et al., 2017; Brugger and Howes, 2017; Chen et al., 2017). Neurotrophic factors, including brain derived neurotrophic factor (BDNF), contribute to neuroplasticity, and are therefore key components for cognition, which is a well-known key dysfunction of both schizophrenia and MDD (Rao et al., 2017; Benraiss et al., 2001; Pencea et al., 2001). Reduced BDNF levels in peripheral blood have often been demonstrated in schizophrenia and MDD (Fernandes et al., 2015; Molendijk et al., 2014). Increasing evidence shows that neuroinflammation plays an important role in the pathophysiology of schizophrenia and MDD, in both disorders components of the immune system in the brain (i.e. microglia) are in an altered state of activity (Fineberg and Ellman, 2013; Brites and Fernandes, 2015). As a result, microglia and other glia may reduce their neurotrophic function and produce less growth factors, such as BDNF, leading to decreased neuron proliferation, resulting in reduced connectivity and this may finally result in neurodegeneration (Brites and Fernandes, 2015; Chew et al., 2013). Neuroinflammation may enhance the production of peripheral neurotoxic inflammatory factors (Monji et al., 2009; Drexhage et al., 2011).

There is accumulating evidence that dysregulations in components of the immune system are linked to schizophrenia and MDD. Findings of a large Danish cohort study suggest the existence of shared immune factors for schizophrenia and endocrine autoimmune diseases (including type 1 diabetes) as they have a relatively high familial co-occurrence (Eaton et al., 2010). Genetic associations show that patients with schizophrenia or MDD on average may have an immune system subtly more prone to being activated, as expressed for example in major histocompatibility complex molecules in schizophrenia and associations between polymorphisms in immune genes and MDD (Debnath et al., 2013; Mokhtari and Lachman, 2016; Barnes et al., 2017). There is meta-analytic evidence that peripheral cytokines are altered in first-episode psychosis (Pillinger et al., 2018) and in depression (Kohler et al., 2017). It has been suggested that both anti- and pro-inflammatory factors play a role in healthy brain functioning, and that an imbalance in these factors may lead to detrimental consequences for the brain (Golia et al., 2019). Brain function can be altered by immunological or hormonal changes originating in the periphery, i.e. the brain is integrated in biological functions of the body which is reflected by changes in the molecular composition of the blood (Chan et al., 2014).

Impaired cerebral glucose utilization in brain areas could also play an important role in the pathogenesis of psychiatric disorders, exemplified by metabolic disconnection of the dorsolateral prefrontal cortex and mediodorsal thalamus with the limbic system in schizophrenia (Steiner et al., 2014; Buchsbaum et al., 2007; Mitelman et al., 2005). There is meta-analytic evidence for peripheral glucose metabolism alterations in (antipsychotic-naïve) first-episode patients with schizophrenia compared with controls (Pillinger et al., 2017; Greenhalgh et al., 2017; Perry et al., 2016; Kucukgoncu et al., 2019). A prospective cohort study of a general population sample found an increased incidence of metabolic syndrome and increased fasting glucose levels in the atypical MDD subtype, which could not be attributed to lifestyle factors alone (Lasserre et al., 2017). Taken together, these alterations in growth, immune or glucose metabolism compounds may point to shared neurobiological processes between schizophrenia and MDD.

Therefore, in recent years there has been an increasing interest in the transdiagnostic aspects of schizophrenia and MDD (Wigman et al., 2015; Van Os et al., 2009). Accumulating evidence presents similarity in altered growth, immune and glucose metabolism factors in schizophrenia and MDD. However, most studies report measurements of peripheral blood compounds of patients who use psychotropic medication or are chronically ill. Therefore, it is unknown to what extent treatment or other factors associated with chronicity influence these alterations in both disorders. A better understanding of the underlying pathophysiology of both psychiatric disorders is mandatory in order to plan for shared preventive strategies and treatment regarding immune and metabolic dysfunctions prevalent in these disorders.

In this meta-analysis we aimed to answer the following question: which peripheral growth, immune or glucose metabolism compounds are altered in drug-naïve first-episode patients with either schizophrenia or MDD compared with healthy controls? Moreover, we aimed to answer the question whether altered compounds in schizophrenia or MDD are changed in a similar or dissimilar direction and magnitude.

2. Methods

2.1. Study selection

The literature was systematically reviewed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (Supplementary Tables 1 and 2) (Moher et al., 2009; Stroup et al., 2000). Two independent investigators (N.Ç. and N.v.B.) searched the PubMed, Embase and PsycINFO databases from inception to January 19th, 2019, for meta-analyses, systematic reviews and case-control studies that reported measurements of peripheral blood compounds which are involved in growth, immune and metabolic processes in drug-naïve first-episode patients with either schizophrenia or MDD compared with healthy controls. Details of the search strategy are provided in Supplementary Table 3. We first screened for meta-analyses and systematic reviews that systematically searched for peripheral blood compounds in schizophrenia and MDD, which did not necessarily restrict their inclusions to drug-naïve or first-episode patients. Next, we extracted drug-naïve first-episode case-control studies from meta-analyses and systematic reviews with high quality, as assessed with the Assessing the Methodological Quality of Systematic Reviews quality assessment. For our final inclusion of studies, we screened for drug-naïve first-episode case-control studies starting from the last search date of inclusion in the retrieved meta-analyses or systematic reviews. If high-quality meta-analyses or systematic reviews were not available for a respective compound, we searched for drug-naïve first-episode case-control studies that reported measurements of these compounds from inception. No language restrictions were applied. Authors were contacted if additional data was needed for analysis (e.g., if drug-naïve or first-episode patients were only a subset of the total study population). We contacted authors for full report of relevant unpublished studies.

We completed the search by hand-searching additional relevant meta-analyses, systematic reviews and case-control studies. Disagreements were resolved by discussion with another author (L.d.H.).

2.2. Inclusion criteria

Inclusion criteria were (1) observational studies including a control group; (2) a Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Statistical Classification of Diseases (ICD) diagnosis of schizophrenia, schizophreniform disorder or MDD; (3) a healthy control group; (4) assessment of peripheral compounds in serum or plasma which are involved in growth, immune or metabolic processes; (5) peripheral compounds that are involved in the glucose homeostasis under fasting conditions; (6) antipsychotic-naïve patients

with schizophrenia and antidepressant-naïve patients with MDD; (8) first-episode of disease.

2.3. Data extraction and processing

Two authors (N.Ç. and N.v.B.) independently extracted means and standard deviation of measures of growth, immune and glucose metabolism compounds from the retrieved case-control studies. If there were multiple publications from the same cohort, we extracted data from the largest or most recent data set.

To identify quality of the studies we used the Newcastle-Ottawa quality assessment scale (NOS) (Wells et al., 2009). For sensitivity analyses we re-ran our analyses including high-quality studies only: as a cut-off value for high-quality studies we chose that all case-control studies should meet at least two thirds of the NOS criteria, implying a cut-off score of 6.

2.4. Statistical analysis

We included a compound for analysis if at least two studies reported measurements on the respective compound. We calculated standardized mean differences, represented as Hedges' *g*, using random-effects meta-analyses. A random-effects model was used in all compounds as we expected high heterogeneity of data across studies. Since the study mean differences are first standardized before weighting is applied, effect sizes could be directly compared across different measurement scales. We assessed heterogeneity across studies using the Cochran Q statistic (Bowden et al., 2011). Inconsistency across studies was assessed with the I_2 statistic, with assigning adjectives of low, moderate and high heterogeneity to I_2 values of 0–<25%, 25%–75% and >75% (Higgins et al., 2003). Since, we observed heterogeneity in the included studies, we used the method of DerSimonian and Laird for calculating the random-effects pooled effect size and 95% confidence interval to provide a lower type I error. We assessed potential publication bias using the Egger test of the intercept (Egger et al., 1997) if 10 or more studies were analysed for the same compound with funnel plots (Supplementary Figs. 1–8) (as recommended by the Cochrane Collaboration). Additionally, we compared the effect sizes statistically of each compound between schizophrenia and MDD using a Wald-type test (Pillinger et al., 2019). We entered each pair of effect size into a fixed effects model, given that the residual heterogeneity has already been accounted for in the initial random effects meta-analyses. Next, we calculated subgroup summary effect size magnitudes by running a combined analysis of all studies assigned to a subgroup, i.e. growth, immune, and glucose. Subsequently, we statistically compared the subgroup summary effect sizes of growth, immune, and glucose in schizophrenia versus MDD. Finally, in a sensitivity analysis, we restricted our analyses to high-quality studies only to reassess the direction of change and magnitude of the compounds in schizophrenia and MDD. We considered a 2-tailed *P* value <0.05 as significant for all analyses. All analyses were performed using the meta- and metafor-packages (Schwarzer, 2007; Viechtbauer, 2010) in R software 3.4.0 (R Development Core Team, 2008).

2.5. Terminology

To keep in line with most authors we chose to use the term first-episode schizophrenia, however not all patients with a first episode of psychosis included fulfil DSM or ICD criteria of schizophrenia. Therefore, it would be appropriate to mention that these patients had experienced a first episode of schizophrenia or a related disorder.

3. Results

3.1. Retrieved studies

A total of 74 case-control studies were retrieved comprising of 3453 drug-naïve and first-episode schizophrenia patients and 4152 controls, and a total of 29 studies were retrieved comprising of 1095 drug-naïve and first-episode MDD patients and 1399 controls. Of the following 17 compounds at least two studies were available for meta-analysis for both disorders: *growth factors* BDNF, nerve growth factor (NGF), and vascular endothelial growth factor (VEGF); *immune factors* C-reactive protein (CRP), interferon gamma (IFNγ), interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, monocyte Chemoattractant Protein-1 (MCP-1), and transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNFα); *glucose factors* fasting glucose and insulin concentration. The selection process is presented in Supplementary Fig. 9. Study characteristics such as setting, number of patients and controls, gender, age and type of control matching are provided in Supplementary Table 4. Additional study characteristics such as catchment area, sample source (serum or plasma), fasting state and criteria used for patients and controls in the included studies are provided in Supplementary Tables 5 and 6. The risk of bias of the included studies is provided in Supplementary Table 7.

3.2. Growth factors

Fig. 1 shows the effect sizes for growth factors in drug-naïve first-episode patients with schizophrenia or MDD compared with controls.

Schizophrenia patients showed significantly decreased levels of BDNF ($g = -0.77$; 95% CI, −0.97 to −0.56; $P < .001$; $I^2 = 78\%$) (Fig. 2) and NGF (Fig. 3) ($g = -2.51$; 95% CI, −4.80 to −0.21; $P = .03$; $I^2 = 98\%$) compared with controls. No indication of publication bias for BDNF studies was found (Egger test $P = .19$). For MDD patients, we found a trend of decreased BDNF levels ($g = -0.47$; 95% CI, −1.18 to 0.24; $P = .19$; $I^2 = 95\%$), without indication of publication bias (Egger test $P = .37$), and a trend toward decreased NGF levels ($g = -0.33$; 95% CI, −0.69 to 0.04; $P = .08$; $I^2 = 0\%$) compared with controls.

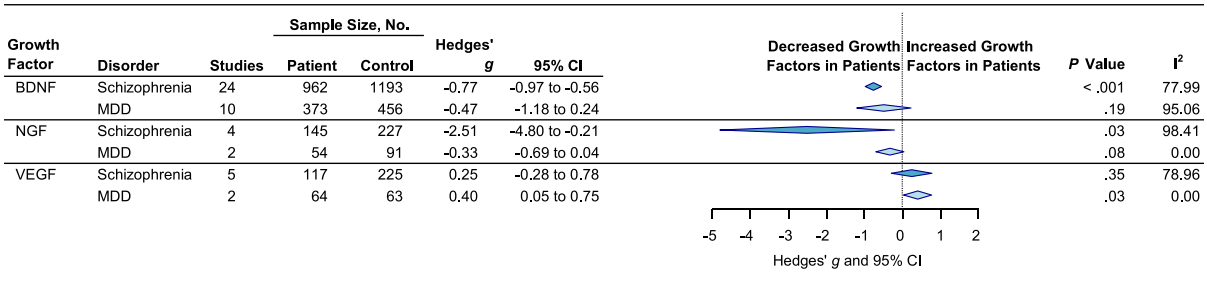

Fig. 1. *Forest Plot Showing Effect Sizes for Growth Factors in Drug-Naïve First-Episode Schizophrenia and MDD.*
Diamonds illustrate the summary effect sizes, the middle of each diamond represents the summary effect size, and the width of the diamond depicts the width of the overall 95% CI. Abbreviations: BDNF, brain-derived neurotrophic factor; MDD, major depressive disorder; NGF, nerve growth factor; VEGF, vascular endothelial growth factor.

Source	Sample Size, No. Patient	Control	Hedges' g	95% CI	Weight
Schizophrenia					
Bakirhan et al, 2017	30	80	-1.31	-1.76 to -0.85	4.43
Bocchio-Chiavetto et al, 2018	17	49	0.29	-0.27 to 0.84	4.01
Buckley et al, 2007	15	14	-4.85	-6.38 to -3.32	1.37
Chen et al, 2009	88	90	-0.92	-1.23 to -0.61	5.02
Chiou et al, 2017	34	34	-0.88	-1.38 to -0.38	4.25
Gonzalez-Pinto et al, 2010	12	18	-0.60	-1.35 to 0.15	3.23
Huang et al, 2006	10	96	-0.41	-1.06 to 0.25	3.60
Jindal et al, 2010	24	41	-0.53	-1.04 to -0.01	4.19
Jockers et al, 2004	102	61	-0.02	-0.33 to 0.30	4.99
Jordan et al, 2018	22	43	-0.95	-1.49 to -0.41	4.07
Kalmady et al, 2013	59	60	-0.60	-0.97 to -0.23	4.80
Li et al, 2018	53	57	-1.28	-1.69 to -0.87	4.62
Man et al, 2018	80	80	-1.22	-1.56 to -0.88	4.91
Palomino et al, 2006	21	18	-0.98	-1.65 to -0.31	3.53
Pillai et al, 2010	47	44	-0.40	-0.81 to 0.02	4.60
Rizos et al, 2010	37	22	-1.27	-1.84 to -0.69	3.91
Rizos et al, 2011	20	21	-0.98	-1.63 to -0.33	3.61
Schwarz et al, 2012	71	59	-0.46	-0.81 to -0.11	4.87
Shimizu et al, 2003	15	40	-0.52	-1.13 to 0.08	3.81
Şimşek et al, 2015	26	26	-0.55	-1.10 to 0.01	4.01
Song et al, 2014	46	30	-0.54	-1.01 to -0.07	4.38
Sotiropoulou et al, 2013	50	50	-0.93	-1.34 to -0.52	4.61
Xiao et al, 2017	58	55	-0.99	-1.39 to -0.60	4.70
Zakharyan et al, 2014	25	105	-0.22	-0.66 to 0.22	4.51
	962	**1193**	**-0.76**	**-0.97 to -0.56**	
MDD					
Aydemir et al, 2006	20	20	-0.91	-1.57 to -0.26	9.87
Chiou et al, 2017	71	71	-0.44	-0.78 to -0.11	10.52
Jordan et al, 2018	18	43	-0.59	-1.15 to -0.03	10.09
Karlovic et al, 2013	122	142	-1.90	-2.19 to -1.60	10.58
Kheirori et al, 2016	44	41	1.48	1.00 to 1.96	10.26
Martocchia et al, 2014	5	10	-0.69	-1.81 to 0.42	8.52
Ristevska-Dimitrovska et al, 2013	23	23	-1.56	-2.23 to -0.90	9.83
Shimizu et al, 2003	16	50	-0.88	-1.46 to -0.30	10.04
Skibinska et al, 2018	30	30	0.33	-0.18 to 0.84	10.20
Tsuchimine et al, 2015	24	26	0.38	-0.18 to 0.94	10.09
	373	**456**	**-0.47**	**-1.18 to 0.24**	

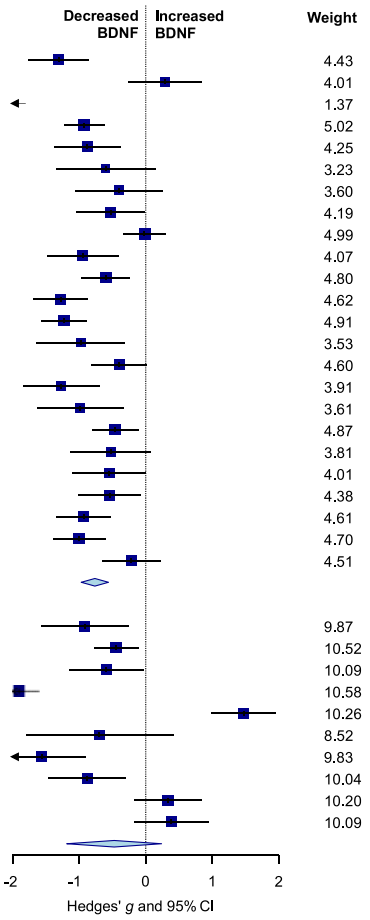

Fig. 2. *BDNF Levels in Patients with Drug-Naïve First-Episode Schizophrenia or MDD and Controls.*
Each square resembles the effect size for a single study. The horizontal line running through each square illustrates the width of the 95% CI. The size of the squares reflects the weight attributed to each study. Diamonds illustrate the summary effect sizes and the width of the diamonds reflect the width of the overall 95% CI. Abbreviations: BDNF, Brain-Derived Neurotrophic Factor; MDD, Major Depressive Disorder.

Conversely, VEGF levels were not altered in schizophrenia patients (g = 0.25; 95% CI, −0.28 to 0.78; P = .35; I^2 = 79%), whereas MDD patients showed significantly elevated VEGF levels compared with controls (g = 0.40; 95% CI, 0.05 to 0.75; P = .03; I^2 = 0%). See Supplementary Figs. 10–12 for effect size estimates for individual studies.

3.3. Immune factors

Fig. 4 shows the effect sizes for immune factors in drug-naïve first-episode patients with schizophrenia or MDD compared with controls.

For CRP, we observed a trend of increased levels in schizophrenia patients compared with controls (g = 0.57; 95% CI, −0.09 to 1.23; P = .09; I^2 = 93%). CRP levels were significantly increased in MDD with a similar effect size compared with schizophrenia (g = 0.53; 95% CI, 0.24 to 0.82; P < .001; I^2 = 41%). For IFNγ, we observed a trend of

Source	Sample Size, No. Patient	Control	Hedges' g	95% CI	Weight
Schizophrenia					
Jockers-Scherübl et al, 2006	66	51	-0.27	-0.64 to 0.10	25.41
Kale et al, 2009	30	42	-0.76	-1.24 to -0.27	25.29
Parikh et al, 2003	24	14	-1.64	-2.41 to -0.88	24.87
Zakharyan et al, 2014	25	120	-10.62	-11.68 to -9.56	24.44
	145	**227**	**-2.51**	**-4.80 to -0.21**	
MDD					
Kheirori et al, 2016	44	41	-0.26	-0.69 to 0.17	72.00
Liu et al, 2014	10	50	-0.50	-1.18 to 0.19	28.00
	54	**91**	**-0.33**	**-0.69 to 0.04**	

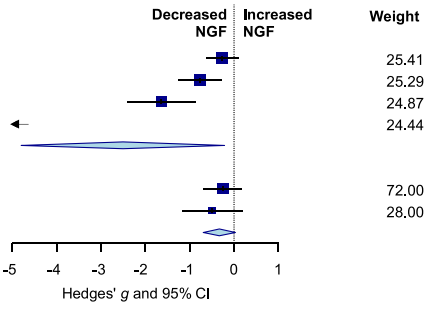

Fig. 3. *NGF Levels in Patients with Drug-Naïve First-Episode Schizophrenia or MDD and Controls.*
Each square resembles the effect size for a single study. The horizontal line running through each square illustrates the width of the 95% CI. The size of the squares reflects the weight attributed to each study. Diamonds illustrate the summary effect sizes and the width of the diamonds reflect the width of the overall 95% CI. Abbreviations: NGF, Nerve Growth Factor; MDD, Major Depressive Disorder.

Immune Factor	Disorder	Studies	Sample Size, No. Patient	Control	Hedges' g	95% CI	P Value	I^2
CRP	Schizophrenia	6	283	431	0.57	-0.09 to 1.23	.09	92.77
	MDD	5	179	210	0.53	0.24 to 0.82	< .001	41.02
IFNγ	Schizophrenia	11	334	468	0.33	-0.08 to 0.73	.11	83.12
	MDD	2	66	71	-0.33	-1.31 to 0.66	.51	86.70
IL-1β	Schizophrenia	9	298	413	0.42	-0.30 to 1.15	.25	94.27
	MDD	5	249	239	1.52	0.38 to 2.66	.009	96.36
IL-2	Schizophrenia	10	249	401	0.13	-0.38 to 0.63	.63	87.11
	MDD	3	76	76	4.41	0.13 to 8.69	.04	98.15
IL-4	Schizophrenia	8	308	366	0.44	-0.08 to 0.96	.10	88.14
	MDD	2	49	49	-1.71	-4.73 to 1.31	.27	96.99
IL-6	Schizophrenia	14	540	728	0.95	0.57 to 1.32	< .001	87.92
	MDD	6	334	291	0.62	0.17 to 1.06	.007	85.40
IL-8	Schizophrenia	6	123	262	0.59	0.23 to 0.95	.001	54.08
	MDD	2	143	126	-0.84	-1.48 to -0.20	.01	75.97
IL-10	Schizophrenia	10	567	1003	0.13	-0.21 to 0.46	.46	85.45
	MDD	3	170	153	-0.75	-2.77 to 1.28	.47	97.71
IL-12	Schizophrenia	2	15	86	0.35	-0.20 to 0.91	.22	0.00
	MDD	2	49	49	1.92	-1.10 to 4.94	.22	96.81
MCP-1	Schizophrenia	3	57	127	0.29	-0.24 to 0.81	.29	56.25
	MDD	2	49	49	1.89	-1.06 to 4.84	.21	96.71
TGFß	Schizophrenia	2	98	63	4.16	-4.03 to 12.34	.32	99.33
	MDD	4	221	193	-0.91	-1.98 to 0.16	.10	95.20
TNFα	Schizophrenia	11	376	557	0.48	0.19 to 0.78	.002	74.53
	MDD	5	267	239	1.21	0.57 to 1.85	< .001	89.47

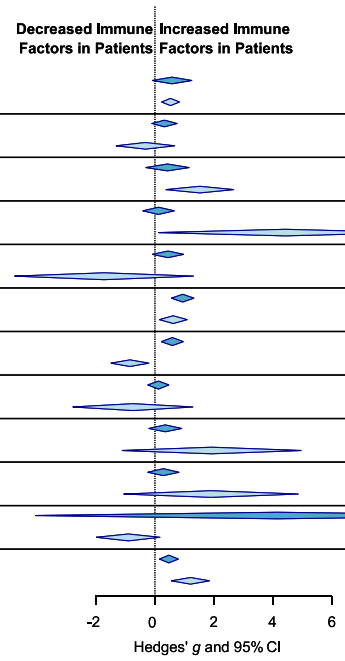

Fig. 4. *Forest Plot Showing Effect Sizes for Immune Factors in Drug-Naïve First-Episode Schizophrenia and MDD.*
Diamonds illustrate the summary effect sizes, the middle of each diamond represents the summary effect size, and the width of the diamond depicts the width of the overall 95% CI. Abbreviations: CRP, C-reactive protein; IFNγ, interferon gamma; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; MDD, major depressive disorder; TGFß, transforming growth factor beta; TNFα, tumor necrosis factor alpha.

Source	Sample Size, No. Patient	Control	Hedges' g	95% CI	Weight
Schizophrenia					
Akiyama et al, 1999	14	27	0.92	0.24 to 1.60	6.67
Bocchio-Chiavetto et al, 2018	17	49	0.72	0.15 to 1.29	7.14
Borovcanin et al, 2012	88	36	3.08	2.53 to 3.63	7.21
Di Nicola et al, 2012	5	24	0.96	-0.04 to 1.96	5.32
Ding et al, 2014	69	60	0.62	0.27 to 0.98	7.92
Frydecka et al, 2018	9	36	1.15	0.38 to 1.93	7.63
Ganguli et al, 1994	24	110	-0.02	-0.46 to 0.42	7.45
Haring et al, 2015	33	37	0.81	0.32 to 1.30	7.58
Hayes et al, 2014	46	35	0.72	0.27 to 1.17	8.04
Kalmady et al, 2018	65	102	0.56	0.24 to 0.88	5.73
Lesh et al, 2018	6	49	1.55	0.65 to 2.45	6.27
Noto et al, 2016	72	77	0.64	0.31 to 0.97	8.00
Şimşek et al, 2016	30	26	0.19	-0.33 to 0.72	7.30
Song et al, 2014	62	60	1.63	1.22 to 2.04	7.74
	540	**728**	**0.95**	**0.57 to 1.32**	
MDD					
Ho et al, 2015	26	24	-0.02	-0.58 to 0.53	15.18
Kakeda et al, 2018	40	47	0.38	-0.04 to 0.81	16.81
Kéri et al, 2014	50	30	0.63	0.16 to 1.09	16.35
Leo et al, 2006	46	46	1.18	0.74 to 1.62	16.58
Muthuramalingam et al, 2016	55	42	1.39	0.94 to 1.84	16.53
Zou et al, 2018	117	102	0.16	-0.11 to 0.42	18.55
	334	**291**	**0.62**	**0.17 to 1.06**	

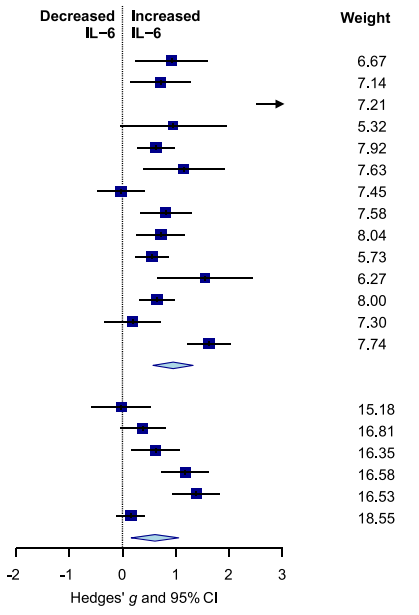

Fig. 5. *IL-6 Levels in Patients with Drug-Naïve First-Episode Schizophrenia or MDD and Controls.*
Each square resembles the effect size for a single study. The horizontal line running through each square illustrates the width of the 95% CI. The size of the squares reflects the weight attributed to each study. Diamonds illustrate the summary effect sizes and the width of the diamonds reflect the width of the overall 95% CI. Abbreviations: IL, Interleukin; MDD, Major Depressive Disorder.

elevated levels in schizophrenia (g = 0.33; 95% CI, −0.08 to 0.73; P = .11; I^2 = 83%). MDD patients did not show significantly altered IFNγ levels compared with controls (g = −0.33; 95% CI, −1.31 to 0.66; P = .51; I^2 = 87%). IL-1β levels were not significantly altered in schizophrenia (g = 0.42; 95% CI, −0.30 to 1.15; P = .25; I^2 = 94%). MDD patients showed significantly elevated IL-1β levels compared with controls (g = 1.52; 95% CI, 0.38 to 2.66; P = .009; I^2 = 96%). IL-2 levels were not altered in schizophrenia patients compared with controls (g = 0.13; 95% CI, −0.38 to 0.63; P = .63; I^2 = 87%). No indication of publication bias was found (Egger test P = .14). MDD patients showed significantly elevated IL-2 levels compared with controls (g = 4.41; 95% CI, 0.13 to 8.69; P = .04; I^2 = 98%). For IL-4, we observed a trend of elevated levels in schizophrenia (g = 0.44; 95% CI, −0.08 to 0.96; P = .10; I^2 = 88%). IL-4 levels were not significantly altered in MDD patients compared with controls (g = -1.71; 95% CI, −4.73 to 1.31; P = .27; I^2 = 97%). IL-6 levels were significantly

elevated in schizophrenia patients compared with controls (g = 0.95; 95% CI, 0.57 to 1.32; P < .001; I^2 = 88%) (Fig. 5). Findings of the Egger test (P = .31) suggested that publication bias was not significant. IL-6 levels were also significantly elevated in MDD patients compared with controls (g = 0.62; 95% CI, 0.17 to 1.06; P = .007; I^2 = 85%). IL-8 levels were significantly elevated in schizophrenia patients compared with controls (g = 0.59; 95% CI, 0.23 to 0.95; P = .001; I^2 = 54%). In contrast to schizophrenia, IL-8 levels were significantly decreased in MDD patients compared with controls (g = −0.84; 95% CI, −1.48 to −0.20; P = .01; I^2 = 76%). IL-10 levels were not significantly altered in schizophrenia patients compared with controls (g = 0.13; 95% CI, −0.21 to 0.46; P = .46; I^2 = 85%). Indication of publication bias was not present (Egger test P = .77). In MDD, IL-10 levels were also not significantly altered (g = −0.75; 95% CI, −2.77 to 1.28; P = .47; I^2 = 98%). For IL-12, we observed no altered levels in schizophrenia (g = 0.35; 95% CI, −0.20 to 0.91; P = .22; I^2 = 0%) and MDD (g = 1.92; 95% CI, −1.10 to 4.94; P = .22; I^2 = 97%). MCP-1 levels were not significantly altered in schizophrenia patients (g = 0.29; 95% CI, −0.24 to 0.81; P = .29; I^2 = 56%) nor in MDD patients (g = 1.89; 95% CI, −1.06 to 4.84; P = .21; I^2 = 97%), compared with controls. TGF-β levels were not significantly altered in schizophrenia patients compared with controls (g = 4.16; 95% CI, −4.03 to 12.34; P = .32; I^2 = 99%). For MDD, we observed a trend of decreased TGF-β levels (g = −0.91; 95% CI, −1.98 to 0.16; P = .10; I^2 = 95%). TNFα levels were significantly elevated in schizophrenia patients compared with controls (g = 0.48; 95% CI, 0.19 to 0.78; P = .002; I^2 = 75%) (Fig. 6). Findings of the Egger test (P = .77) suggested that publication bias was not significant. TNFα levels were also significantly elevated in MDD patients compared with controls (g = 1.21; 95% CI, 0.57 to 1.85; P < .001; I^2 = 89%). See Supplementary Figs. 13–24 for effect size estimates for individual studies.

3.4. Glucose metabolism factors

Fig. 7 shows the effect sizes for fasting glucose metabolism factors in drug-naïve first-episode patients with schizophrenia or MDD compared with controls.

Fasting glucose concentration was significantly elevated in schizophrenia patients compared with controls (g = 0.24; 95% CI, 0.08 to 0.39; P = .003; I^2 = 62%) (Fig. 8). Indication of publication bias was not present (Egger test P = .20). For MDD patients, glucose levels seemed to be higher in MDD patients, but this difference did not reach statistical significance (g = 0.12; 95% CI, −0.07 to 0.32; P = .22; I^2 = 0%). Fasting insulin concentration was significantly elevated in schizophrenia patients compared with controls (g = 0.38; 95% CI, 0.13 to 0.64; P = .003; I^2 = 75%). No indication of publication bias was found (Egger test P = .17). MDD patients did not show altered fasting insulin concentration levels compared with controls (g = -0.09; 95% CI, −0.64 to 0.47; P = .75; I^2 = 76%). See Supplementary Figs. 25 and 26 for effect size estimates for individual studies.

3.5. Statistical comparison of effect sizes

We statistically compared the overall magnitude of alteration of compounds separately in schizophrenia versus MDD using a Wald-type test (Supplementary Table 8). For IL-8, we observed a statistical difference of the overall effect size in schizophrenia versus MDD (Wald score: 3.82; P < .005). For all other compounds there was no significant difference between the overall effect size of alterations in schizophrenia versus MDD.

Next, we statistically compared the subgroup summary effect sizes of growth, immune, and glucose in schizophrenia versus MDD. There was no significant difference between the overall effect size of alterations of growth and immune compounds in schizophrenia versus MDD (P = .117 and P = .625, respectively). The overall effect size of alterations of glucose compounds in schizophrenia was significantly higher than in MDD (Wald score: 0.27; P = .042).

3.6. Effect of study quality

In a sensitivity analysis, we restricted our analyses to high-quality studies indicated by a cut-off score of 6 or more NOS criteria (Supplementary Tables 7 and 9). Our results of similarly altered immune factors, IL-6 and TNFα, remained comparable in both schizophrenia (P < .0001 and P < .01, respectively) and MDD (P < .01 and P < .001, respectively). Also, growth factor BDNF was still decreased in schizophrenia (P < .0001), but for growth factor NGF we observed a trend of decreased levels using two studies (P = .09). In MDD, BDNF levels were not significantly altered (P = .28), and NGF portrayed a trend of decreased levels (P = .08). Compared to the initial meta-

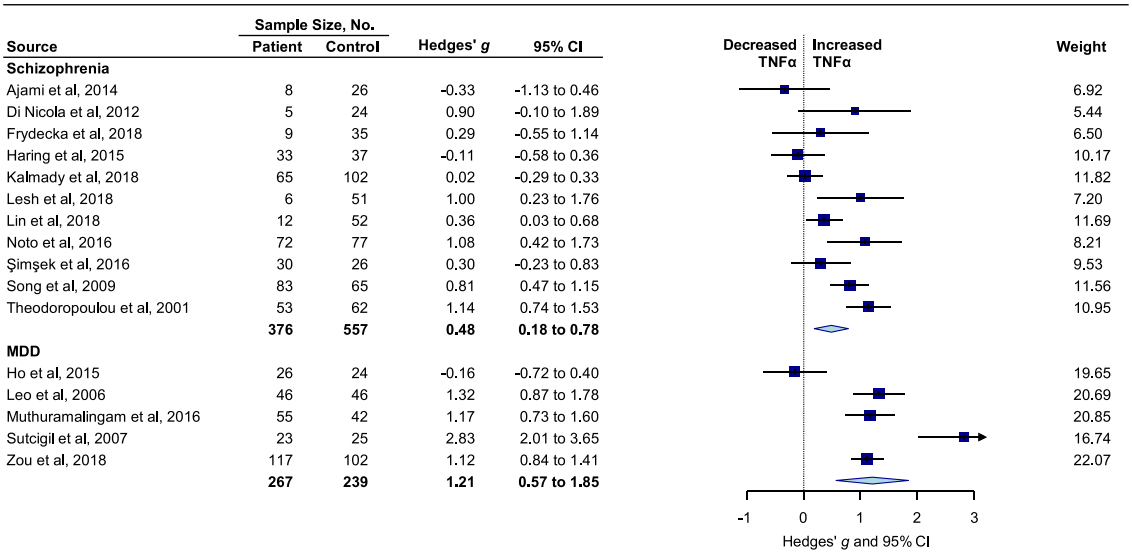

Fig. 6. *TNFα Levels in Patients with Drug-Naïve First-Episode Schizophrenia or MDD and Controls.*
Each square resembles the effect size for a single study. The horizontal line running through each square illustrates the width of the 95% CI. The size of the squares reflects the weight attributed to each study. Diamonds illustrate the summary effect sizes and the width of the diamonds reflect the width of the overall 95% CI. Abbreviations: MDD, Major Depressive Disorder; TNFα, Tumor necrosis factor alpha.

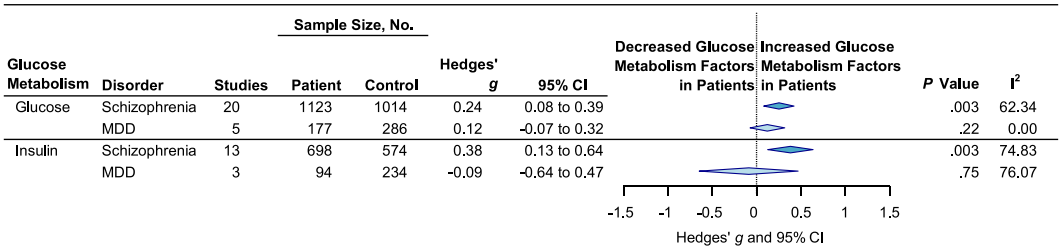

Fig. 7. *Forest Plot Showing Effect Sizes for Glucose Metabolism Factors in Drug-Naïve First-Episode Schizophrenia and MDD.*
Diamonds illustrate the summary effect sizes, the middle of each diamond represents the summary effect size, and the width of the diamond depicts the width of the overall 95% CI. Abbreviations: MDD, major depressive disorder.

analysis, both schizophrenia and MDD now showed increased VEGF levels ($P = .03$ and $P = .03$, respectively) that were significant. The results for immune factor CRP remained the same for schizophrenia, a trend of increased levels ($P = .09$), and for MDD, increased levels ($P = .03$). Immune factor IL-1β remained elevated in MDD ($P < .01$). In contrast to our initial meta-analysis, we did not observe altered IL-2 levels in MDD using two studies ($P = .27$). In the current sensitivity analysis, immune factor IL-8 was still increased in schizophrenia ($P = .03$) and decreased in MDD ($P < .01$). Compared to the initial meta-analysis, for schizophrenia, the increased levels of IL-4 ($P = 0.02$) and IL-10 ($P < .01$) became significant. For immune factor TGF-β we observed a trend of elevated levels in MDD ($P < .10$). Glucose metabolism factors fasting glucose concentration and fasting insulin concentration remained elevated in schizophrenia ($P < .01$ and $P = .01$, respectively).

4. Discussion

In this meta-analysis, we found that drug-naïve first-episode patients with either schizophrenia or MDD show generally similar but some different changes in growth factors, immune factors and glucose metabolism. *Growth factors* BDNF and NGF were decreased in schizophrenia, and growth factor VEGF was elevated in MDD. Both schizophrenia and MDD show significantly elevated levels of *immune factors* IL-6 and TNF-α. For other immune factors we observed a differentiated representation of significant alterations in schizophrenia and MDD. Immune factor IL-8 was elevated in schizophrenia and, in contrast, decreased in MDD. Immune factors CRP, IL-1β and IL-2 were elevated in MDD. *Glucose metabolism factors* fasting glucose and fasting insulin were elevated in schizophrenia. The overall magnitude of alteration for subgroups growth and immune were not statistically different between schizophrenia and MDD, except for glucose, for which the effect size was higher for schizophrenia.

Our findings suggest that dysfunctions in immune and growth factors are already present in schizophrenia and MDD from disease onset. Altered glucose metabolism factors seem to be already present in schizophrenia only.

Below we will discuss findings concerning growth factors, immune factors and glucose metabolism separately in more detail.

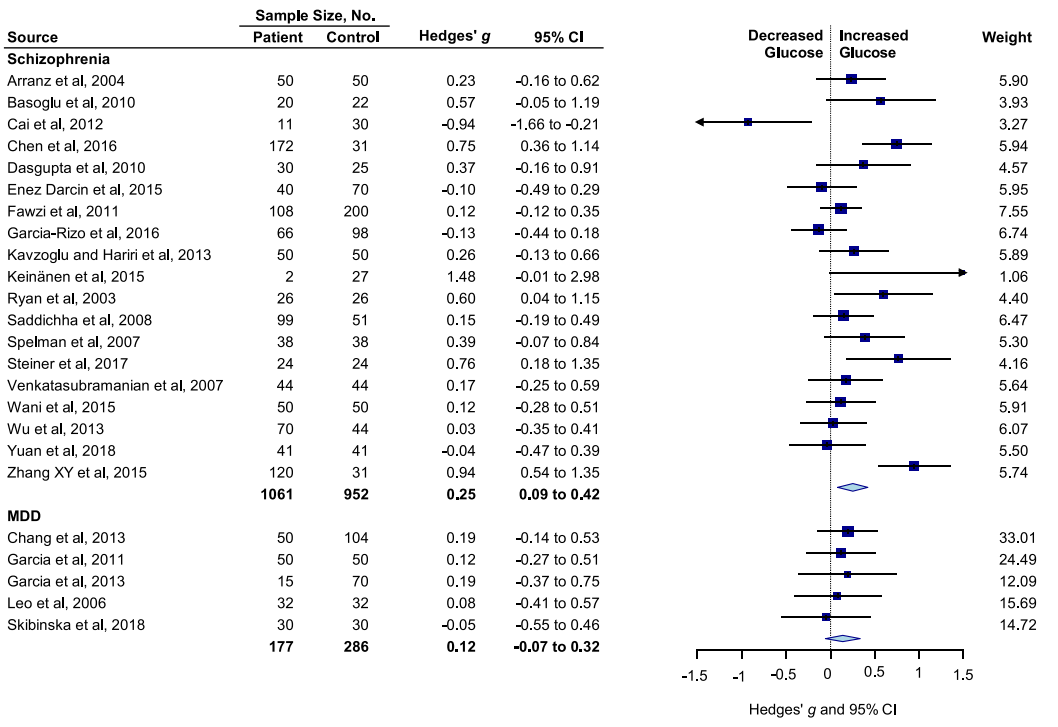

Fig. 8. *Fasting Glucose Levels in Patients with Drug-Naïve First-Episode Schizophrenia or MDD and Controls.*
Each square resembles the effect size for a single study. The horizontal line running through each square illustrates the width of the 95% CI. The size of the squares reflects the weight attributed to each study. Diamonds illustrate the summary effect sizes and the width of the diamonds reflect the width of the overall 95% CI. Abbreviations: MDD, Major Depressive Disorder.

4.1. Growth factors

Deficient myelination leading to dysfunctional interneuron activity and excessive excitatory pruning during (late) adolescence is thought to underlie schizophrenia (Insel, 2010). It has been hypothesized that impairment of neuroplasticity is implicated in the pathophysiology of both MDD and schizophrenia (Rao et al., 2017). Growth factors, such as BDNF and NGF, contribute to maintaining the plasticity of neurons. Our findings of decreased BDNF and NGF levels in schizophrenia and a similar trend of decreased BDNF and NGF levels in MDD are in line with meta-analyses with less strict inclusion criteria (i.e., drug-free, medicated or long-term patients). BDNF levels were found to be decreased in drug-free schizophrenia patients (not exclusively drug-naïve) and in first-episode schizophrenia patients, (Fernandes et al., 2015) as well as in antidepressant-free multi-episode depressed patients, comparable with current findings (Molendijk et al., 2014). In the meta-analysis of Rao and colleagues, NGF levels were decreased in both schizophrenia and MDD (Rao et al., 2017).

VEGF is a signal protein that promotes vasculogenesis and angiogenesis, (Misiak et al., 2018) and is involved in neurogenesis in the adult brain (Misiak et al., 2018). In the meta-analysis of Misiak and colleagues, VEGF levels were unaltered in first-episode schizophrenia patients, but decreased in multi-episode medicated schizophrenia patients (Misiak et al., 2018). These findings might reflect effects of selection bias, illness progression, medication effects or comorbidities such as hypertension or diabetes. In contrast, VEGF levels were elevated in drug-naïve first-episode MDD patients compared with controls. Interestingly, links between VEGF-related single nucleotide polymorphism and risk for MDD have been presented by a genome wide association study, demonstrating a relationship between VEGF genetic determinants and MDD specifically (Xie et al., 2017). Furthermore, it has been demonstrated that VEGF might be regulated by proinflammatory cytokines in patients with MDD (Schmidt et al., 2011).

4.2. Immune factors

Our current meta-analysis shows that signs of a low-grade peripheral inflammation are recognizable in both drug-naïve first-episode schizophrenia and MDD. Notably, mainly pro-inflammatory cytokines (i.e., TNFα and IL-6) seem to be dysregulated at disease onset in both schizophrenia and MDD patients. Our findings are in line with two other meta-analyses which reported increased levels of IL-6 and TNFα in medication-naïve first-episode psychosis patients and multi-episode MDD patients (Kohler et al., 2017; Upthegrove et al., 2014). We observed elevated CRP levels in MDD patients and a trend of elevated CRP levels in schizophrenia patients, with similar effect sizes. Subclinical systemic inflammation has been associated with an increased risk of new onset depression, psychosis and other psychiatric disorders (Pasco et al., 2010; Osimo et al., 2018).

Despite these similarities found in schizophrenia and MDD, we also observed a differentiated representation of other immune related compounds in schizophrenia and MDD. In the current study, IL-2 was elevated in MDD patients compared with controls. IL-2 plays an important role in activating regulatory T-cells which control inflammation. It is unclear whether these increased IL-2 levels are a reaction to the ongoing inflammation in patients with MDD. Currently, low-dose IL-2 trials are ongoing aiming at decreasing depressive symptoms (Ellul et al., 2018). For IL-4 we observed a trend of increased levels in schizophrenia. IL-4 activates B-cell and T-cell proliferation and is a target in the treatment of allergies (anti-IL4/anti-IL13 combination therapy) (Gooderham et al., 2018). IL-8 is a chemokine and, among other processes, primarily attracts neutrophils to infection sites (Nordsieck et al., 2018). We found in our meta-analysis that IL-8 was increased in schizophrenia and decreased in MDD. TGF-β has regulatory properties in regard to the immune system. For TGF-β we observed a trend of decreased levels in MDD (Massague, 2012).

Similar to our study, Goldsmith and colleagues reported elevated levels of IL-6 and TNFα in acutely ill psychosis patients and acutely ill MDD patients – even though the majority was not drug-naïve (Goldsmith et al., 2016). Elevated levels of IFNγ, IL-1β, IL-8, IL-10, and IL-12 in acutely ill psychosis patients compared with controls were reported, of which we found the same direction of alteration for these compounds, but not significantly for each compound (Goldsmith et al., 2016). As compared to our study, Goldsmith *et al.* found the same direction of alterations, but significant, for IL-12, IFNγ and IL-4 in acutely ill MDD patients (Goldsmith et al., 2016). In contrast, we observed increased levels of IL-4 in current meta-analysis, and Goldsmith and colleagues reported decreased IL-4 levels in acutely ill psychosis (Goldsmith et al., 2016). Most differences are likely derived from the fact that we lacked power for most compounds, since we could generally include less studies due to our strict drug-naïve study criteria. However, some differences could have been influenced by medication effects, such as the IL-4 levels (Sobis et al., 2015).

4.3. Prodromal course and inflammation

Schizophrenia often shows a prodromal course in which immune-mechanisms may already play a role. Genetic association studies showed that the immune system of patients with schizophrenia is subtly more prone to activation, as expressed for example in major histocompatibility complex molecules, (Debnath et al., 2013; Mokhtari and Lachman, 2016) its enhancers, (Takao et al., 2013) and environmental factors that activate the immune system (i.e. prenatal infection and the experience of stress), may put components of the immune system in an altered state of activity (Fineberg and Ellman, 2013; Brown and Derkits, 2010). A prospective general population birth cohort study found an association between higher inflammatory marker IL-6 in childhood (at age 9) and the development of psychosis in young adulthood (Khandaker et al., 2014). A longitudinal study showed that 15 immune-related compounds can predict conversion to psychosis in a clinical-high risk for psychosis group (Perkins et al., 2015). Also, baseline TNFα and IL-6 could predict negative symptom trajectories in persons at clinical-high risk for psychosis, independent of baseline depression (Goldsmith et al., 2019).

For MDD, there is less evidence for an inflammatory prodromal course, but some data suggests that inflammation could be a precursor for developing depression. The same prospective birth cohort study mentioned above for psychosis, also found associations between elevated IL-6 levels, measured at age 9, and specific symptoms of depression (i.e. diurnal variation in mood, concentration difficulties, fatigue and sleep disturbances) at age 18 years after adjusting for potential confounders (including self-reported infections) (Khandaker et al., 2014; Chu et al., 2019). Indeed, associations have been found between polymorphisms in immune genes and MDD (Debnath et al., 2013; Mokhtari and Lachman, 2016; Barnes et al., 2017). However, there are inconsistencies between the immune effects of these genetic variants and the resulting effects on depression (Barnes et al., 2017). Environmental and gene × environmental interactions are likely to have a greater influence on inflammation in depression than genetic variants alone, whereby the expression of some polymorphisms may only become evident when accompanied with life stressors (Barnes et al., 2017). Furthermore, epidemiologic studies have shown that early-life infections and auto-immune diseases (including diabetes) are linked with developing schizophrenia or depression later in life (Benros et al., 2013; Benros et al., 2014; Kohler-Forsberg et al., 2018).

4.4. Inflammatory subtypes

The inflammatory dysregulations found in schizophrenia and MDD could indicate that low-grade inflammation is present in both disorders, at least in some patients. Inflammatory subtypes could be present among patients with schizophrenia or MDD. However, a meta-analysis

looking at immune factors found evidence against the existence of an immune subgroup of psychosis (Pillinger et al., 2018). Lower variability of especially IL-6 found in psychosis patients could represent a core component in the immunobiology of psychosis (Pillinger et al., 2018). These findings suggest that an inflammatory subtype cannot be defined using peripheral immune data. The evidence presented by Pillinger and colleagues could indicate that immune alterations in schizophrenia patients are truly a sign of intrinsic immune dysfunction, instead of a feature of physiological differences between patients and controls, such as age, sex, body-mass index (BMI), and ethnicity. However, only a small proportion of the included studies matched for these confounders. Conversely, another study found genetic evidence for an immune-related subgroup of schizophrenia (Trossbach et al., 2019).

MDD is a highly heterogeneous disorder and the presence of an inflammatory subtype could be relevant in this disorder. Data from a longitudinal cohort study showed that higher inflammatory markers (CRP, IL-6, and TNFα), BMI, and metabolic syndrome components are associated with the atypical subtype, not with melancholic depression (Lamers et al., 2013). A subsequent study, using network analysis, showed that the most likely symptoms to share associations with inflammatory markers are: sleep problems, energy level, appetite/weight change, aches and pains, and irritability (adjusted for age, sex, BMI, exercise, smoking, alcohol, and chronic diseases) (Fried et al., 2019). Fried and colleagues observed that BMI was strongly associated with CRP (Fried et al., 2019). Given that CRP is released in adipose tissue, an increase in appetite and weight would be expected to be associated with CRP. Lamers and colleagues showed indeed that increased appetite was related to inflammation, specifically CRP and TNFα (Lamers et al., 2018). A longitudinal population-based study found an unidirectional association between current MDD subtype with atypical features and high-sensitivity CRP levels at follow-up – suggesting that inflammation may be a consequence of this condition (Glaus et al., 2018). Increasing evidence shows that inflammation may play an important role in an etiologically distinct depression subtype, characterized by resistance to antidepressant medication (Barnes et al., 2017; Hughes and Kumari, 2017). Of note, Rantala and colleagues proposed a model of multiple subtypes of depression, based on *proximate mechanisms* that caused the depressive episode (e.g., infection, long-term stress, and somatic diseases) (Rantala et al., 2018). In short, modern lifestyle could increase susceptibility to inflammatory dysregulation and chronic stress, which both increase peripheral proinflammatory cytokines, leading to low mood and sickness behavior. Inflammation may aggravate the previously adapted short-term mood changes to a chronic dysfunctional depressive state by preventing the normalization of mood, escalating into an episode of MDD. For an elaborative discussion on this topic see (Rantala et al., 2018).

Finally, the inflammation present in schizophrenia and MDD, at least in high-inflammatory subgroups, is in line with large epidemiological studies that reported an increased prevalence of immune diseases in both schizophrenia and MDD including type 1 diabetes mellitus, but with notable exceptions such as rheumatoid arthritis (Eaton et al., 2006; Benros et al., 2012; Sellgren et al., 2014).

4.5. Glucose metabolism

In this meta-analysis, evidence for a dysfunctional glucose metabolism was found in drug-naïve first-episode patients with schizophrenia, but not in those with MDD. Although alterations in glucose metabolism are observed frequently during use of antipsychotics, it has become clear that an altered state of glucose homeostasis in schizophrenia is present from the onset of the disorder, even when comparing antipsychotic-naïve first-episode cases with BMI-matched controls (Pillinger et al., 2017). Indeed, the presence of diabetes in schizophrenia was already reported well in the 19th century, long before the advent of antipsychotics and eating habits did not easily induce metabolic dysfunctions as they do today (Kohen, 2004). 'Diabetes is a disease which often shows itself in families in which insanity prevails' as stated in the book 'The Pathology of Mind' written in 1879 (Maudsley, 1879). In the 17th century, Thomas Willis, a physician who observed that the urine is sweet in patients with diabetes (glycosuria), stated that diabetes was caused by 'sadness or long sorrow and other depressions' (Willis, 1971). As of today, meta-analytic evidence showed that MDD increases the risks of hyperglycemia, insulin resistance and type 2 diabetes (Kan et al., 2013; Mezuk et al., 2008). Garcia-Rizo and colleagues showed that patients with a serious mental illness have an altered glycemic homeostasis already at onset of the disease, (Garcia-Rizo et al., 2016) as measured with a two hour glucose load. Implicating that a similar glycemic pathway might be shared between serious mental illnesses. Indeed, similar prevalence for metabolic syndrome in schizophrenia (33.4%) and MDD (31.3%) has been presented (Vancampfort et al., 2015). Glycemic abnormalities might have a familial background, as psychiatric disorders and endocrine auto-immune diseases (including diabetes) have a relatively high familial co-occurrence. Psychiatric disorders and endocrine auto-immune diseases could be the cause or consequence of each other – i.e. immune pathogenic factors and environmental (stress) factors for psychiatric disorders and endocrine autoimmune diseases may be shared (Eaton et al., 2010; Steiner et al., 2014; Garcia-Rizo et al., 2015). However, in our meta-analysis we only observed a trend of elevated fasting glucose levels in drug-naïve first-episode MDD patients. The results of glucose metabolism markers in MDD should be interpreted with caution owing to the small sample size of the studies included in these analyses.

4.6. Clinical relevance

Given the alterations in immune, growth, and glucose metabolism factors in schizophrenia and MDD, it is worthwhile to consider the clinical relevance of these alterations. Firstly, associations between inflammation and metabolic dysfunction, and treatment response have been found in schizophrenia and MDD. Psychosis patients with high inflammation have a worse treatment response to antipsychotics compared with psychosis patients with low inflammation. Nettis and colleagues found an association between increased high-sensitivity CRP, triglycerides, and BMI at baseline, and higher Positive and Negative Syndrome Scale scores and reduced rate of treatment response at 1-year follow-up using a factor analysis in a longitudinal study of first-episode psychosis patients (Nettis et al., 2019). A multinational, multi-centered, randomized, double-blind study used a clustering approach to stratify 325 first-episode psychosis patients into four clinical subtypes. Those with the most severe symptoms were the most at risk of non-remission. This group of patients exhibited before treatment higher serum levels of several pro-inflammatory compounds compared with the other patient groups (Martinuzzi et al., 2019).

MDD patients with high inflammation also seem to be more prone for chronicity. Regular antidepressant treatment fail in over 30% of patients with a depression, and those with high inflammation and/or BMI are in particular resistant to treatment (Bekhbat et al., 2018; Haroon et al., 2018). A longitudinal cohort study showed that high IL-6 levels at baseline could predict chronicity of depression (Lamers et al., 2019). Moreover, a meta-analysis showed that signs of inflammation contribute to treatment resistance in patients with depression (Strawbridge et al., 2015).

Secondly, signs of inflammation or metabolic dysfunction in schizophrenia and MDD readily suggest augmentation therapy for those patients in which the underlying pathophysiology is related to inflammatory or metabolic dysfunctions. Although antipsychotics already have some anti-inflammatory actions (Hu et al., 2012), a meta-analysis on the efficacy of augmentation with anti-inflammatory agents for patients with schizophrenia showed that the anti-inflammatory agents aspirin, estrogens, minocycline, and N-acetylcysteine improved symptom severity (Cakici et al., 2019). In depression TNF has been consistently shown to be elevated. Bekhbat and colleagues observed

that TNF antagonism seems to be in particular effective in patients with treatment-resistant depression with high inflammation (CRP > 5 mg/L), and elevated plasma lipids and cholesterols (Bekhbat et al., 2018). Also, there is meta-analytic evidence for beneficial effects of other anti-inflammatory agents, in particular celecoxib, for improving symptom severity in depression (Kohler et al., 2014).

Taken together, both schizophrenia and MDD have a heterogenous presentation of symptoms which could also apply for their underlying disease biological mechanisms. However, further research is warranted to identify whether growth factor, inflammatory and/or metabolic subgroups are present, and if so, which underlying disease biological mechanisms are responsible. The latter readily suggests research into advanced diagnostics and augmentation therapy for those subgroups. Possibly in the future, a blood-based clinical decision support system in schizophrenia and MDD could identify inflammatory and/or metabolic aberrant subgroups, in order to augment their regular therapy with anti-inflammatory or metabolic medications.

4.7. Limitations

To our best knowledge, this is the first meta-analysis that analyzes peripheral growth, immune and glucose metabolism compounds in drug-naïve first-episode patients with schizophrenia and drug-naïve first-episode patients with MDD compared with healthy controls. Ideally, for a meta-analysis, a sufficient number of studies and sample sizes is needed (e.g., at least 5 studies). However, based on our approach to include only drug-naïve first-episode patients, we could make a better estimation of the alterations in compounds measured in peripheral blood, without the influence of treatment or chronic illness. Therefore, our significant findings of altered compounds in schizophrenia and MDD are truly not influenced by chronicity or medication effects. The compounds that were analyzed in a meta-analysis of less than five studies merit further investigation. When interpreting the results, one should take into account that the number of studies and sample sizes differed among the two disorders for each compound. Unfortunately, evidence regarding peripheral blood compounds in drug-naïve first-episode MDD patients is relatively scarce. Therefore, due to our strict study criteria of including only drug-naïve first-episode patients, we could include less and smaller sample size studies for MDD than for schizophrenia. Possibly, more drug-naïve first-episode schizophrenia studies have been published, because in clinical care the implementation of early recognition teams for first-episode psychosis has become a standard intervention over the years whereas, this is less so for MDD (McGorry, 2015). Not all cytokines, either pro- or anti-inflammatory, have been sufficiently investigated to include them into our meta-analysis. Another important limitation is that we did not include other major psychiatric disorders such as bipolar disorder. Generally, schizophrenia and bipolar disorder are seen as more related to one another than schizophrenia and depression. As a consequence, there is a substantial body of research investigating similarities between schizophrenia and bipolar disorder, both from a clinical perspective, as well as the biological underpinnings of both disorders. However, only recently, trends diagnostics approaches have been applied to schizophrenia and major depression. Current findings therefore could point at transdiagnostic biological disturbances, underscoring the importance of studying neurobiologic disturbance more broadly in psychiatric disorders.

5. Conclusions

We found meta-analytic evidence that dysfunctions in peripheral growth and immune factors are already present in schizophrenia and MDD from disease onset. An altered glucose homeostasis might be uniquely present at the onset of schizophrenia. More drug-naïve and first-episode studies, especially for MDD, are needed for further validation of our results. Our findings suggest further research into the importance of developing advanced diagnostics – possibly a blood-based clinical decision support system – and augmentation therapy with anti-inflammatory or metabolic agents for those with high inflammation or metabolic disturbances.

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Declaration of competing interest

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

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Appendix A. Supplementary data

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