TECHNICAL COMMENTARY

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Neurological soft signs

Introduction

Neurological soft signs (NSS) are neurological abnormalities that can be identified by clinical examination using valid and reliable testing measures. They are referred to as 'soft' because they are not related to a localized pathological lesion and are not thought to be part of a well-defined neurological syndrome[1]. Categories of NSS are varied but they are commonly grouped into three categories: integrative sensory functioning, motor coordination, and complex motor sequencing. Integrative sensory functioning can include deficits in bilateral extinction (difficulty perceiving stimuli when presented to both hemispheres simultaneously), impaired audio-visual integration, agraphaesthesia (inability to recognize by touch, letters and numbers drawn on the skin) and astereognosis (inability to identify an object by touch without visual input). Motor coordination involves general coordination, intention tremor, finger thumb opposition, balance, and gait. Motor sequencing measures complex motor tasks, such as repetitive alternating hand positions, i.e., fist-edge-palm test where subjects place their hand in three different positions sequentially: a fist resting horizontally, a palm resting vertically, and a palm resting horizontally. Abnormalities in eye movements and developmental reflexes may also be apparent[2].

Instruments for measuring NSS include the Woods scale, the Condensed Neurological Examination (CNE), Heidelberg scale, Cambridge Neurological Inventory, Modified Quantified Neurological Scale (MQNS), and the Neurological Evaluation Scale (NES)[3].

Method

We have included only systematic reviews with detailed literature search, methodology, and inclusion/exclusion criteria that were published in full text, in English, from the year 2000. Reviews were identified by searching the databases MEDLINE, EMBASE, and PsycINFO. Reviews with pooled data are prioritized for inclusion. Reviews reporting fewer than 50% of items on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA[4]) checklist have been excluded from the library. The evidence was graded guided by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach[5]. 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 eight systematic reviews that met our inclusion criteria[1, 2, 6-11].

- Moderate to high quality evidence suggests a large effect of increased NSS in people with schizophrenia compared to controls. Specific domains affected include motor coordination and sequencing, sensory integration, and disinhibition.
- Moderate quality evidence suggests medium-sized associations between increased NSS scores and increased symptom severity. Both people with remitting or chronic psychiatric symptoms show improvements in NSS over time, although people with remitting symptoms show the greatest improvement.
- Moderate to high quality evidence suggests medium-sized relationships between increased NSS scores and decreased cognitive performance (but not language function).
- Moderate to high quality evidence suggests medium to large effects of increased total NSS scores, motor coordination, motor sequencing, disinhibition, and sensory integration in people with schizophrenia compared to first-degree relatives.
- Moderate to high quality evidence shows medium to large effects of increased total NSS scores, motor coordination and sensory

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integration, but not motor sequencing, in relatives of people with schizophrenia compared to controls.

- Moderate quality evidence suggests NSS are present in people with first-episode psychosis at a higher rate than controls.
- Moderate quality evidence suggests people with schizophrenia showed reduced activation of basal ganglia and inferior frontal cortex, and increased activation of superior temporal gyrus, which were associated with increased severity of NSS. They also showed reduced grey matter volume of the precentral and inferior frontal gyri and thalamus, and white matter volume of the middle temporal and cerebellum regions.
- Compared to people with bipolar disorder, moderate to high quality evidence suggests a small to medium-sized effect of more NSS in people with schizophrenia. Subgroup analyses showed only motor coordination tasks were significantly different, with no differences in sensory integration or motor sequencing. There were also no significant differences in NSS between people with bipolar disorder with psychotic symptoms and people with schizophrenia. There were no moderating effects of age, sex, duration of illness or age of onset.

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Neurological soft signs

Bachmann S, Degen C, Geider FJ, Schröder J

Neurological soft signs in the clinical course of schizophrenia: results of a meta-analysis

Frontiers in Psychiatry 2014; 5: Article 185

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Comparison	**Changes in NSS scores over time in people with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests a medium-sized overall effect of improved NSS over time. People with remitting psychiatric symptoms show a greater improvement in NSS than people with chronic symptoms.**
NSS scores	
17 longitudinal studies, N = 787 *A medium-sized, overall effect of reduced NSS scores over time. Patients with remitting psychiatric symptoms show a steeper decrease in NSS scores than people with a chronic illness course;* Overall mean effect size: *d* = 0.53, CIs and p-values are not reported Remitting psychiatric symptoms: *d* = 0.81, CIs and p-values are not reported Chronic psychiatric symptoms: *d* = 0.15, CIs and p-values are not reported Greater reduction in effect sizes was associated with increased length of follow-up (*r* -0.64, *p* = 0.001), but not with increased age (*r* = 0.28, *p* > 0.05).	
Consistency in results	Unable to assess; no measure of consistency is reported.
Precision in results	Unable to assess; no CIs are reported.
Directness of results	Direct

Bora E, Akgul O, Ceylan D, Ozerdem A

Neurological soft signs in bipolar disorder in comparison to healthy controls and schizophrenia: A meta-analysis

European Neuropsychopharmacology 2018; 28: 1185-93

Neurological soft signs

View online review abstract	
Comparison	**NSS in people with bipolar disorder vs. people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large sample inconsistent, precise, direct) suggests a small to medium-sized effect of more NSS in people with schizophrenia than in people with bipolar disorder. Subgroup analyses showed only motor coordination tasks were significantly different. There were also no significant differences between people with bipolar disorder with psychotic symptoms and people with schizophrenia. There were no moderating effects of age, sex, duration of illness or age of onset.**
NSS	
A significant, small to medium-sized effect of increased total NSS scores in people with schizophrenia; 10 studies, N = 862, d = 0.42, 95%CI 0.18 to 0.65, $p < 0.001$, I^2 = 59% The results were similar in subgroup analyses of studies using the Neurological Evaluation Scale, but only studies of motor coordination tasks showed a significant result (higher NSS in schizophrenia; d = 0.40). Subgroup analysis of studies comparing people with bipolar disorder and psychotic symptoms with people with schizophrenia showed no significant differences (d = 0.14). There were no moderating effects of age, sex, duration of illness or age of onset.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Chan RCK, Xu T, Heinrichs RW, Yu Y, Wang Y

Neurological Soft Signs in Schizophrenia: A Meta-analysis

Schizophrenia Bulletin 2009; 36(6): 1089-1104

View review abstract online

Comparison	**NSS scores in people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, inconsistent,**

	precise, direct) suggests large effect sizes of increased NSS scores in people with schizophrenia compared to healthy controls. Specific domains affected include motor coordination and sequencing, sensory integration, and disinhibition. There are also medium-sized relationships between increased NSS scores and increased symptomatology. Moderate to high quality evidence (consistent) suggests medium-sized relationships between increased NSS scores and decreased cognitive performance.
NSS scores	
Significant, large effects of higher NSS scores in people with schizophrenia compared to controls; Total NSS score: 33 studies, N = 4,329, *d* = 1.591, 95%CI 1.377 to 1.805, *p* < 0.05, Q = 277.093, *p* < 0.05 Motor coordination: 24 studies, N = 3,436, *d* = 0.977, 95%CI 0.793 to 1.161, *p* < 0.05, Q = 126.686, *p* < 0.05 Complex motor sequencing: 15 studies, N = 1,722, *d* = 0.795, 95%CI 0.546 to 1.044, *p* < 0.05, Q = 71.407, *p* < 0.05 Sensory integration: 23 studies, N = 3,295, *d* = 0.823, 95%CI 0.652 to 0.994, *p* < 0.05, Q = 104.487, *p* < 0.05 Disinhibition: 8 studies, N = 1,620, *d* = 0.970, 95%CI 0.617 to 1.322, *p* < 0.05, Q = 69.388, *p* < 0.05	
Cognitive variables	
Significant, medium-sized correlations between increased total NSS score and poorer cognitive abilities (but not language function) in people with schizophrenia; All cognitive abilities: 48 studies, N = 3,789, *r* = -0.331, 95%CI -0.362 to -0.299, *p* < 0.05, Q = 54.972, *p* > 0.05 Verbal memory: 4 studies, N = 383, *r* = -0.305, 95%CI -0.394 to -0.210, *p* < 0.05, Q = 0.955, *p* > 0.05 Nonverbal memory: 6 studies, N = 608, *r* = -0.374, 95%CI -0.485 to -0.252, *p* < 0.05, Q = 13.851, *p* < 0.05 Motor function: 4 studies, N = 360, *r* = -0.299, 95%CI -0.392 to -0.291, *p* < 0.05, Q = 0.363, *p* > 0.05 Attention: 8 studies, N = 579, *r* = -0.292, 95%CI -0.382 to -0.197, *p* < 0.05, Q = 9.892, *p* > 0.05 IQ: 6 studies, N = 580, *r* = -0.336, 95%CI -0.443 to -0.218, *p* < 0.05, Q = 10.952, *p* > 0.05 Spatial ability: 5 studies, N = 233, *r* = -0.268, 95%CI -0.386 to -0.141, *p* < 0.05, Q = 1.958, *p* > 0.05 Executive function: 10 studies, N = 641, *r* = -0.361, 95%CI -0.428 to -0.290, *p* < 0.05, Q = 8.974, *p* > 0.05 Language function: 4 studies, N = 344, *r* = -0.354, 95%CI -0.257 to 0.445, *p* > 0.05, Q = 2.597, *p* =	

NS	
Clinical variables	
Significant, medium-sized correlations between increased total NSS score and increased symptom severity in people with schizophrenia; Total symptom score: 11 studies, N = 696, r = 0.327, 95%CI 0.213 to 0.432, $p < 0.05$, Q = 23.341, $p < 0.05$ Negative symptoms: 15 studies, N = 758, r = 0.346, 95%CI 0.260 to 0.426, $p < 0.05$, Q = 20.728, $p > 0.05$ Positive symptoms: 10 studies, N = 529, r = 0.192, 95%CI 0.067 to 0.312, $p < 0.05$, Q = 16.578, $p > 0.05$	
Consistency in results	Inconsistent for all NSS scores, nonverbal memory, and total symptom scores
Precision in results	Precise apart from language function
Directness of results	Direct

Chan CK, Xu T, Heinrichs RW, Yu Y, Gong QY

Neurological soft signs in non-psychotic first-degree relatives of patients with schizophrenia: A systematic review and meta-analysis

Neuroscience and Biobehavioral Reviews 2010; 34: 889-896

View review abstract online

Comparison 1	**NSS scores in people with schizophrenia vs. first-degree relatives of people with schizophrenia.**
Summary of evidence	**Moderate to high quality evidence (large samples, some inconsistencies, precise, direct) shows increased NSS scores in people with schizophrenia compared to first-degree relatives. Specific domains affected include motor coordination and sequencing, and disinhibition (large effects), and sensory integration (medium-sized effect).**
NSS scores	
Significant, medium to large effects of increased NSS scores in people with schizophrenia;	

Neurological soft signs

Overall score: 11 studies, N = 1,089, *d* = 0.813, 95%CI 0.587 to 1.039, *p* < 0.05, Q = 32.353, *p* < 0.05 Motor Coordination: 5 studies, N = 616, *d* = 0.917, 95%CI 0.745 to 1.088, *p* < 0.05, Q = 2.443, *p* > 0.05 Complex Motor Sequencing: 2 studies, N = 296, *d* = 0.607, 95%CI 0.193 to 1.022, *p* < 0.05, Q = 2.922, *p* > 0.05 Sensory Integration: 5 studies, N = 616, *d* = 0.492, 95%CI 0.189 to 0.796, *p* < 0.05, Q = 11.724, *p* < 0.01	
Consistency in results	Consistent apart from total score and sensory integration
Precision in results	Precise
Directness of results	Direct
Comparison 2	**NSS scores in first-degree relatives of people with schizophrenia vs. controls.**
Summary of evidence	**Moderate to high quality evidence (large samples, some inconsistencies, precise, direct) shows medium to large effects of increased NSS scores, motor coordination and sensory integration, but not motor sequencing, in relatives of people with schizophrenia compared to controls.**
NSS scores	
Significant, medium to large effects of increased total NSS scores, motor sequencing and sensory integration in relatives of people with schizophrenia compared to controls; Total NSS score: 11 studies, N = 1,443, *d* = 0.974, 95%CI 0.553 to 1.394, *p* < 0.05, Q = 119.04, *p* < 0.001 Motor coordination: 7 studies, N = 796, *d* = 0.364, 95%CI 0.070 to 0.657, *p* < 0.05, Q = 21.051, *p* < 0.01 Sensory integration: 7 studies, N = 796, *d* = 0.369, 95%CI 0.207 to 0.530, *p* < 0.05, Q = 6.742, *p* > 0.05 *No significant difference for complex motor sequencing:* 3 studies, N = 301, *d* = 0.143, 95%CI -0.214 to 0.499, *p* > 0.05, Q = 4.586, *p* > 0.05	
Consistency in results	Consistent apart from total score and motor coordination
Precision in results	Precise
Directness of results	Direct

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Dazzan P, Murray RM

Neurological soft signs in first-episode psychosis: a systematic review

British Journal of Psychiatry 2002; 43: s50-57

View review abstract online

Comparison 1	**NSS prevalence in people with first-episode psychosis.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency or precision, direct) suggests NSS are present in people with a first episode of psychosis.** **Low quality evidence (one small study) is unclear about the temporal stability of NSS in first-episode psychosis.**
NSS prevalence	
Nine studies (N = 806) considered NSS prevalence in people experiencing first episode psychosis, 5 of the 9 studies used a healthy control group, 2 of the 9 used people deemed at high genetic risk of developing psychosis as a control group and the remaining 2 did not use a control group; NSS prevalence rates in patients ranged from 20% to 97.1% across studies and was consistently higher than control groups. Comparable NSS rates were observed in high-risk individuals, though in general, patients showed the highest prevalence rates, and controls the lowest rates. One study reported on the temporal stability of NSS prevalence with a 5 year follow up, N = 28. At the first episode of psychosis, NSS prevalence was significantly higher than controls. At follow up, the difference between patients and controls increased particularly for frontal, corticospinal and temporo-parietal functions.	
Consistency in results	No measure of consistency reported, appears consistent
Precision in results	No measure of precision reported
Directness of results	Direct
Comparison 2	**NSS prevalence in people with first-episode psychosis and a family history of schizophrenia vs. people with first-episode psychosis and no family history of schizophrenia.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, unable to assess consistency or precision, direct) is unable to determine the differences in NSS between these groups.**

NSS prevalence	
Three studies, N = 347, reported no difference in NSS prevalence between patients with a family history of schizophrenia and those without a family history of schizophrenia. One study, N = 76, reported an association between family history and a specific laterality pattern in psychomotor performance. One study, N = 54, reported an association between family history and NSS progression, such that patients with a positive family history showed significantly greater neurological deterioration at the 5-year follow up.	
Consistency in results	No measure of consistency reported, appears inconsistent
Precision in results	No measure of precision reported
Directness of results	Direct
Comparison 3	**Association of antipsychotic treatment and NSS prevalence in people with first-episode psychosis.**
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess consistency or precision, direct) is unclear as to the association between antipsychotic treatment and NSS prevalence.**
NSS prevalence	
Two studies, N = 132, found no difference in NSS prevalence between medicated and unmedicated patients. One study, N = 54, reported significantly higher rates of NSS in neuroleptic-naive patients compared to controls. This study also reported an increase in NSS in patients at a 5-year follow up that was more marked in untreated patients than patients on neuroleptic medication and was particularly noted for corticospinal NSS.	
Consistency in results	No measure of consistency reported, appears inconsistent
Precision in results	No measure of precision reported
Directness of results	Direct comparison of NSS prevalence in first episode psychosis in the context of antipsychotic administration
Comparison 4	**Association of demographic characteristics with NSS prevalence in people with first-episode psychosis.**
Summary of evidence	**Moderate to low quality evidence (small samples, unable to assess consistency or precision, mostly direct) is unclear as to any associations between NSS prevalence and demographic**

	characteristics
NSS prevalence	
One study, N = 32, reported no association between NSS prevalence and age of patients. Two studies, N = 103, reported some association between NSS prevalence and males, showing a significant increase in NSS prevalence at 5-year follow up. Two studies, N = 125, reported some association between NSS prevalence and lower education. One study, N = 137, reported some association between NSS prevalence and lower socio-occupational outcome. Note that these associations are not reported as being significant (reporting unclear).	
Consistency in results	No measure of consistency reported
Precision in results	No measure of precision reported
Directness of results	Direct for all outcomes apart from education
Comparison 5	**Association of NSS prevalence with brain structural abnormalities in people with first-episode psychosis.**
Summary of evidence	**Moderate to low quality evidence (small sample, unable to assess consistency or precision, direct) is unclear as to any association between NSS prevalence and structural abnormalities in the brain.**
NSS prevalence	
One study, N = 69, used CT to investigate structural changes and reported an association between NSS prevalence and shorter brain length, smaller brain volume, smaller temporal horn volume, and wider Sylvian fissure.	
Consistency in results	No measure of consistency reported
Precision in results	No measure of precision reported
Directness of results	Direct
Comparison 6	**Association of NSS prevalence and psychopathology in people with first-episode psychosis.**
Summary of evidence	**Moderate to low quality evidence (small studies, inconsistent, unable to assess precision, direct) is unclear as to any association between NSS prevalence and psychopathology.**

NSS prevalence	
One study, N = 56, reported an association between NSS prevalence and total symptoms and positive symptoms. Two studies, N = 98 reported no association between NSS and psychopathology. Authors state inconsistent results could be due to different scales used to measure NSS.	
Consistency in results	No measure of consistency reported, appears inconsistent
Precision in results	No measure of precision reported
Directness of results	Direct

Neelam K, Garg D, Marshall M

A systematic review and meta-analysis of neurological soft signs in relatives of people with schizophrenia

BMC Psychiatry 2011; 11: 139

View review abstract online

Comparison	**NSS in people with schizophrenia vs. healthy controls and vs. first-degree relatives.**
Summary of evidence	**Moderate quality evidence (large samples, imprecise, inconsistent, direct) suggests large effect sizes for increased levels of NSS in people with schizophrenia compared to healthy controls, and in first-degree relatives compared to healthy controls.** **Moderate to high quality evidence (large samples, precise, inconsistent, direct) suggests a large effect size for increased levels of NSS in people with schizophrenia compared to first-degree relatives.**
NSS severity scores	
A significant, large effect size shows increased levels of NSS in people with schizophrenia compared to healthy controls; 7 studies, N = 995, d = 1.24, 95%CI 0.59 to 1.89, I^2 = 94.9, p < 0.001 *A significant, large effect size shows increased levels of NSS in first-degree relatives of people with*	

schizophrenia compared to healthy controls; 7 studies, N = 1082, *d* = 1.83, 95%CI 1.28 to 2.38, I^2 = 93.1, *p* < 0.001 *A significant, large effect size shows increased levels of NSS in people with schizophrenia compared to their first-degree relatives;* 7 studies, N = 1040, *d* = 0.92, 95%CI 0.64 to 1.12, I^2 = 74.6, *p* < 0.001	
Consistency in results	Inconsistent
Precision in results	Imprecise for control comparisons, precise for comparison between schizophrenia and first-degree relatives
Directness	Direct

Ruiz-Veguilla M, Callado L, Ferrin M

Neurological soft signs in patients with psychosis and cannabis abuse: a systematic review and meta-analysis of paradox

Current Pharmaceutical Design 2012; 18: 5156-5164

View review abstract online

Comparison	**NSS in people with schizophrenia who abuse cannabis compared to people with schizophrenia who do not use cannabis.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized sample, inconsistent, unable to assess precision, direct) is unable to determine differences in levels of NSS in people with schizophrenia who abuse cannabis compared to people with schizophrenia who do not use cannabis.**
NSS severity scores	
A significant effect of increased levels of NSS in people with schizophrenia who do not use cannabis compared to those who do use cannabis. 4 studies, N = 284, X^2 = 42,066, *p* < 0.001, I^2 = 55%, *p* < 0.001 Authors report that primary study quality is limited	
Consistency in results	Inconsistent

Precision in results	Unable to assess
Directness	Direct

Zhao Q, Li Z, Huang J, Yan C, Dazzan P, Pantelis C, Cheung EFC, Lui SSY, Chan RCK

Neurological soft signs are not "soft" in brain structure and functional networks: evidence from ALE meta-analysis

Schizophrenia Bulletin 2013; doi:10.1093/schbul/sbt063

View review abstract online

Comparison	**Localised brain regions associated with neurological soft signs in patients with schizophrenia.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess precision or consistency, direct) suggests that people with schizophrenia showed reduced activation of basal ganglia and inferior frontal cortex, and increased activation of superior temporal gyrus, that were associated with increased severity of neurological soft signs. They also showed reduced grey matter volume of the precentral and inferior frontal gyri and thalamus, and white matter volume of middle temporal and cerebellum.**

NSS

15 functional MRI studies assessed correlates of neurological soft sign severity while performing motor inhibition tasks (go/no-go) in people with schizophrenia compared to controls.

Controls alone (9 studies)

NSS severity correlated with activation in:

Right inferior frontal gyrus (40 28 0)

Right middle temporal gyrus (44 -58 22)

Left fusiform gyrus (-38-64 8)

Right lingual gyrus (8 -94 2)

Left parahippocampal gyrus (-26 -8 -12)

Left middle frontal gyrus (-40 12 44)

Neurological soft signs

Patients alone (9 studies)

NSS severity correlated with activation in:

Left insula (-32 22 -2)

Right superior temporal gyrus (50 -54 18)

Left middle temporal gyrus (-40 -60 26)

Right lentiform nucleus (18 0 4)

Right insula (36 16 6)

Right precuneus (24 -70 42)

Controls > patients (12 studies)

NSS severity correlated with activation in:

Left lentiform nucleus (putamen) (-24 10 -4)

Right lentiform nucleus (putamen) (20 4 -4)

Left lentiform nucleus (globus pallidus) (-22 -6 12)

Right inferior frontal gyrus (40 22 4)

Left brainstem (-2 -30 -10)

Patients > controls (7 studies)

NSS severity correlated with activation in:

Left superior temporal gyrus (-46 0 -10)

11 MRI studies assessed correlates of neurological soft sign severity with brain volume in people with schizophrenia compared to controls.

Controls > patients (6 studies)

NSS severity correlated with grey matter volume in:

Left precentral gyrus (-56 -6 40)

Thalamus (2 -12 14)

Left precentral gyrus (-46 -8 50)

Left inferior frontal gyrus (-54 20 20)

Right precentral gyrus (56 -4 40)

Left postcentral gyrus (-48 -26 52)

Left inferior parietal lobe (-50 -40 44)

NSS severity correlated with white matter volume in:

Right middle temporal gyrus (44 -68 22)

Cerebellar culmen (0 -56 -16)

Left inferior frontal gyrus (-36 34 -6)

Neurological soft signs

Consistency in results	No measure of heterogeneity is provided.
Precision in results	No confidence intervals are provided.
Directness of results	Direct measures and comparison of functional activity

Explanation of acronyms

CI = confidence interval, CT = Computed Tomography, *d* = Cohen's d, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, NSS = Neurological Soft Signs, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = test for heterogeneity, *r* = correlation coefficient, vs. = versus, X^2 = Chi-square

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Neurological soft signs

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results, 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[12].

† Different effect measures are reported by different reviews.

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.

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) that 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 moderate effect, and 0.8 and over represents a large treatment effect[12].

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that 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, an 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. An 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[13]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

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measure the effect of an explanatory variable on the hazard or risk of an event.

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 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, these criteria should be relaxed[14].

‖ 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 that 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 and is therefore 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.

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