TECHNICAL COMMENTARY

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Hormonal changes

Introduction

Hormones are chemical messengers secreted by the endocrine glands. Hormones travel through the bloodstream to tissues and organs, and control most of the body's major systems including heart rate, metabolism, mood, sexual function, and growth and development.

Neuroactive steroids, including testosterone, dehydroepiandrosterone (DHEA) and its sulphide ester (DHEA-S), are important for brain development as they influence synaptic connectivity and neuronal differentiation. They influence dopaminergic, glutamatergic, and GABAergic neurotransmission that have been found to be dysregulated in schizophrenia.

Estrogen has been proposed to confer a protective effect for schizophrenia. Women generally have a later onset of schizophrenia than males with an increased risk after menopause (see the risk factor topic on sex differences). Estrogen levels drop over time, particularly with the onset of menopause. This protection may also mean that pre-menopausal women who develop schizophrenia may experience a less severe illness than males.

Prolactin is another hormone implicated in schizophrenia. It is a polypeptide secreted by the pituitary gland, and is involved in many biological functions including reproduction, pregnancy and lactation, and growth and development. Some medications, such as antipsychotics are among the factors that can affect blood prolactin concentrations. Increased prolactin (hyperprolactinemia) is associated with a variety of adverse effects, including risk of breast cancer, lack of menstruation, and early osteoporosis in women, and a lack of libido and erectile function in men.

Body weight is regulated by anorexigenic or appetite suppressing hormones (e.g., insulin, leptin, peptide YY, and cholecystokinin) and orexigenic or appetite stimulating hormones (e.g., neuropeptide Y, orexins, agouti-related peptide, galanin, and ghrelin). These hormones are mostly produced by adipose tissue (e.g., adiponectin, leptin, resistin, vaspin and visfatin) or by the gastrointestinal tract (e.g., cholecystokinine, glucagon-like peptide 1, ghrelin and peptide YY). Alterations in the production of appetite-regulating hormones might be present in psychotic disorders.

Melatonin is primarily synthesised by the pineal gland. Secretion of melatonin by the pineal gland shows a circadian rhythm synchronised to the light-dark cycle. Melatonin has been reported to be involved in various important biological functions in the body: sleep regulation, circadian rhythm, immune modulation, reproduction, anti-inflammation, antioxidant, and energy metabolism. Various studies have reported the beneficial effects of taking melatonin for improving metabolic problems; problems often observed in people on antipsychotic medications.

Oxytocin and vasopressin are peptide hormones, which are released through the posterior pituitary gland where they regulate a range of physiological functions. They are also released in the central nervous system, acting on multiple brain regions as neuromodulators and influencing a range of neurophysiological processes and behaviours, including feeding, anxiety, aggression, social recognition, and the stress/fear response to social stimuli.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are given priority for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[1]. Reviews rated as having less than 50% if items checked are excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large, there is a dose dependent response or if results are reasonably consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found 11 systematic reviews that met our inclusion criteria[3-13].

- Moderate to high quality evidence finds a small to medium-sized increase in leptin levels in people with chronic schizophrenia compared to controls, particularly in patients taking second generation antipsychotics olanzapine and clozapine.
- Moderate to high quality evidence finds a small to medium-sized effect of higher insulin levels and a trend effect of lower leptin levels in people with first-episode psychosis compared to controls. These effects were both significant in subgroup analyses of antipsychotic-naïve patients. The severity of negative symptoms was associated with increased effect size estimates for insulin.
- Moderate to high quality evidence finds no differences in adiponectin levels between people with schizophrenia and controls, although patients taking clozapine or olanzapine may show reduced adiponectin levels. Aduoinectin, ghrelin, orexin, resistin, and visfatin were not altered in people with first-episode psychosis.
- Moderate quality evidence finds a large increase in prolactin levels in antipsychotic-naïve males with schizophrenia and a medium-sized increase in antipsychotic-naïve females with schizophrenia.
- Moderate quality evidence finds a medium to large effect of elevated DHEA-S levels in people with schizophrenia compared to controls. Testosterone levels were elevated only in first-episode psychosis patients and in patients in an acute relapse. There were no differences in DHEA. We found no systematic review specifically assessing estrogen levels in schizophrenia.
- Moderate quality evidence finds reduced midnight melatonin plasma levels in people with schizophrenia.
- Moderate quality evidence finds decreased vasopressin in plasma of patients with

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Hormonal changes

schizophrenia. There were no differences in vasopressin in CSF.

- Moderate to low quality evidence finds a significant, large effect of decreased oxytocin levels in serum and a medium-sized effect of increased oxytocin levels in CFS of people with schizophrenia. There were no differences in plasma.
- Moderate to high quality evidence finds a small increase in thyroid-stimulating hormone in people with multi-episode schizophrenia, with no differences in triiodothyronine or thyroxine. In people with first-episode psychosis, there was a small decrease in thyroid-stimulating hormone and a medium-sized decrease in total triiodothyronine. There was also a medium-sized increase in free thyroxine in first-episode patients.

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Hormonal changes

Bartoli F, Lax A, Crocamo C, Clerici M, Carra G

Plasma adiponectin levels in schizophrenia and role of second-generation antipsychotics: a meta-analysis

Psychoneuroendocrinology 2015; 56: 179-89

View review abstract online

Comparison	**Adiponectin levels in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples inconsistent, precise, direct) finds no differences in adiponectin levels, although patients taking clozapine or olanzapine may show reduced levels.**
Adiponectin	
There were no significant differences between groups; 18 studies, N = 2,735, SMD = -0.28, 95%CI -0.59 to 0.04, p = 0.09, I^2 = 91% Subgroup analysis showed patients taking clozapine and olanzapine showed reduced adiponectin levels. There were no differences in subgroup analysis of drug free/drug naïve subjects.	
Consistency	Inconsistent
Precision	Precise
Directness	Direct

Bastos M, Bastos P, Portella R, Soares L, Conde R, Rodrigues P, Lucchetti G

Pineal gland and schizophrenia: A systematic review and meta-analysis

Psychoneuroendocrinology 2019; 104: 100-14

View review abstract online

Comparison	**Midnight melatonin plasma levels in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small sample, consistent, imprecise, direct) finds reduced midnight melatonin plasma levels in people with schizophrenia.**

Hormonal changes

Melatonin	
A large effect of reduced melatonin in people with schizophrenia; 5 studies, N = 156, *g* = -1.32, 95%CI -0.10 to -1.98, *p* < 0.01, I^2 = 46%	
Consistency in results	Consistent.
Precision in results	Imprecise
Directness of results	Direct

Fraguas D, Diaz-Caneja CM, Ayora M, Hernandez-Alvarez F, Rodriguez-Quiroga A, Recio S, Leza JC, Arango C

Oxidative stress and inflammation in first-episode psychosis: A Systematic Review and Meta-analysis

Schizophrenia Bulletin 2019; 45(4): 742-51

View review abstract online

Comparison	**DHEA-S in people with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small sample, unable to assess consistency, imprecise, direct) finds no differences in DHEA-S levels in people with first-episode psychosis.**
DHEA-S	
No significant differences between groups; 3 studies, N = 163, *d* = 0.449, 95%CI -1.014 to 1.912, *p* > 0.995, I^2 not reported	
Consistency in results	Unable to assess consistency.
Precision in results	Imprecise
Directness of results	Direct

Gonzalez-Blanco L, Greenhalgh AM, Garcia-Rizo C, Fernandez-Egea E, Miller BJ, Kirkpatrick B

Prolactin concentrations in antipsychotic-naive patients with

schizophrenia and related disorders: A meta-analysis **Schizophrenia Research 2016; 174: 156-160** View review abstract online	
Comparison	**Prolactin levels in antipsychotic-naïve people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (small to medium-sized samples, inconsistent, precise, direct) finds a large increase in prolactin levels in antipsychotic-naïve males and a medium-sized increase in antipsychotic-naïve females.**
Prolactin	
A significant, large effect of increased prolactin levels in males with schizophrenia and a medium-sized effect in females with schizophrenia; Males: 7 studies, N = 332, g = 1.02, 95%CI 0.77 to 1.26, $p < 0.001$, I^2 = 81%, $p < 0.001$ Females: 5 studies, N = 183, g = 0.43, 95%CI 0.11 to 0.76, $p < 0.01$, I^2 = 66%, $p < 0.02$ Meta-regression analyses showed no associations with the effect size and age, smoking, body mass index, year of publication, or cortisol levels.	
Consistency	Inconsistent
Precision	Precise
Directness	Direct

Hernandez-Diaz Y, Gonzalez-Castro TB, Tovilla-Zarate CA, Lopez-Narvaez ML, Genis-Mendoza AD, Castillo-Avila RG, Ramos-Mendez MA, Juarez-Rojop IE **Oxytocin levels in individuals with schizophrenia are high in cerebrospinal fluid but low in serum: A systematic review and meta-analysis: Oxytocin and Schizophrenia** **Metabolic Brain Disease 2021; 36(8): 2415-24** View review abstract online	
Comparison	**Oxytocin levels in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, inconsistent, imprecise, direct) finds a significant,**

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	large effect of decreased oxytocin levels in serum and a medium-sized effect of increased oxytocin levels in CFS of people with schizophrenia.
Oxytocin	
A significant, large effect of decreased oxytocin levels in serum and a medium-sized effect of increased oxytocin levels in CFS of people with schizophrenia; Serum: 5 studies, N = 430, SMD = -1.74, 95%CI -3.22 to -0.26, $p = 0.02$, $I^2 = 77\%$, $p < 0.01$ CFS: 3 studies, N = 147, SMD = 0.55, 95%CI 0.05 to 1.04, $p = 0.03$, $I^2 = 50\%$, $p = 0.03$ *There were no significant differences in oxytocin levels in plasma;* Plasma: 6 studies, N = 350, SMD = -0.27, 95%CI -1.10 to 0.5, $p = 0.51$, $I^2 = 71\%$, $p < 0.01$ The effect sizes for plasma and serum were larger in younger samples and in samples with more males.	
Consistency	Inconsistent
Precision	Imprecise
Directness	Direct

Misiak B, Frydecka D, Loska O, Moustafa AA, Samochowiec J, Kasznia J, Stanczykiewicz B

Testosterone, DHEA and DHEA-S in patients with schizophrenia: A systematic review and meta-analysis

Psychoneuroendocrinology 2018; 89: 92-102

View review abstract online

Comparison	**Testosterone, DHEA, and DHEA-S in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate quality evidence (unclear sample size, inconsistent, some imprecision, direct) finds a medium to large effect of elevated dehydroepiandrosterone – sulfate levels in people with schizophrenia. Testosterone levels were elevated only in first-episode psychosis patients and patients with an acute relapse.**
Testosterone, DHEA, and DHEA-S	
A significant, medium to large effect of elevated DHEA-S levels in people with schizophrenia;	

13 studies, N = unclear, $g = 0.75$, 95%CI 0.23 to 1.28, $p = 0.005$, $I^2 = 95\%$ *There were no significant differences in;* Testosterone: 20 studies, N = unclear, $g = -0.04$, 95%CI -0.31 to 0.24, $p = 0.80$, $I^2 = 86\%$ DHEA: 7 studies, N = unclear, $g = 0.02$, 95%CI -0.36 to 0.40, $p = 0.90$, $I^2 = 81\%$ Subgroup analyses found people with first-episode psychosis had significantly higher levels of free testosterone ($g = 1.21$, $p = 0.009$) and DHEA-S ($g = 1.19$, $p < 0.001$) than controls. Acutely relapsed patients had higher levels of total testosterone ($g = 0.50$, $p < 0.001$). Total testosterone was elevated in stable multi-episode females ($g = 0.56$, $p < 0.001$) and reduced in stable multi-episode males ($g = -0.62$, $p = 0.006$).	
Consistency	Inconsistent
Precision	Imprecise for DHEA-S, precise for testosterone and DHEA.
Directness	Direct

Misiak B, Bartoli F, Stramecki F, Samochowiec J, Lis M, Kasznia J, Jarosz K, Stanczykiewicz B

Appetite regulating hormones in first-episode psychosis: A systematic review and meta-analysis

Neuroscience and Biobehavioral Reviews 2019; 102: 362-70

View review abstract online

Comparison	**Appetite regulating hormones in people with first-episode psychosis vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds a small to medium-sized effect of higher insulin levels and a trend effect of lower leptin levels in people with first-episode psychosis. These effects were both significant in subgroup analyses of antipsychotic-naïve patients. The severity of negative symptoms was associated with increased effect size estimates for insulin.**
Adiponectin, insulin, leptin, ghrelin, orexin, resistin, and visfatin	
A small to medium-sized effect of higher insulin levels in first-episode psychosis patients; 24 studies, N = 2,714, $g = 0.34$, 95%CI 0.19 to 0.49, $p < 0.001$, $I^2 = 70.5\%$ This effect was similar in the subgroup analysis of antipsychotic-naïve patients.	

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

The severity of negative symptoms was associated with increased effect size estimates. *There was a trend effect of lower levels of leptin in first-episode psychosis patients;* 10 studies, N = 845, *g* = -0.33, 95%CI -0.70 to 0.04, *p* = 0.079, I^2 = 84% The effect was significant in the subgroup analysis of antipsychotic-naïve patients (*g* = -0.62, *p* = 0.015). Meta-regression showed no moderating effects of age, sex, BMI, study quality score, and the type of biological material (serum or plasma). There were no significant differences in levels of any other appetite regulating hormone.

Consistency	Inconsistent
Precision	Precise
Directness	Direct

Misiak B, Stanczykiewicz B, Wisniewski M, Bartoli F, Carra G, Cavaleri D, Samochowiec J, Jarosz K, Rosinczuk J, Frydecka D

Thyroid hormones in persons with schizophrenia: A systematic review and meta-analysis. Progress in

Neuro-Psychopharmacology and Biological Psychiatry 2021; 111: 110402

View review abstract online

Comparison 1	**Thyroid hormones in multi-episode schizophrenia (medicated and unmedicated) vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds a small effect of increased thyroid-stimulating hormone in people with multi-episode schizophrenia.**

Thyroid hormones

A small effect of increased thyroid-stimulating hormone in people with multi-episode schizophrenia;

Thyroid-stimulating hormone: 13 studies, N = 1,386, *g* = 0.20, 95%CI 0.02 to 0.39, *p* = 0.031, I^2 = 50.0%

There were no significant differences in thyroxine (free or total) or triiodothyronine (total).

No analysis was conducted on free triiodothyronine for multi-episode schizophrenia.

There were no moderating effects of age or sex.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Comparison 2	**Thyroid hormones in first-episode psychosis (all medication naïve) vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, some inconsistency, precise, direct) finds a small decrease in thyroid-stimulating hormone and a medium-sized decrease in total triiodothyronine in people with first-episode psychosis. There was also a medium-sized increase in free thyroxine.**
Thyroid hormones	
A small effect of decreased thyroid-stimulating hormone and a medium-sized effect of decreased total triiodothyronine in people with first-episode psychosis; Thyroid-stimulating hormone: 5 studies, N = 961, g = -0.26, 95%CI -0.47 to -0.06, p = 0.013, I^2 = 21.3% Total triiodothyronine: 2 studies, N = 720, g = -0.60, 95%CI -0.82 to -0.37, $p < 0.001$, I^2 = 0% *A medium-sized effect of increased free thyroxine in people with first-episode psychosis;* Free thyroxine: 3 studies, N = 789, g = 0.58, 95%CI 0.15 to 1.01, p = 0.008, I^2 = 64.6% No analysis was conducted on total thyroxine or free triiodothyronine for first-episode psychosis.	
Consistency	Consistent for thyroid-stimulating hormone and total triiodothyronine in first-episode psychosis. Inconsistent for thyroid-stimulating hormone in multi-episode schizophrenia and free thyroxine in first-episode psychosis.
Precision	Precise
Directness	Direct

Ragguett RM, Hahn M, Messina G, Chieffi S, Monda M, De Luca V

Association between antipsychotic treatment and leptin levels across multiple psychiatric populations: An updated meta-analysis

Human Psychopharmacology 2017; 32: e2631

View review abstract online

Comparison	**Pre-post treatment leptin levels in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds a medium to large increase in leptin levels post treatment with antipsychotics, particularly olanzapine and**

	clozapine.
Leptin	
A significant, medium to large increase in leptin levels in people with schizophrenia; 35 studies, N = 1,012, *g* = 0.720, 95%CI 0.442 to 0.998, *p* ≤ 0.001 Subgroup analyses of all patients (bipolar disorder and schizophrenia) showed olanzapine and clozapine produced more prominent increases in leptin levels than quetiapine and aripiprazole. Studies using enzyme-linked immunosorbent assay (ELISA) measures of leptin showed more prominent increases than studies using radioimmunoassay.	
Consistency in results	Authors report results are inconsistent
Precision in results	Precise
Directness of results	Direct

Rutigliano G, Rocchetti M, Paloyelis Y, Gilleen J, Sardella A, Cappucciati M, Palombini E, Dell'Osso L, Caverzasi E, Politi P, McGuire P, Fusar-Poli P

Peripheral oxytocin and vasopressin: Biomarkers of psychiatric disorders? A comprehensive systematic review and preliminary meta-analysis

Psychiatry Research 2016; 241: 207-20

View online review abstract

Comparison	**Oxytocin and vasopressin levels in people with a psychotic disorder vs. controls.**
Summary of evidence	**Moderate quality evidence (medium to large samples, inconsistent, mostly precise, direct) finds decreased vasopressin in plasma of patients with schizophrenia. There were no significant differences in vasopressin in CSF, or in oxytocin in plasma or CSF.**
Oxytocin	
No significant differences between groups; Plasma: 8 studies, N = 691, *g* = -0.005, 95%CI -0.304 to 0.294, *p* = 0.974, I^2 = 72%, *p* = 0.001 CSF: 3 studies, N = 147, *g* = 0.287, 95%CI -0.330 to 0.903, *p* = 0.362, I^2 = 69%, *p* = 0.039	

Hormonal changes

Vasopressin	
A significant, medium-sized reduction in vasopressin in plasma of patients; Plasma: 11 studies, N = 630, *g* = -0.554, 95%CI -0.966 to -0.142, *p* = 0.008, I^2 = 82%, *p* < 0.001 Subgroup analysis revealed a significant effect only in the studies that employed peptide extraction. There were no differences in the effect between first-episode and chronic patients. *No significant differences in vasopressin in CSF;* CSF: 2 studies, N = 105, *g* = 0.033, 95%CI -0.424 to 0.491, *p* = 0.886, I^2 not reported	
Consistency in results	Inconsistent where reported
Precision in results	Mostly precise
Directness of results	Direct

Stubbs B, Wang AK, Vancampfort D, Miller BJ

Are leptin levels increased among people with schizophrenia versus controls? A systematic review and comparative meta-analysis

Psychoneuroendocrinology 2016; 63: 144-54

View review abstract online

Comparison	**Leptin levels in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent, precise, direct) finds a small increase in leptin levels in people with schizophrenia compared to controls.**
Leptin	
A small trend effect of increased leptin levels in people with schizophrenia; 27 studies, N = 3,707, *g* = 0.164, 95%CI -0.014 to 0.341, *p* = 0.07, I^2 = 83%, *p* < 0.01 *The effect was significant with one outlier removed;* 26 studies, N = 3,687, *g* = 0.196, 95%CI 0.210 to 0.370, *p* = 0.02 Subgroup analysis found increased leptin levels in people with multi-episode schizophrenia (*g* = 0.245, *p* = 0.01), in females (*g* = 0.557, *p* = 0.006) and in people taking second generation antipsychotics (*g* = 0.40, *p* = 0.001) compared to controls. Meta-regression showed a lower percentage of males but not BMI moderated the results.	
Consistency in results	Inconsistent

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Hormonal changes

Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, CSF = cerebrospinal fluid, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), SMD = standardised mean difference, vs. = versus

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Hormonal changes

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small.

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a medium effect, and 0.8 and over represents a large effect [14].

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives which are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives which are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[15]. ORs and RRs are similar when the outcome is rare. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

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Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the dependent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of treatment effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity and 75% to 100%: considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula;

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, this criteria should be relaxed [16].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C, which allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available so is inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Ragguett RM, Hahn M, Messina G, Chieffi S, Monda M, De Luca V (2017): Association between antipsychotic treatment and leptin levels across multiple psychiatric populations: An updated meta-analysis. *Human Psychopharmacology* 32: e2631.
4. Gonzalez-Blanco L, Greenhalgh AM, Garcia-Rizo C, Fernandez-Egea E, Miller BJ, Kirkpatrick B (2016): Prolactin concentrations in antipsychotic-naive patients with schizophrenia and related disorders: A meta-analysis. *Schizophrenia Research* 174: 156-60.
5. Bartoli F, Lax A, Crocamo C, Clerici M, Carra G (2015): Plasma adiponectin levels in schizophrenia and role of second-generation antipsychotics: a meta-analysis. *Psychoneuroendocrinology* 56: 179-89.
6. Misiak B, Frydecka D, Loska O, Moustafa AA, Samochowiec J, Kasznia J*, et al.* (2018): Testosterone, DHEA and DHEA-S in patients with schizophrenia: A systematic review and meta-analysis. *Psychoneuroendocrinology* 89: 92-102.
7. Stubbs B, Wang AK, Vancampfort D, Miller BJ (2016): Are leptin levels increased among people with schizophrenia versus controls? A systematic review and comparative meta-analysis. *Psychoneuroendocrinology* 63: 144-54.
8. Misiak B, Bartoli F, Stramecki F, Samochowiec J, Lis M, Kasznia J*, et al.* (2019): Appetite regulating hormones in first-episode psychosis: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews* 102: 362-70.
9. Fraguas D, Diaz-Caneja CM, Rodriguez-Quiroga A, Arango C (2017): Oxidative Stress and Inflammation in Early Onset First Episode Psychosis: A Systematic Review and Meta-Analysis. *International Journal of Neuropsychopharmacology* 20: 435-44.
10. Bastos MAV, Jr., Oliveira Bastos PRHd, Portella RB, Soares LFG, Conde RB, Rodrigues PMF, Jr.*, et al.* (2019): Pineal gland and schizophrenia: A systematic review and meta-analysis. *Psychoneuroendocrinology* 104: 100-14.
11. Hernandez-Diaz Y, Gonzalez-Castro TB, Tovilla-Zarate CA, Lopez-Narvaez ML, Genis-Mendoza AD, Castillo-Avila RG*, et al.* (2021): Oxytocin levels in individuals with schizophrenia are high in cerebrospinal fluid but low in serum: A systematic review and meta-analysis: Oxytocin and Schizophrenia. *Metabolic Brain Disease* 36(8): 2415-24.
12. Rutigliano G, Rocchetti M, Paloyelis Y, Gilleen J, Sardella A, Cappucciati M*, et al.* (2016): Peripheral oxytocin and vasopressin: Biomarkers of psychiatric disorders? A comprehensive systematic review and preliminary meta-analysis. *Psychiatry Research* 241: 207-20.
13. Misiak B, Stanczykiewicz B, Wisniewski M, Bartoli F, Carra G, Cavaleri D*, et al.* (2021): Thyroid hormones in persons with schizophrenia: A systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 111: 110402.
14. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
15. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
16. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*