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Increased serum levels of leptin and insulin in both schizophrenia and major depressive disorder: A cross-disorder proteomics analysis

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Abstract
We investigated whether there are similar serum alterations in schizophrenia and major depressive disorder (MDD). We investigated serum analytes in two epidemiological studies on schizophrenia ($N = 121$) and MDD ($N = 1172$) versus controls. Serum analytes ($N = 109$) were measured with a multi-analyte profiling platform and analysed using linear regression models, adjusted for site, age, gender, ethnicity, anti-inflammatory agents, smoking, cardiovascular disease and diabetes, and adjusted for multiple comparisons. An increase in leptin and insulin levels was observed for both schizophrenia patients (Cohen's d (d): 0.26 and 0.65, respectively)

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and MDD patients (d: 0.29 and 0.12, respectively) compared to their respective controls. Lower angiopoietin-2 levels were seen in both schizophrenia (d: -0.22) and MDD (d: -0.13). Four analytes differed in only schizophrenia patients (increased levels of C-peptide and prolactin, and decreased levels of CD5 antigen-like and sex hormone binding globulin) and one analyte differed in only MDD patients (increased angiotensinogen levels) compared to their respective controls. Restricting analyses to patients with a current episode of disease showed even more marked elevations of insulin and leptin. Our results suggest the presence of insulin and leptin resistance as cross-disorder mechanisms that could contribute to the higher somatic comorbidity and decreased life-span seen in both disorders.

1. Introduction

Historically, schizophrenia and major depressive disorder (MDD) have been regarded as separate clinical entities, based on the differential dominant symptoms present, course of the two disorders, and response to pharmacological treatment. This view has culminated in the distinction between psychotic disorders on the one hand and mood disorders on the other hand, present in the DSM system and ICD, and dates back to the classic distinction made by Kraeplin (1990). This distinction is the hallmark of clinical practice worldwide.

Recently, researchers have challenged the idea of these separate diagnostic entities. Instead they argue that psychiatric disorders, as distinguished in current classification systems, should be seen as pragmatic, man-made constructs meant to guide clinical decision making rather than entities that represent biological concepts (Wigman et al., 2015). Evidence for this line of thought comes from findings that genetic effects for these diagnostics entities appear to be subtle and polygenic despite the high heritability (Buckholtz and Meyer-Lindenberg, 2012), and do not adhere to traditional diagnostic boundaries (Kendell and Jablensky, 2003). Likewise, endophenotypes such as cognitive alterations are also associated with several disorders rather than showing disorder-specific associations (Buckholtz and Meyer-Lindenberg, 2012; Hill et al., 2009; Weiser et al., 2005). Additionally, many risk factors for psychopathology, such as rumination or experiencing stress, increase risk for all psychiatric diagnoses (Buckholtz and Meyer-Lindenberg, 2012).

As for schizophrenia and MDD, recent research has reported intriguing similarities between both disorders, which may point to shared underlying mechanisms supporting the general idea outlined above. Familial and twin studies found correlations between schizophrenia and MDD (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013; Smoller and Finn, 2003). A large pooled genetic study found evidence that individual and aggregate molecular genetic risk factors are shared between five psychiatric disorders, including schizophrenia and MDD (Cross-Disorder Group of the Psychiatric Genomics Consortium et al., 2013). In individual studies of schizophrenia and MDD alterations in peripheral biomarkers have been reported, some of which overlap (Chan et al., 2014). Alterations in glucose homeostasis for both schizophrenia and MDD have been demonstrated (Kan et al., 2013; Mezuk et al., 2008; Pillinger et al., 2017; Van Welie et al., 2013). Furthermore, serum leptin disturbances have been associated with both schizophrenia and MDD. A meta-analysis of 27 studies found increased levels of leptin in patients with schizophrenia (Stubbs et al., 2016). A large international consortium showed that 15% of patients with atypical depression carried a higher number of genetic risk variants for increased BMI and leptin (Milaneschi et al., 2017b). Atypical depression and obesity-related traits might therefore be part of the same underlying pathophysiology (Milaneschi et al., 2017b).

Furthermore, alterations in inflammation markers have been reported extensively for schizophrenia (Miller et al., 2014; Misiak et al., 2017; Potvin et al., 2008) and MDD (Eyre et al., 2016; Kohler et al., 2017; Liu et al., 2012). A recent meta-analysis found a similar pattern of cytokine alterations in both schizophrenia and MDD during acute and chronic phases of these diseases (Goldsmith et al., 2016).

However, the exact nature and effect size of the reported alterations are not easy to interpret, as virtually all studies have investigated the diagnostic categories separately, but not considered schizophrenia and MDD together. As a result, patient samples between the studies tend to differ with respect to clinical characteristics such as phase of the disorder, and with respect to methodological characteristics, such as method of analysis and handling of covariates. This has been brought forward as a general major impediment in comparing the results of biomarkers studies (Kapur et al., 2012).

In the current study, we have less methodological differences by using a subset of two epidemiological studies, which used the same multi-analyte immunoassay platform, to measure a proteomic profile while applying similar analytical procedures across schizophrenia, MDD and controls.

The main objective of the current study is to investigate whether serum proteins and small molecules (henceforth called analytes) differ in schizophrenia and MDD compared to their respective controls, and whether these alterations overlap between schizophrenia and MDD.

2. Experimental procedures

2.1. Study design and participants

Both the ‘Genetic Risk and OUtcome in Psychosis’ (GROUP) (www.group-project.nl) (Korver et al., 2012) and the ‘Netherlands Study of Depression and Anxiety’ (NESDA) (www.nesda.nl) (Penninx et al., 2008) are multi-site naturalistic longitudinal cohort studies focussing on patients with psychotic disorders, and patients with anxiety and depressive disorders respectively, and healthy controls. In contrast to previous reports utilizing these datasets to identify analytes which are related to schizophrenia or MDD that used different methodologies (Bot et al., 2015; Lamers et al., 2016; Van Beveren et al., 2014), the current study aligns the analytical and statistical methods which enables comparison across these studies. Detailed descriptions of both studies can be found elsewhere (Korver et al., 2012; Penninx et al., 2008). From the GROUP study we studied a subset of 121 patients with schizophrenia and 83 controls for which serum analyte measurements were available. Similarly, we studied a subset from the NESDA study consisting of 1172 patients with a lifetime diagnosis of MDD and 426 controls. Schizophrenia and MDD were classified using the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV) criteria. Controls were participants without a DSM-IV diagnosis. Both studies were approved by their local ethical committees.

2.2. Demographic and clinical variables

The participants from both subsets were interviewed and blood was taken from them on the same day.

Current psychotic episode patients were defined as patients not in remission according to the following remission criteria: patients scored $\geq$4 on the items P1, P2, P3, N1, N4, N6, G5 and G9, of the Positive and Negative Syndrome Scale (PANSS) (Andreasen et al., 2005). Current depressive episode patients were defined when patients scored $\geq$14 on the Inventory of Depressive Symptomatology (IDS) self-report version (Rush et al., 2003).

2.3. Serum measurements

Serum samples were not necessarily collected under fasting conditions and were stored at $-80\,^{\circ}$C. Analytes, which are involved in various hormonal, immunological, metabolic and neurotrophic pathways, were measured using the RBM Myriad Human DiscoveryMAP, a commercially available quantitative, multiplexed immunoassay (Myriad RBM, Austin, TX, USA), for both studies. Both collections were processed at the same laboratory, Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory at Rules Based Medicine (http://www.rulesbasedmedicine.com).

2.4. Data preparation and statistical analyses

We measured 169 analytes which overlapped in the schizophrenia and MDD subsets. Analytes for which more than 30% of the values was either missing, below or above detection limits in the control groups were omitted from further analyses (Table S4). Ultimately, we omitted 60 analytes. Values measured below the lower detection limit of an analyte were replaced by half of the lowest concentration for the respective analyte. Values which were beyond the upper detection limit were replaced with the value of the upper detection limit to prevent outliers. The methodology described above has been carried out previously (Bot et al., 2015; Lamers et al., 2016; Van Beveren et al., 2014). Finally, 109 analytes were available for analyses.

Initially, we intended to combine the control groups of both cohorts. However, differences in the method of control recruitment were viewed as too large. We therefore conducted all analyses independently for schizophrenia and MDD patients versus their own controls.

Dichotomous baseline characteristics were analysed using χ^2-tests and continuous baseline characteristics were analysed using independent t-tests. We prepared the dataset by performing a '$\log_{10}$-transformation+1' to stabilize the variance distributions and to avoid negative outcome values. The possible influence of batch effects that may arise out of batch-wise array measurement were controlled for by the ComBat procedure (Leek et al., 2012).

We conducted linear regressions repeatedly for each serum analyte, with each analyte as the dependent variable, and a group variable (patient or control) as the predictor, controlling for assessment site, age, gender, ethnicity, anti-inflammatory agents, corticosteroids, smoking, cardiovascular disease and diabetes type 2. To assess for multicollinearity we calculated the variance inflation factor (VIF) to assess whether a predictor has a strong relationship with other predictors.

In order to examine whether the proteomic profile was more dysregulated when patients were in a current episode, we ran a post-hoc analysis for only those patients with a current episode of either psychosis ($N = 76$) or depression ($N = 926$) at the time of serum sample collection.

To account for the possible influence of psychopharmacology use, we performed an additional analysis with each analyte as a dependent variable and the type of psychopharmacology use as a predictor. All models contained the covariates assessment site, age, gender, ethnicity, anti-inflammatory agents, corticosteroids, smoking, cardiovascular disease and diabetes type 2. The models were run for antipsychotics (subdivided in typical antipsychotics, atypical antipsychotics and other antipsychotics), antidepressants (subdivided in selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and other antidepressants including St. John's wort) and mood stabilizers. Supplementary Table 2 shows the ATC codes used for defining the type of (psycho)pharmacology use.

As there is evidence that, at least in MDD, body mass index (BMI; body weight in kg/m2) and MDD share common pathophysiological processes (Milaneschi et al., 2017b), we did not initially adjust for BMI as this could be considered overcorrection for etiological roots. However, in a post-hoc-analysis, the impact of obesity was assessed by conducting an analysis in which we excluded all persons with a BMI $\geq$ 30.

Finally, we assessed the similarities in the serum protein profiles of schizophrenia and MDD using a significance analysis of microarrays (SAM) (Tusher et al., 2001). In this analysis SAM identified significant analytes by carrying out an analyte specific t-test which measured the strength of the relationship between analyte expression and status (patient or control) on the basis of a change in the level of analyte expression relative to the standard deviation of repeated measurements. Accordingly, SAM calculated a score for each analyte on the basis of the change in expression relative to the standard deviation of all 109 measurements. A cut-off of 28 was chosen based on the number of altered analytes whose level of expression differed from the geometric mean the most (reflecting 14 analytes increased and 14 analytes decreased) in each patient group (vs respective controls).

Multiple comparisons were controlled for according to the Benjamini-Hochberg procedure (Benjamini, 1995) and false discovery rates were calculated. We provide both p-values and false-discovery rates (q), and findings of $q < 0.05$ were designated as significant. We calculated Cohen's d effect sizes (d), using the log-transformed data, for the patient groups versus the controls (Cohen, 1998). For calculating the fold change we used untransformed data and calculated the ratio between the means of the analytes from the patient groups and the means of the respective analytes from the control groups. All analyses were performed in R software 3.4.0 (R Development Core Team, 2008).

3. Results

3.1. Demographic and clinical characteristics of the participants

Table 1 shows the demographic and clinical characteristics of the participants stratified by schizophrenia patients versus controls, and MDD patients versus controls.

Table 1 Demographic and clinical characteristics of the participants.

	GROUP ($n = 204$)			NESDA ($n = 1598$)		
	Schizophrenia patients $n = 121$	Controls $n = 83$	Overall *p*-value	MDD patients $n = 1172$	Controls $n = 426$	Overall *p*-value
Assessment area NESDA (%)						0.081
Amsterdam				18.2%	15.7%	
Leiden				40.9%	37.1%	
Groningen				41.0%	47.2%	
Assessment area GROUP (%)			0.724			
Amsterdam and region[a]	54.2%	61.0%				
GGZ-NHN	20.0%	15.9%				
Rivierduinen	14.2%	14.6%				
EMC	11.7%	8.5%				
Age, mean (s.d.)	24.6 (5.7)	26.3 (9.9)	0.207	42.1 (12.6)	39.0 (14.8)	<0.001
Gender (% female)	14.0%	30.1%	0.005	68.8%	60.6%	0.002
Ethnicity (% North European)	73.2%	83.8%	0.084			
BMI, mean (s.d.)	25.0 (4.3)	22.2 (2.9)	0.645	26.0 (5.4)	24.8 (4.6)	0.032
Current smoker (%)	66.1%	32.5%	<0.001	40.1%	28.2%	<0.001
Anti-inflammatory agents, *n* (%)	2.5%	9.6%	0.026	5.4%	0.9%	<0.001
Corticosteroids, *n* (%)	2.9%	4.8%	0.189	7.2%	4.2%	0.033
CVD (%)	13.3%	0.0%	<0.001	7.0%	5.2%	0.189
Diabetes Mellitus (%)	[b]2.6%	0.0%	0.144	[c]4.3%	3.1%	0.270
Psychopharmacology use	89.3%	0.0%	NA	56.5%	1.4%	NA
Antipsychotics use	85.1%	0.0%	NA	2.3%	0.0%	NA
Typical antipsychotics, *n* (%)	38.8%	0.0%	NA	0.3%	0.0%	NA
Atypical antipsychotics, [d]*n*(%)	82.6%	0.0%	NA	2.0%	0.0%	NA
Other antipsychotics, *n* (%)	0.8%	0.0%	NA	0.0%	0.0%	NA
Antidepressants use	14.9%	0.0%	NA	35.5%	1.2%	NA
SSRI, *n* (%)	10.7%	0.0%	NA	23.8%	0.7%	NA
TCA, *n* (%)	5.0%	0.0%	NA	3.5%	0.0%	NA
Other antidepressants, [e]*n*(%)	0.0%	0.0%	NA	35.5%	1.2%	NA
Mood stabilizers	5.8%	0.0%	NA	0.8%	0.2%	NA

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; EMC, Erasmus Medical Center; GGZ-NHN, geestelijke gezondheidszorg Noord-Holland-Noord; MDD, major depressive disorder; NA, not applicable; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

[a] Regions included AMC, Dijk en Duin and Geestgronden.

[b] Three patients had a current psychotic episode.

[c] Five patients had a lifetime diagnosis of MDD and 45 patients had a current depressive episode.

[d] 35.8% used olanzapine and 13.7% used clozapine.

[e] Other antidepressants including St. Johns Worth.

3.2. Similarities in serum alterations between schizophrenia and MDD

Of the 109 included serum analytes, 35 analytes were altered ($p < 0.05$) between either schizophrenia patients versus controls and/or MDD patients versus controls (Fig. 1, Table 2).

The only analyte for which we identified a significant, Benjamini-Hochberg corrected ($q < 0.05$), alteration in both disorders was leptin, which was increased in schizophrenia patients (regression coefficient (b): 0.20; $q = 0.002$; Cohen's d (d): 0.26) and in MDD patients (b: 0.06; $q < 0.05$; d: 0.29) compared to their respective controls. Insulin was significantly increased in schizophrenia patients (b: 0.20; $q < 0.002$; d: 0.65) compared to controls, and we observed a trend towards significance in MDD patients (b: 0.02; $p = 0.02$; d: 0.12) compared to controls although the significance of insulin levels for MDD did not survive Benjamini-Hochberg correction ($q = 0.15$). Angiopoietin-2 was significantly decreased in MDD patients (b: −0.03; $q < 0.05$; d: −0.13) compared with controls, and a trend towards decreased levels of angiopoietin-2 was observed in schizophrenia patients compared with controls (b: −0.06; $p = 0.03$; $q = 0.22$; d: −0.22).

In schizophrenia, but not in MDD, we observed significantly increased levels of C-peptide and prolactin and significantly decreased levels of CD5 antigen-like and sex hormone binding globulin ($q < 0.05$). Angiotensinogen was significantly increased ($q = 0.02$) in MDD patients, but not in schizophrenia patients.

Supplementary Table 3 shows the results on the 74 analytes which did not reach significance based on *p*-values in our analyses.

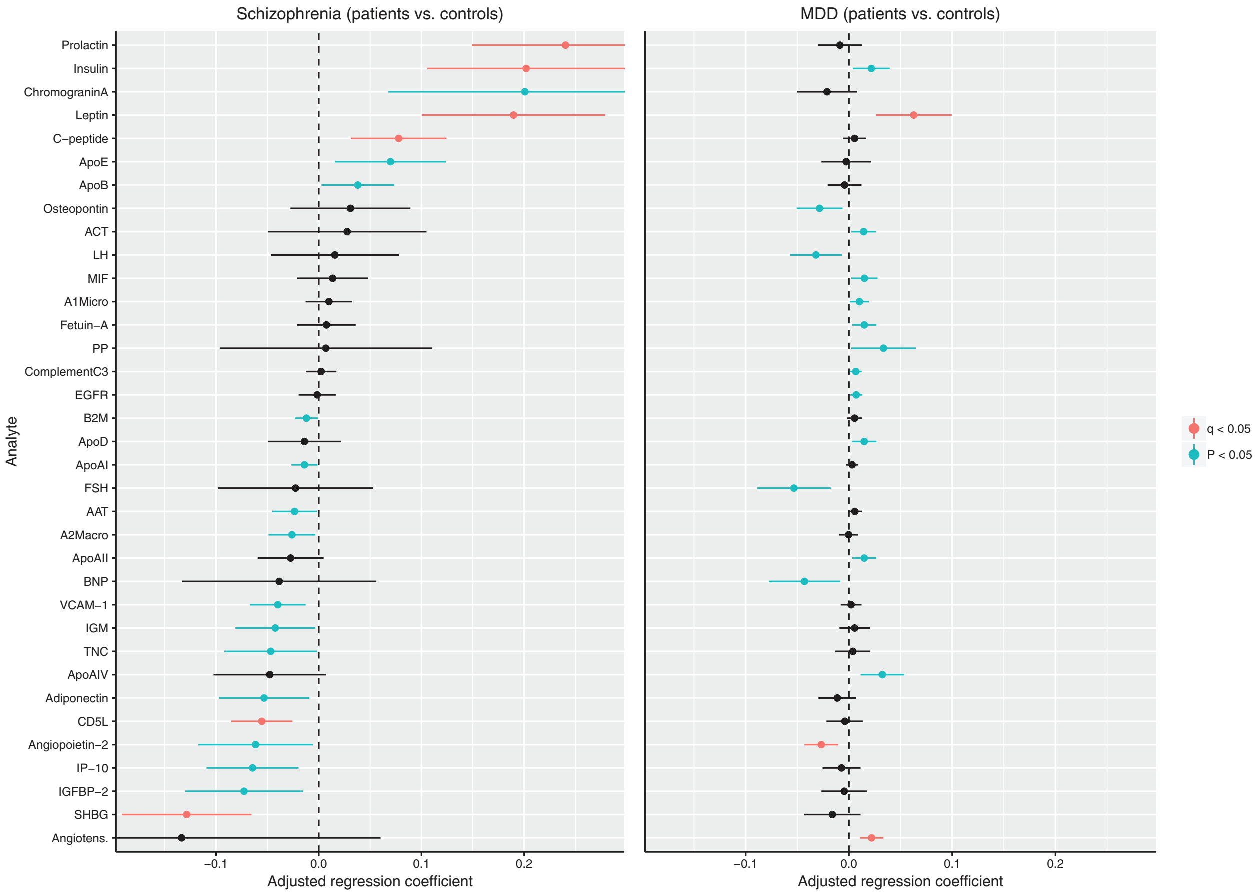

Fig. 1 Similarities in serum alterations between schizophrenia and MDD.
Adjusted regression coefficients and error bars (s.e.). Analytes ordered based on size-adjusted regression coefficients of schizophrenia patients vs controls. Model corrected for age, gender, ethnicity, anti-inflammatory agents, corticosteroids, smoking, cardiovascular disease and diabetes type 2.
Abbreviations: A1Micro, alpha-1-microglobulin; A2Macro, alpha-2-macroglobulin; AAT, alpha-1 antitrypsin; ACT, alpha 1-antichymotrypsin; Angiotens, angiotensinogen; ApoAI, apolipoprotein A-I; ApoAIV, apolipoprotein A-IV; ApoB, apolipoprotein B; ApoD, apolipoprotein D; ApoE, apolipoprotein E; B2M, beta-2-microglobulin; BNP, brain natriuretic peptide; CD5L, CD5 antigen-like; EGFR, epidermal growth factor receptor; FSH, follicle-stimulating hormone; IGFBP-2, insulin-like growth factor-binding protein 2; IGM, immunoglobulin M; IP-10, interferon gamma-induced protein 10; LH, luteinizing hormone; MDD, major depressive disorder; MIF, macrophage migration inhibitory factor; P, *p*-value; PP, pancreatic polypeptide; q, Benjamini-Hochberg procedure; SHBG, sex hormone-binding globulin; TNC, tenascin-C; VCAM-1, vascular cell adhesion molecule 1.

3.3. Current episode

To investigate the influence of clinical status, we selected schizophrenia patients with high PANSS scores (Andreasen et al., 2005) and MDD patients with high IDS scores (Rush et al., 2003) and compared them to their respective controls.

Notably, we identified an even more substantial pattern of elevated levels of insulin and leptin in both disorders (Fig. 2, Table S4). In patients that were currently symptomatic, leptin and insulin levels both survived Benjamini-Hochberg in schizophrenia patients (leptin, b: 0.23; $q < 0.001$; d: 0.34 and insulin, b: 0.24; $q = 0.001$; d: 0.77) and MDD patients (leptin, b: 0.09; $q = 0.001$; d: 0.35 and insulin, b: 0.03; $q = 0.04$; d: 0.15) compared to their respective controls.

C-peptide and prolactin were significantly increased ($q < 0.05$) and higher regression coefficients were observed for schizophrenia patients with a current psychotic episode compared to the total schizophrenia patient group from the main analysis. For schizophrenia patients with a current psychotic episode, CD5 antigen-like and sex hormone-binding globulin were significantly decreased ($q < 0.05$) and lower regression coefficients were observed compared to the total schizophrenia patient group. For MDD patients with a current depressive episode, alpha 1-microglobulin, complement C3, fetuin-A, follicle-stimulating hormone and serum amyloid P-component were significantly increased ($q < 0.05$) and higher regression coefficients were observed compared to patients with a lifetime diagnosis of MDD from the main analysis. Additionally, angiotensinogen, angiopoietin-2, apolipoprotein

Table 2 Overview of analytes significantly[a] differing between schizophrenia and/or MDD versus controls.

Analyte	Schizophrenia (Patients vs. Controls)					MDD (Patients vs. Controls)				
	b	q	P	d	FC	b	q	P	d	FC
Prolactin	0.240	**6.788E-05**	6.228E-07	0.870	2.293	−0.009	0.777	0.419	−0.094	0.961
Leptin	0.190	**0.002**	4.777E-05	0.258	1.432	0.063	**0.045**	0.001	0.285	1.291
Insulin	0.202	**0.002**	5.854E-05	0.653	2.182	0.022	0.146	0.017	0.118	1.188
SHBG	−0.129	**0.003**	9.533E-05	−0.695	0.622	−0.016	0.704	0.250	0.004	0.936
CD5L	−0.056	**0.008**	3.459E-04	−0.664	0.874	−0.004	0.860	0.665	−0.017	1.014
C-peptide	0.078	**0.023**	0.001	0.505	1.387	0.005	0.704	0.343	0.095	1.070
ChromograninA	0.201	0.056	0.004	0.477	1.323	−0.021	0.537	0.153	0.029	1.100
VCAM-1	−0.040	0.060	0.004	−0.392	0.913	0.002	0.860	0.684	−0.011	0.989
IP-10	−0.064	0.065	0.005	−0.409	0.861	−0.007	0.811	0.446	−0.024	0.955
ApoE	0.070	0.134	0.012	0.506	1.298	−0.003	0.946	0.828	0.049	1.127
IGFBP-2	−0.073	0.136	0.014	−0.377	0.851	−0.005	0.860	0.686	0.077	1.036
Adiponectin	−0.053	0.170	0.019	−0.537	0.785	−0.011	0.699	0.224	0.001	1.005
A2Macro	−0.026	0.219	0.026	−0.251	0.915	0.000	0.984	0.952	−0.014	1.016
Angiopoietin-2	−0.062	0.219	0.032	−0.215	0.826	−0.027	**0.049**	0.001	−0.133	0.862
ApoAI	−0.014	0.219	0.033	−0.545	0.851	0.003	0.704	0.310	0.129	1.047
IGM	−0.042	0.219	0.034	−0.486	0.850	0.006	0.812	0.462	0.022	1.054
AAT	−0.024	0.219	0.035	−0.319	0.946	0.006	0.399	0.094	0.115	1.036
ApoB	0.038	0.219	0.037	0.132	1.095	−0.004	0.860	0.613	0.052	1.021
B2M	−0.012	0.219	0.038	−0.263	0.965	0.005	0.516	0.142	0.142	1.069
TNC	−0.047	0.237	0.044	−0.314	0.896	0.004	0.860	0.659	0.008	0.999
ApoAIV	−0.048	0.390	0.089	−0.182	0.906	0.032	0.073	0.003	0.156	1.224
ApoAII	−0.027	0.404	0.096	−0.156	0.999	0.015	0.146	0.013	0.186	1.081
Angiotensinogen	−0.133	0.589	0.178	−0.106	0.897	0.022	**0.018**	1.640E-04	0.189	1.032
Osteopontin	0.031	0.717	0.303	0.203	1.084	−0.028	0.146	0.012	−0.184	0.889
A1Micro	0.010	0.808	0.394	0.324	1.078	0.010	0.195	0.030	0.221	1.075
BNP	−0.039	0.808	0.426	−0.270	0.855	−0.043	0.146	0.015	−0.032	0.984
MIF	0.014	0.808	0.444	0.217	1.230	0.015	0.155	0.021	0.189	1.061
ApoD	−0.014	0.808	0.445	−0.113	0.973	0.015	0.146	0.015	0.153	1.065
ACT	0.028	0.809	0.484	0.031	1.237	0.014	0.146	0.019	0.208	1.039
FSH	−0.023	0.822	0.560	−0.165	1.065	−0.053	0.077	0.004	0.084	1.089
Fetuin-A	0.007	0.824	0.610	0.113	1.037	0.015	0.146	0.013	0.077	1.020
LH	0.016	0.824	0.623	0.058	1.318	−0.032	0.146	0.013	0.046	0.707
ComplementC3	0.002	0.885	0.763	0.003	1.020	0.007	0.164	0.024	0.150	1.050
EGFR	−0.002	0.945	0.867	0.032	0.998	0.007	0.146	0.019	0.087	0.997
PP	0.007	0.957	0.896	0.043	1.073	0.033	0.219	0.036	0.205	1.257

Abbreviations: b, regression coefficient; A1Micro, alpha-1-microglobulin; A2Macro, alpha-2-macroglobulin; AAT, alpha-1 antitrypsin; ACT, alpha 1-antichymotrypsin; Angiotens., angiotensinogen; ApoAI, apolipoprotein A-I; ApoAIV, apolipoprotein A-IV; ApoB, apolipoprotein B; ApoD, apolipoprotein D; ApoE, apolipoprotein E; B2M, beta-2-microglobulin; BNP, brain natriuretic peptide; CD5L, CD5 antigen-like; d, Cohen's d; EGFR, epidermal growth factor receptor; FC, Fold Change; FSH, follicle-stimulating hormone; IGFBP-2, insulin-like growth factor-binding protein 2; IGM, immunoglobulin M; IP-10, interferon gamma-induced protein 10; LH, luteinizing hormone; MIF, macrophage migration inhibitory factor; MDD, major depressive disorder; P, *p*-value; PP, pancreatic polypeptide; q, Benjamini-Hochberg procedure; SHBG, sex hormone-binding globulin; TNC, tenascin-C; VCAM-1, vascular cell adhesion molecule 1.

[a] On the basis of *p*-value. Model corrected for site, age, gender, ethnicity, anti-inflammatory agents, corticosteroids, smoking, cardiovascular disease and diabetes type 2.

A-II, apolipoprotein A-IV and osteopontin were significantly decreased ($q < 0.05$) and lower regression coefficients were found for MDD patients with a current depressive episode compared to patients with a lifetime diagnosis of MDD.

3.4. Post-hoc analysis for psychotropic medication effects

To account for possible psychotropic treatment influences we performed an exploratory within-patient analysis on overlapping altered analytes (based on the *p*-value) in schizophrenia and MDD (Table S5A and S5B). For leptin we found a trend of elevated levels in MDD patients between TCAs users vs non-users. However, this effect did not reach significance for the Benjamini-Hochberg correction. Antipsychotics use (e.g., olanzapine or clozapine) and mood stabilizers use did not show significant interactions with the observed elevated insulin and leptin levels in both disorders. However, we could not fully account for psychotropic treatment effects, since we had insufficient drug-free patients for this analysis.

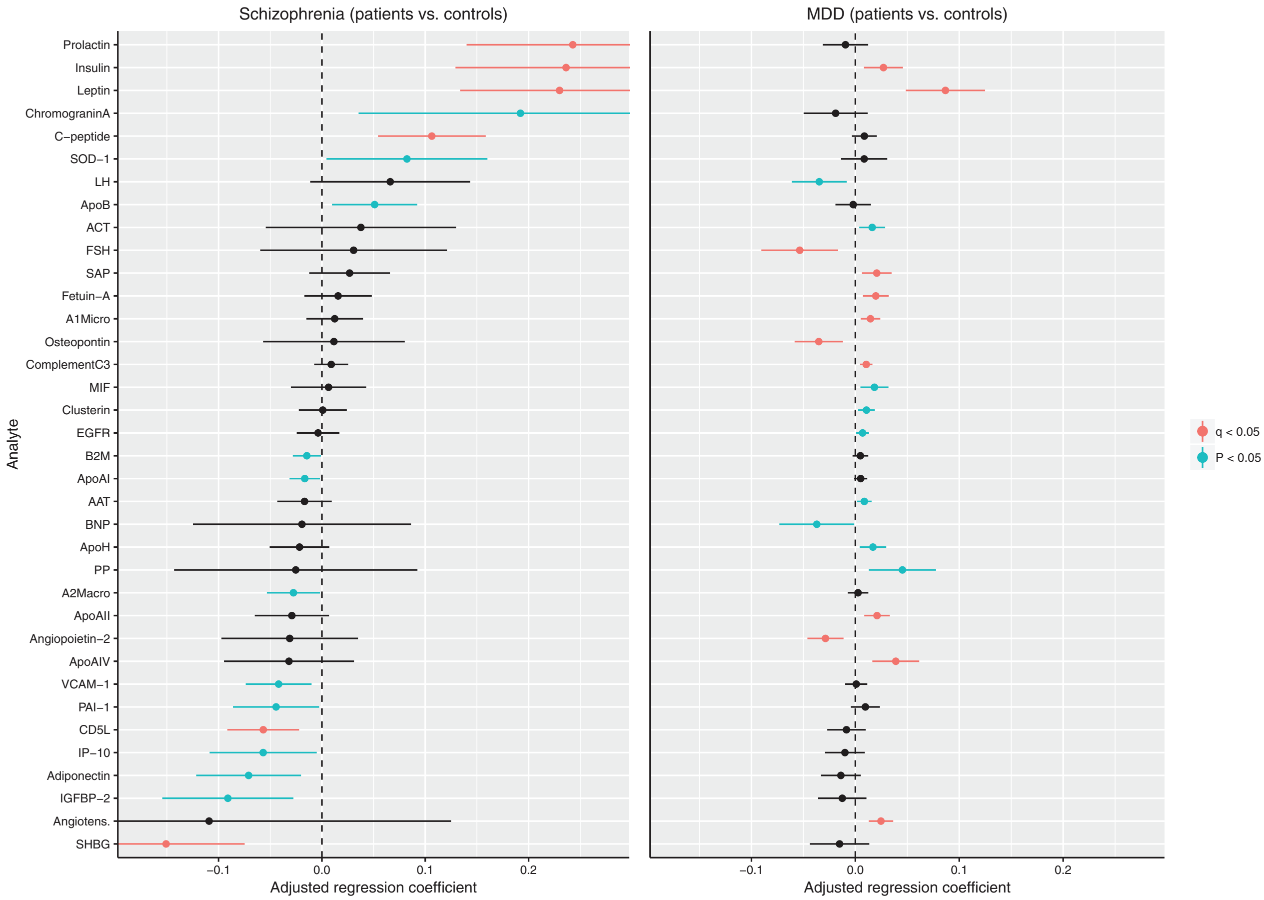

Fig. 2 Similarities in serum alterations between current episode schizophrenia and MDD.
Adjusted regression coefficients and error bars (s.e.). Analytes ordered based on size-adjusted regression coefficients of schizophrenia patients vs controls. Model corrected for age, gender, ethnicity, anti-inflammatory agents, corticosteroids, smoking, cardiovascular disease and diabetes type 2.
Abbreviations: A1Micro, alpha-1-microglobulin; A2Macro, alpha-2-macroglobulin; AAT, alpha-1 antitrypsin; ACT, alpha 1-antichymotrypsin; Angiotens., angiotensinogen; ApoAI, apolipoprotein A-I; ApoAII, Apolipoprotein A-II; ApoAIV, apolipoprotein A-IV; ApoB, apolipoprotein B; Apolipoprotein H; B2M, beta-2-microglobulin; BNP, brain natriuretic peptide; CD5L, CD5 antigen-like; d, Cohen's d; EGFR, epidermal growth factor receptor; FSH, follicle-stimulating hormone; IGFBP-2, insulin-like growth factor-binding protein 2; IP-10, interferon gamma-induced protein 10; LH, luteinizing hormone; MDD, major depressive disorder; MIF, macrophage migration inhibitory factor; Osteopont., osteopontin; PP, pancreatic polypeptide; PAI-1, plasminogen activator inhibitor-1; SAP, serum amyloid P-component; SHBG, sex hormone-binding globulin; SOD-1, Superoxide Dismutase-1; VCAM-1, vascular cell adhesion molecule 1.

The most significantly pronounced alteration was for prolactin in schizophrenia, but not in MDD, which we ascribe to the well-described prolactin increasing effects of antipsychotics.

3.5. Post-hoc analysis in non-obese participants

Given the strong association between high levels of metabolic analytes with both disorders, we performed a post-hoc analysis on all analytes in which we excluded patients and controls with obesity, defined as having a BMI ≥ 30 (Table S6). For schizophrenia, the association with elevated leptin and insulin levels remained significant. For MDD, we observed a trend of elevated leptin levels.

3.6. Assessment of serum analyte profile similarity

SAM identified the top 14 increased and top 14 decreased analytes of each patient group (vs respective controls). Of the 28 analytes eleven appeared in both patient groups, of which six were altered in the same direction in both patient groups. Among these were: insulin, leptin, apolipoprotein E, C-peptide, FAS ligand receptor and glutathione S-transferase alpha (Table S7).

4. Discussion

In the current study, using similar analytical procedures to measure serum analytes and analyse results, we investigated whether there are similar alterations in serum analyte markers in both schizophrenia and MDD compared to controls. We observed elevated levels of leptin and insulin for both schizophrenia and MDD patients. When selecting schizophrenia and MDD patients with current episodes the effect sizes of elevated leptin and insulin levels became more substantial in both patient groups. Notably, the leptin and insulin alterations were more substantial for schizophrenia than for MDD. These findings seem to be independent of antipsychotics or antidepressants use.

Taken together, our findings of elevated insulin and leptin levels point towards the presence of insulin resistance and leptin resistance in both schizophrenia and MDD, which may indicate the presence of similar pathological processes present in both disorders. Insulin and leptin resistance are important risk factors for the onset of diabetes mellitus type II and cardiovascular disease, which are more common in schizophrenia and MDD compared to the healthy population. As these cardiometabolic diseases contribute significantly to decreased life-span, increased morbidity and cost of health care, our findings are important from a general health perspective, as they enhance our understanding of the origins of diminished general health in schizophrenia and MDD patients.

Our findings of elevated leptin levels for schizophrenia and MDD are in line with several studies. A recent meta-analysis of 27 studies comparing schizophrenia patients to controls identified significant elevated leptin levels in schizophrenia in which BMI and antipsychotic medication could not completely account for these findings (Stubbs et al., 2016). Leptin levels seem to be increased in MDD, but only in a specific subgroup, namely those with atypical features (Carvalho et al., 2014; Gecici et al., 2005). Two recent studies reported associations between increased leptin levels and especially MDD with atypical features based on restricted samples of NESDA (Lamers et al., 2016; Milaneschi et al., 2017a).

For schizophrenia and MDD patients with a current episode, alterations in apolipoprotein levels were more pronounced compared to the total patient groups. This finding might point towards disturbances in fat metabolism present in both disorders. There was however no overlap between the identified altered apolipoproteins in both disorders.

The identified elevated insulin levels in both schizophrenia and MDD from this cross-disorder study are also in line with a large body of evidence. The presence of altered glucose homeostasis in schizophrenia has been described extensively (De Hert et al., 2009; Mitchell et al., 2013; Pillinger et al., 2017; Van Welie et al., 2013). A prevalence of 10–15% for diabetes in schizophrenia has been reported (De Hert et al., 2009; Mitchell et al., 2013), and an increased prevalence of diabetes in close relatives of patients with non-affective psychotic disorder has been reported as well (Van Beveren et al., 2014; Van Welie et al., 2013). Although alterations in glucose metabolism are observed frequently during use of antipsychotics (Smith et al., 2008), an altered state of glucose homeostasis in schizophrenia has been confirmed by a recent meta-analysis of antipsychotic-naïve patients with first-episode schizophrenia compared to BMI-matched controls (Pillinger et al., 2017). Indeed, the presence of diabetes in schizophrenia was already reported well before the advent of antipsychotics (Kohen, 2004).

For depression, there is meta-analytic evidence for increased risk of insulin resistance, hyperglycaemia and diabetes mellitus type II (Kan et al., 2013; Mezuk et al., 2008; Vancampfort et al., 2014). A prospective cohort study investigated underlying associations between MDD and cardiometabolic diseases in depression subtypes, and found a higher incidence for 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). Similar prevalence numbers for metabolic syndrome in schizophrenia (33.4%) and in MDD (31.3%) have been described (Vancampfort et al., 2015).

Although the observed effect size of Cohen's d 0.12 in MDD patients is not large, such an effect size for MDD is in line with the literature in depression investigating biomarkers. For BDNF, HPA-axis, telomere length, autonomic nervous system activity and inflammation markers have been confirmed in meta-analyses but the summarized effect sizes are in general not large. It is suggested that these relatively small effect sizes are typical for depression, likely due to heterogeneity.

Taken together, the results from this direct comparison study on the one hand and the evidence regarding insulin and leptin disturbances in both disorders on the other hand, indicate a shared underlying metabolic dysfunction in both schizophrenia and MDD.

Additionally, we identified alterations in analytes which are involved in glucose homeostasis. For schizophrenia we observed increased levels of C-peptide, which is an insulin precursor and is increased in insulin resistance and diabetes mellitus type II (Broedbaek and Hilsted, 2016). Decreased levels of sex hormone-binding globulin could be explained by high insulin levels (Abdella and Mojiminiyi, 2017) in schizophrenia patients. For patients with a current depressive episode we observed increased levels of fetuin-A, which could point towards insulin resistance (Jung et al., 2013).

Our observations do certainly not imply that the overall protein alterations in schizophrenia and MDD are similar, or point to completely similar deranged processes. Based on our findings we conclude that to a certain extent both similarity and dissimilarity are present. The profiles of the two patient groups clearly differ, as indicated by the presence of several different deregulated analytes between the patient groups. At the same time, there are some analytes which are altered similarly, and which point to possible cross-disorder underlying biological processes.

Obviously, our findings regarding altered insulin and leptin levels raise the question as to whether the presence of obesity and increased BMI alone can explain these alterations. If elevated leptin and insulin levels are thought to underlie schizophrenia and MDD, one might expect that high BMI influences these alterations. However, considering a bidirectional relationship between altered insulin and leptin levels, and schizophrenia and MDD, simply correcting for BMI in our initial regressions may lead to overcorrection as there is increasing evidence that mechanisms of body fat regulation share (genetic) overlap with regulation of mood (Milaneschi et al., 2016).

MDD is a heterogeneous disorder in which alterations in insulin and leptin levels, and immune alterations has been mostly linked to the atypical variant of MDD

(Lamers et al., 2016). Clinical features as increased appetite and weight gain which occur in atypical depression could underlie a bidirectional relationship between BMI and depressive symptoms (Lamers et al., 2016). However, data from a large international consortium identified that 15% of patients with atypical depression carried a higher number of genetic risk variants for increased BMI, leptin and C-reactive protein, meaning atypical depression and obesity-related traits could be part of the same syndrome (Milaneschi et al., 2017b).

The same could possibly apply for schizophrenia as this disorder could be seen as a spectrum disease consisting of many subtypes (Heckers et al., 2013; Nestler, 2014; Van Os et al., 1998). More speculative, one may consider schizophrenia and MDD on the one hand, and increased BMI on the other hand as manifestations of an underlying syndrome.

We consider that the effects of prolonged insulin resistance and leptin resistance, such as the presence of metabolic syndrome, and an increased incidence of type II diabetes in both disorders, are not solely caused by the behavioural effects of both disorders (i.e., altered diet, sedentary life style), but may be closely related to the pathological mechanisms underlying schizophrenia and MDD.

Various analytes, which are involved in the immune system, mainly in inflammatory processes, were altered in our study. However we observed mostly a different profile regarding the alterations of immune related analytes for schizophrenia and MDD.

For angiopoietin-2 we observed significantly decreased levels in MDD patients and a non-significant trend of decreased levels in schizophrenia patients, compared with controls. When restricting analyses to current episode patients only, angiopoietin-2 levels remained significantly altered in MDD patients but not in schizophrenia patients. Angiopoietin-2, an angiopoietin cytokine, is involved in angiogenesis, and thereby controls microvascular permeability, vasodilation and vasoconstriction (Gilbert, 2010). To our knowledge, there is limited evidence for a role of angiopoietin-2 in MDD. Interestingly, angiogenesis-related pathways, such as downregulating of angiopoietin-signaling, have been associated with schizophrenia (Katsel et al., 2017). However, the implication of angiopoietin-2 in psychiatric disorders merits further investigation.

Associations of altered inflammatory processes with these two disorders are also found in other studies (Bergink et al., 2014; Chan et al., 2014; Howren et al., 2009; Miller et al., 2009). A recent study published results on microglial cell signalling network responses (in vitro) after exposure to serum of first-episode and antipsychotic-naïve schizophrenia patients, indicating proinflammatory activation in resident brain immune cells (Van Rees et al., 2018). These findings support the thought that patients with either schizophrenia or MDD could be in a chronic (sub-) inflammatory state due to chronic activated stress mechanisms (Miller et al., 2009; Singh and Chaudhuri, 2014).

Importantly, we would like to point out that we observed no significant alterations for C-reactive protein (CRP), nor for brain-derived neurotrophic factor (BDNF), two compounds of which alterations have been previously associated with both disorders (Fernandes et al., 2016, 2015; Haapakoski et al., 2015; Molendijk et al., 2014). We cannot fully explain why we did not observe alterations in these two compounds. Insufficient sample size may be a factor. However, BDNF and CRP have been found to be significantly altered in considerably smaller samples (Buckley et al., 2007; Jordan et al., 2018). Other factors may play a role, of which prolonged duration of the disorder or the use of medication deserve consideration (e.g., BDNF alterations could normalize following psychotropic treatment) (Jordan et al., 2018; Zhou et al., 2017).

We did not analyse several analytes which have been previously associated with either or both of the disorders: among these were tumor necrosis factor alpha, interleukin 6 and interleukin-1 receptor antagonist for which elevated levels were previously identified in schizophrenia and MDD because these analytes did not survive the cut-off criterion of being present in more than 30% of the control- and patient groups (Goldsmith et al., 2016; Haapakoski et al., 2015; Kohler et al., 2017; Upthegrove et al., 2014). Therefore, there is a probability that more analytes are similarly altered in both schizophrenia and MDD, than only leptin and insulin.

The main strength of our study is that our samples were analysed using the same multi-analyte platform. The cohorts consist of well-characterized schizophrenia patients, MDD patients and healthy controls. We had the possibility to analyse a large quantity of analytes which were equally processed.

An important limitation is that due to the distinction between schizophrenia and MDD, the patients have primarily been recruited as part of separate epidemiological projects, aimed at either disorder. Therefore, the control groups were matched for their respective disorders. As a consequence, the differences between the control groups prohibited us from grouping them together. This limitation stresses the importance of designing future research from a transdiagnostic perspective.

Furthermore, since we analysed the data cross-sectionally, we could not investigate any cause-effect relationship between leptin, insulin, and BMI. Hence, we cannot unravel the possible causal relationships that may exist between insulin and leptin alterations and schizophrenia and MDD, and the effects of BMI, insulin and leptin. Finally, most patients included in our study were not drug free. We observed multicollinearity between the predictors psychotropic medication use and status participant (patient or control). We could not therefore rule out possible treatment interferences, although post-hoc analyses suggest the role of medication was probably limited. Moreover, our findings of elevated leptin and insulin levels in both schizophrenia and MDD are in line with a great body of evidence.

Although the same multiplexed immunoassay was used in both studies (which we consider a strength), we observed batch effects between the schizophrenia and MDD samples, because the schizophrenia/control set and the MDD/control set were analysed separately. As a result, we noticed batch effect related differences in protein intensity measurements across the schizophrenia and MDD sample groups, which we could not control for. Due to these differences a truly direct comparison between the two patient groups was not possible. Future directions for cross-disorder protein profile studies investigating subgroups should analyse serum proteins using identical (i.e., mixed batches) conditions.

Further research should focus on disentangling cause-effect relationships, and identifying factors which determine the trajectory towards the phenotypical expression of either MDD or schizophrenia. Finding common biological ground between MDD and schizophrenia, could help to plan for shared preventive strategies and treatment regarding metabolic dysfunctions prevalent in these disorders. In conclusion, we found increased levels of leptin and insulin in both schizophrenia patients and MDD patients – in particular in patients with a current episode – compared to their respective controls. Which could be suggestive of the presence of insulin and leptin resistance that may act as cross-disorder mechanisms contributing to the higher somatic comorbidity and decreased life-span seen in both disorders.

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Contributors

N.J.M. van Beveren, L. de Haan, B. Penninx, N. Çakici, M. Bot and F. Lamers designed the research. N. Çakici, M. Bot, F. Lamers and P.J. van der Spek analysed and visualised the data. T. Janssen helped with visualising the data in R. N.J.M. van Beveren, N. Çakici, L. de Haan, B. Penninx, S. Bahn, P.J. van der Spek, M. Bot and F. Lamers drafted the article and made critical revisions related to important intellectual content of the manuscript. N. Çakici and N.J.M. van Beveren wrote the article. All authors contributed to and have approved the final manuscript.

Conflict of interest

Prof. Dr. Bahn is director of Psynova Neurotech Ltd and PsyOmics Ltd and was a consultant for Myriad Genetics until June 2014. The remaining authors declare no conflict of interest.

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Supplementary materials

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