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Prader Willi syndrome: systematic review of the prevalence and nature of presentation of unipolar depression

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Introduction

Prader-Willi Syndrome (PWS) is a neurodevelopmental disorder with an estimated birth incidence of 1 in 22 000 (Whittington et al, 2001). It is caused by a lack of paternal expression of imprinted genes at the critical region 15q11-q13. The main mechanisms are deletion at 15q11-q13 (delPWS) of paternal origin, which occurs in 70% of cases, or maternal uniparental disomy (mUPD) of chromosome 15, occurring in 25% of cases. Less than 5% of cases have other causes such as unbalanced chromosomal translocations or defects in imprinting (Roof et al., 2000).

Prader, Labhart and Willi first defined the phenotypic characteristics in 1956. These included short stature, obesity, intellectual disability (ID), and small hands and feet. Other characteristics now described include a narrow bitemporal diameter, almond-shaped palpebral fissures, down-turned mouth with thin upper lip, hypopigmentation, scoliosis and hypogonadism (Bittel & Butler, 2005). The behavioural phenotype is characterised by temper tantrums, skin picking, lability of mood, compulsive and ritualistic behaviour (Clarke et al., 2002). Cognitive deficits range from mild to severe ID, with corresponding language difficulties (Reddy & Pfeiffer, 2007).

Subjects with mUPD have been shown to have better verbal skills on intelligence testing than their delPWS counterparts (Roof et al., 2000). In contrast, those with delPWS have shown superior visuospatial skills (Whittington & Holland, 2004). Differentiation between the genetic subtypes is important. Not only does it help to build a more complete picture of the relationship between the behavioural phenotype and its genetic basis, but also informs on the genetic abnormalities that could be associated with psychiatric morbidity in both the PWS and the general population.

Studies have shown a higher level of psychopathology in individuals with PWS in comparison to those with other causes of ID (Soni et al, 2007). Clarke et al (2002) showed individuals with PWS have an increased propensity to suffering from symptoms of obsessive-compulsive disorder. Autistic traits have been illustrated (Veltman et al, 2004).

Depression is characterised by a broad range of symptoms, including loss of positive affect plus related cognitive, emotional, physical and behavioural difficulties. Differentiating between 'normal' mood changes and those that are clinically significant is a challenge in the general population (National Collaborating Centre for Mental Health, 2010). These difficulties are compounded in the PWS population, in particular those with severe ID who are, by definition, unable to communicate their thoughts and feelings. Changes in behaviour can often be attributed to the ID as opposed to recognition of mental illness (Matson et al, 1999).

The recognition of depressive symptoms in individuals with ID and a complex behavioural phenotype such as PWS will be be beneficial to the individual concerned, their families and the team whom support their care. The ability of clinicians to recognise the symptoms of depression in PWS remains a diagnostic challenge, and it therefore may be under diagnosed; to the detriment of the quality of life of the individual.

The aim of this systematic review is to assess for the frequency and the nature of presentation of unipolar depression in PWS. The use of systematic review to investigate depression in PWS allows for an assessment of the quality of current literature and can guide future research.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement (2009) checklist for systematic review was followed where possible. The PRISMA checklist was developed specifically to improve the assessment of original research and reporting quality in systematic reviews.

Eligibility Criteria

Participants

- Individuals with PWS; and
- No limitations for age or gender.

Intervention or test of interest

- Primary research investigating the prevalence and nature of presentation of symptoms of unipolar depression in PWS;
- Exclude challenging behaviour (see Appendix 1);
- Exclude bipolar affective disorder;
- Exclude studies pre-dating 1990; and
- Exclude studies not in the English language.

Comparison: the aim is to complete a systematic review analysis of the studies found.
Outcome: data for the prevalence of unipolar depression in PWS and the nature of its presentation.
Study design of interest: primary research excluding individual case studies.

Information Sources

A computerised search using Cardiff University's Electronic Portal of the following databases was undertaken; Medline, Embase, PsychInfo, Web of Science, and CINAHL. This was for English language, peer reviewed journals published between 1st January 1990 and 30th September 2013.

Search Strategy

At this stage, search terms were kept broad, for as many studies to be found as possible. "Prader Willi Syndrome" combined with: "psychopathology", "depression", "mood disorder" or "affective disorder".

Study Selection

The authors assessed articles from the database search. A hand-search of relevant journals and review articles was also undertaken at this stage.

Summary Measures and Synthesis of Results

In order to aid objective comparison of the selected studies an adapted version of the system developed by Hermans & Evenhuis (2010) was utilised. Hermans & Evenhuis (2010) used this system to evaluate screening tools for the identification of depression in the general ID population. (See Appendix 2).

Results

Figure 1: Results of search strategy as per PRISMA Guidance
Source: Adapted from Moher et al (2009)

261 records were identified by database searches. The abstracts of the 261 studies were read and 14 studies were selected for full review. The two authors independently appraised this part of the literature search. Seven studies were selected with original research regarding PWS and depression; these studies fully met the inclusion and exclusion criteria for this systematic review.

Study characteristics

A total of 7 studies were assessed. Two were cohort studies (Soni et al., 2007 and Hiraiwa, et al. (2007)) and the remaining 5 were cross-sectional studies.

Table 1 shows an assessment of the quality of each study using the criteria developed by Hermans and Evenhuis (2010). Scores ranged from between 3 and 6, out of a possible total of 6, showing a wide range in the quality of the studies included.

Table 1: Assessment of the quality of the study designs plus descriptive data for individual studies

Soni et al (2008) utilised a cross-sectional study design to screen 119 genetically confirmed PWS participants for psychopathology. The remit was to investigate for psychotic and/or affective disorders in subjects using the Psychiatric Assessment Scale for Adults with Developmental Disability (PAS-ADD) (Moss et al, 1998) and the Operational Criteria Checklist for psychotic and affective illness (OPCRIT) (McGuffin et al, 1991).

Forty-six participants had confirmed psychiatric symptoms (24 delPWS and 22 mUPD). There were no significant differences between the two groups for age, IQ or gender. Overall, those with mUPD were significantly more likely to have a history of any psychiatric symptoms (22/34 mUPD in comparison to 24/85 delPWS, $p<0.001$). In terms of depression, 10/24 with delPWS were found to suffer from non-psychotic depressive illness, and 9/24 had depressive psychosis. In the group with mUPD 1/22 was found to have non-psychotic depressive illness and 6/22 had depressive psychosis. There was a significant difference ($p<0.005$) between the two groups for non-psychotic depressive illness. In total 26/119, or 22%, had a form of depressive illness.

There was no significant difference in symptoms of depression between the two groups, whether psychosis was reported or not. The most commonly reported symptoms were irritability, low mood, loss of concentration, anhedonia and increased appetite. Low scoring items included guilt and suicidal acts/thoughts.

Utilising the same subjects as the preceding study, **Soni et al (2007)** utilised a cohort design in order to investigate the clinical course of psychiatric illness in PWS. All 119 subjects were re-contacted by telephone between 12 weeks and 2.5 years after the original study had ended. If psychiatric problems had occurred since the initial screening then the PAS-ADD and OPCRIT were used to assess for phenomenology and course of the illness. On the basis of information taken from the interview an ICD-10 (World Health Organisation, 1992) diagnosis was assigned.

Three of the 46 individuals with psychopathology identified in the original study were lost to follow-up. Of the remainder, 5/22 (22.7%) delPWS and 8/21 (38.1%) mUPD experienced at least one further episode. Those with delPWS had a single further episode and those with mUPD had episodes ranging from one further to six. However, no specific differences in phenomena were found pre- and post initial screening (Soni et al, 2007).

Two individuals with delPWS developed new symptoms and were given a diagnosis of non-psychotic depressive illness. One person with mUPD received a diagnosis of depressive psychosis. This gave an overall incidence of psychiatric illness (depressive

psychosis or non-psychotic depressive illness) of 2.3 per 100-person years in delPWS and 6.7 per 100-person years in those with mUPD.

Soni et al (2007) surmised that the diagnosis of affective disorder in individuals with PWS remained stable over time i.e. recurrent episodes of depression were reported, but the diagnosis did not change.

Sinnema et al (2011) undertook a cross-sectional study of individuals with PWS. The PAS-ADD and the Developmental Behaviour Checklist for Adults (DBC-A) (Einfeld et al, 2002 in Sinnema et al (2011) were used in order to assess for psychiatric symptoms.

Of the 97 assessed, 63 people were identified as having a history of psychiatric treatment or diagnosis, on psychotropic medication or scoring positively on the behavioural questionnaires. Each of these individuals had a case vignette written which were independently rated according to ICD-10 criteria (World Health Organisation, 1992).

Overall, 13 (13%) individuals had a diagnosis of depressive illness with psychotic symptoms, and 5 (5%) were diagnosed with depressive illness without psychotic symptoms. Of the delPWS, 9% were found to suffer from depression with psychotic symptoms, and 4% depression without psychotic symptoms. The mUPD group were found to have more individuals with a diagnosis of depression with psychotic symptoms, (18%), and 7% had depressive illness without psychotic symptoms. Statistical comparison was not undertaken due to the small sample size; this reflects the comparatively low score (4/6) the study design gained (see Table 1).

Hiraiwa et al (2007) utilised a questionnaire in order to undertake a retrospective cohort study. In total 165 individuals with PWS were recruited; these were split into 4 groups (2-5 years, 6-11 years, 12-17 years, 18-31 years). Control groups of children were graduates of intellectual disability (ID) schools.

In terms of psychiatric symptoms ‘depressive state’ was reported over the past 5 years in no children between 2 to 5 years. 1 child (1.8%) aged between 6-11 years was reported as suffering from ‘depressive state’, as was another child aged 12-17 years

(2.2%). A further 4 participants (10.3%) were reported in the 18-31 age group. Prevalence of 'depressive state' in the control group for ages 18-31 in comparison to PWS was not significantly different.

Overall 6/165 (4%) reported as suffering from 'depressive state' over the past 5 years. The prevalence of one or more psychiatric symptoms was significantly different between the two groups: PWS 37.9% versus general ID 11.9% ($p<0.05$). The most common psychiatric symptoms reported for the PWS group appeared to be inactivity and delusion.

Reddy & Pfeiffer (2007) utilised the Devereux Scale of Mental Disorders (DSMD, Naglieri et al., 1994, in Reddy & Pfeiffer, 2007) to compare levels of psychopathology in children and adolescents with PWS to matched controls (general ID population).

The DSMD was developed so that cross-comparison with diagnoses from the DSM-IV (American Psychiatric Association, 1994) was possible. The DSDM consists of three composite scales (Externalising, Internalising and Critically Pathology) and six subscales. 13 children with PWS with a mean age of 17.36 (11.25-20.25) were compared to 30 children with ID and a further 30 children with ID and a psychiatric diagnosis (dual diagnosis group).

Upon comparison of scores for the PWS group with the scores of the group with ID; the total DSDM score was clinically significant for the PWS group (61.54), and also statistically different to the total score for the group with ID only ($p<0.01$), *d*-ratio 0.82. The explanation for this difference comes from the significantly different scores for the PWS in externalizing, internalizing, conduct, attention/delinquency and anxiety subscales. For depression, the PWS group did not show a clinically significant collective score (57.77), nor was it statistically significant to the general ID group. However, there was a medium (clinically meaningful) difference on the *d*-ratio.

In comparison to the dual diagnosis group, there was no statistically significant or clinically meaningful difference in total DSDM scores (*d*-ratio 0.16). For the depression subscale of the DSDM the dual diagnosis group scored 63.8 (PWS 57.77), which was statistically significant ($p<0.05$), and the *d*-ratio showed a clinically

meaningful difference (0.69). This showed that the dual diagnosis group were rated with higher levels of depression. The depression subscale of the DSDM was the only subscale to differ between the two groups.

Skokauskas et al (2012) utilised the Child Behaviour Checklist 6-18 (CBCL/6-18) (Achenbach & Rescorla, 2001) to investigate psychopathology in children with PWS. Matched groups of children were included: 24 with PWS and 24 with ID. The mean age of the PWS group was 9.92 (SD 3.6) years and mean IQ 64.01 (SD 3.1).

CBCL/6-18 mean T-scores were elevated to the clinical range for the PWS group for the total scores. The mean T-score for the PWS group was in clinically significant range for both anxious/depressed (62.79, SD 8.01) and withdrawn/depressed (64.04, SD 9.11). The withdrawn/depressed mean score for PWS was significantly different to the control group (mean T 64.04 SD 9.11 vs. 55.46 SD 6.48, $p<0.05$). Scores for both the PWS and control group did not reach clinical significance on the CSBL DSM-orientated subscales although Skokauskas et al (2012) did state 'borderline' difficulties were reached on the affective CBCL DSM orientated subscales. Results were not statistically significant.

Beardsmore et al (1998) primarily investigated the prevalence of psychosis in adults with PWS. A full psychiatric assessment was undertaken for the study, using the Present Psychiatric State for Adults with Learning Disabilities (PPS-LD) (Cooper, 1997) hence prevalence of depression was also investigated. The study then went on to utilise standardised diagnostic criteria i.e. DCR-ICD 10 (WHO, 1992).

Of the 23 participants, three were found to have a diagnosis of depression and one to have a history of recurrent depressive disorder (in remission). All of these had symptoms of psychosis. Of the four, two were found to have a confirmed cause of delPWS, and the other two were reported as PWS pattern DNA: PWS methylation pattern. All fitted the criteria for major depressive episode according to DCR-ICD 10 Criteria (WHO, 1992).

The point prevalence of depressive disorder was 13%. This compared to 65% having a behaviour disorder, 21% having no disorder, and 4% having schizophrenia or delusional disorder. The unmatched control group had a point prevalence of affective

disorders of 4.1%. The difference between groups was found to be statistically significant ($p<0.05$) (Beardsmore et al, 1998).

Symptoms of depression were described for the three cases. The most commonly occurring were deterioration in self care, reduction in speech, disturbed sleep, worry/apprehension, low mood, social withdrawal and verbal aggression. Mood congruent delusions were apparent in two of the cases, with auditory hallucinations occurring in the other.

Synthesis of results

Prevalence and incidence of depression in PWS

Table 1 illustrates the heterogeneous nature of these studies. The quality scores range from 3-6 between the studies, the reduction in score generally being due to small sample size and, on two occasions, the use of an assessment method not orientated to a 'gold standard' measure (Haraiwa et al, 2007 and Reddy & Pfeiffer, 2007). A questionnaire (Haraiwa et al, 2007) or other scales (Reddy & Pfeiffer, 2007 and Skokauskas et al, 2012) will potentially identify a depressive symptom, or a symptom associated with a depressive disorder (but also other disorders) in comparison to a collection of symptoms meeting robust diagnostic criteria such as ICD-10 (World Health Organisation, 1992). This could reduce diagnostic accuracy ('caseness').

The frequency of depression is assumed to be point prevalence in most cases. Where a survey format has been used (either telephone or postal) it becomes more difficult to assess whether this is indeed true point prevalence, or whether it incorporates historical information and becomes period prevalence.

Despite these points, the results do show trends. The diagnosis of depression does appear to increase in frequency with increasing age. Reddy & Pfeiffer (2007) and Skokauskas et al (2012) found no clinically significant scores for depression in their groups of children and young people. Sinnema et al (2011) found that the age of onset of psychiatric symptoms was 21.9 years.

In comparison, the studies of adult age individuals with PWS showed results ranging from 17.4% (Beardsmore et al, 1998) to 22% (Soni et al, 2008). These results do show a trend in terms of increased prevalence of depression in the adult PWS population in comparison to children. In terms of the incidence of depression, Soni et al (2007) found 3 new cases of depression over the study period of 12 weeks to 2.5 years, giving an incidence in delPWS of 2.3 per 100 person years, and mUPD 6.7 per 100 person years. The reliability of these figures is questioned due to the varied length of time the cohort was investigated for, and the small numbers involved.

Of interest is the differing psychopathology when an individuals' genetic subtype is taken into consideration. Soni, et al (2008) found that the majority of those individuals with mUPD and depressive illness experienced psychotic symptoms (85%). In comparison those with delPWS pattern, where approximately half of the group had psychotic symptoms (47%). However, Sinnema et al's (2011) results showed that 72% with mUPD with depression had psychosis, and 71% subjects with delPWS had psychotic symptoms with the depressive episode. It is therefore difficult to draw firm conclusions from either study data due to the small numbers involved (Sinnema et al, 2011).

Presentation of depression

Psychotic symptoms did appear in approximately 50% or more of those with depression and PWS (Beardsmore et al, 1998, Soni et al, 2007, Soni et al, 2008 & Sinnema et al, 2011). The phenomenology of the depressive episodes was described by two of the studies (Soni et al, 2007 & Beardsmore et al, 1998). Soni et al (2007) showed that there were no significant differences between delPWS and mUPD symptoms (excluding psychosis). The most common symptoms for both groups were: low mood (79.2%, 68.2%), anhedonia (both 70%), irritability (83.3%, 90.9%), loss of concentration (66.7%, 77.2%) and social withdrawal (66.7%, 45.5%). Beardsmore et al (1998) described deterioration in self-care, reduction in speech, disturbed sleep, worry/apprehension, low mood, social withdrawal and verbal aggression in the 3 cases of depression included in the study.

Soni et al (2008) surmised that the broadly similar finding in phenomenology of the affective disorders suggested a similar aetiology for both mUPD and delPWS. However, the progression of the disorder over time, investigated by Soni et al (2007) showed a difference in the genetic subtypes. Those with a diagnosis of depression were more likely to have a recurrence of symptoms if mUPD. It was also suggested that symptoms might have been more severe for those with mUPD; evidenced by the increased likelihood of psychotropic medication and a wider range of medication being prescribed.

Discussion

The frequency of depression in adults with PWS has been shown to range between 17.4% (Beardsmore et al, 1998) to 22% (Soni et al, 2008). When one considers the classical description of the PWS 'infantile hypotonia, mental retardation and hyperphagia' (Hiraiwa, 2007) with high rates of autistic and obsessive compulsive tendencies (Reddy & Pfeiffer, 2007) depressive features do not necessarily spring to mind. The increased rate of associated psychosis (around 50% of those with depression) seen in these studies is also of interest. These results should to be taken in the context of the small study sizes.

Clinically, these results aid in the investigation and management of individuals with PWS. In particular, psychotic symptoms need to be considered. It is acknowledged that the high rates of psychosis in PWS will predominate the differential diagnoses. However, the diagnosis of a depressive episode as opposed to schizophrenia will have different treatments, and perhaps, long-term outcomes and therefore should be considered carefully. Unfortunately, apart from psychotic symptoms, the low number of studies describing symptoms of depression in PWS means that other features of a depressive episode may be less clear. Low mood and social withdrawal were mentioned in both studies describing psychopathology (Beardsmore et al, 1998 & Soni et al, 2007). Soni et al (2007) suggested that the natural history of depression differed between the two genetic subgroups i.e. mUPD having more episodes of depression, and requiring a wider range of treatments. Although this was a suggestion surmised from small numbers of participants, it can be borne in mind when dealing with individual patients in terms of treatment options, and long term monitoring.

The results of the studies also draw attention to the fact that depression is less likely to occur in children than in adult populations. This trend would require further investigation with larger scale studies, however, does aid a clinician's assessment of an individual with PWS with age taken into consideration.

Roof et al (2000) stressed the importance of investigating the genetic links between various phenotypic differences. For example, skin picking has been found more commonly in delPWS (Symons et al, 1999) and Roof et al (2000) found subjects with mUPD had significantly higher verbal IQ scores than those with deletion. Lukoshe et al (2013) utilised high resolution structural magnetic resonance images in children with PWS to illustrate different neurodevelopemental patterns and structural abnormalities between the two genetic subtypes. It could be hypothesised that the structural differences could infer differing vulnerabilities to functional psychiatric illness, and this could pave the way for further investigation of the varied pathophysiology between the two main genetic subtypes.

Future research incorporating greater numbers of participants would allow for in depth analysis of the differing presentations of depression and other psychopathologies for the different genetic subtypes. This would allow for both invaluable knowledge of PWS genetic subtypes and also, potentially, the genetic basis for major psychiatric diseases.

Conclusion

It is acknowledged that the comparisons and conclusions drawn between the studies for this review are weakened by small number of studies included. Two of the studies (Soni et al, 2007; 2008) use the same sample, which could be argued reduces the total number of studies from 7 to 6. The small number of studies is likely to be related to the strict exclusion criteria, a weakness of this review. For example, the exclusion of literature preceding 1990 may also have limited generalisability of the findings of this review.

In terms of study design and variability; the heterogeneous nature of the studies included prevented statistical analysis. However, meta-analysis would be the ideal method of assessing the frequency of depression in this population. The majority of the studies were cross-sectional. This allows for the investigation of the prevalence of depression but no further causal analysis. Further evidence is required to make firm conclusions regarding the nature and presentation of depression in PWS and larger cohort studies would allow for rigorous statistical analysis.

Concerning the exclusion of challenging behaviour, currently, the evidence for an association between challenging behaviour and the diagnosis of depression is inconclusive (see Appendix 1 for rationale). However, it is noted that a weakness of this review was not to set out operational or conceptual definitions of 'challenging behaviour' within the exclusion criteria. Teasing apart pre-existing challenging behaviour from a psychiatric problem is acknowledged as a major diagnostic and therapeutic conundrum for the clinician, and will be a continued challenge for research in this field.

The aim of this systematic review was to assess for the frequency and the nature of presentation of unipolar depression in PWS. The preliminary evidence has shown that the rate of depression in adults with PWS has been shown to range between 17.4% (Beardsmore et al, 1998) to 22% (Soni et al, 2008). The symptoms of depression appear to manifest toward adulthood, as reflected by the studies including children. Further evidence is required in order to compare these results to the ID population in general. It would also be of benefit to compare across the differing levels of intelligence, which within these studies is highly varied.

The observation of an increased rate of psychosis within the PWS population presenting with unipolar depression warrants further attention. The differentiation of genetic subtypes has shown varied results in terms of presentation of depression with psychosis. This differentiation by genetic subtype to behavioural phenotype will require further investigation, but is an exciting observation in terms of future research in this field.

Unipolar depression can be a diagnostic challenge within the general population due to wide-ranging symptomology (NCCMH, 2010). In an individual with PWS these difficulties will be compounded due to the complex behavioural phenotype and possible pre-existing challenging behaviour. These individuals will often encounter difficulties in self-expression, which will further complicate the clinical presentation. This review has investigated literature pertaining to the frequency and nature of presentation of depression in PWS and has made some preliminary observations. Despite the limitations of the review itself, it is hoped that the results will raise awareness of the rate of unipolar depression in the PWS population, and increased rate of psychotic symptoms presenting within this group.

Figure 1: Results of search strategy as per PRISMA Guidance
Source: Adapted from Moher et al (2009)

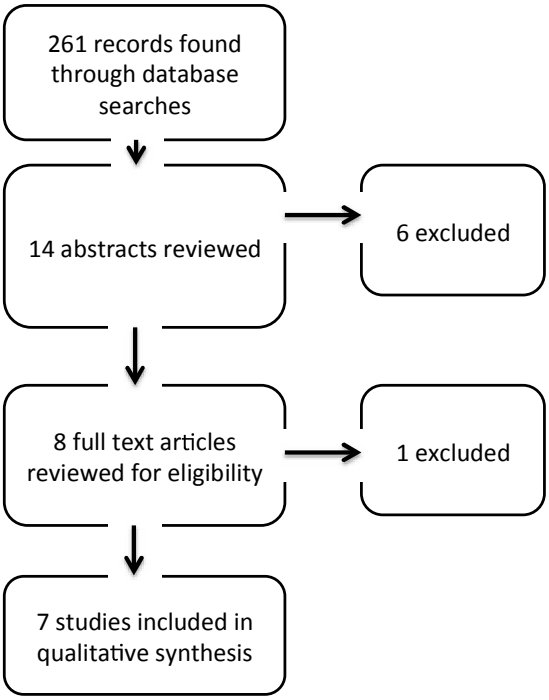

Table 1: Assessment of the quality of the study designs plus descriptive data for individual studies

	Study Design	n	Characteristics	Measure (Gold standard)	Report on measures of variability (if applicable)	Quality score	Frequency of depression in sample (combine psychotic and non-psychotic depression)	Age	Level of ID
Soni et al. (2008)	Cross-sectional	119 46 with evidence of psychiatric illness further investigated	119 participants with confirmed PWS on genetic testing. Multi-regional recruitment via PWS Association (UK) and ID services.	ICD-10	Confidence interval	**6**	delPWS 19/82 (23%) mUPD 7/33 (21%) Total sample 26/119 (22%)	delPWS 31.8 (17-51) mUPD 30.6 (12-50)	Mean IQ (range): delPWS 64.5 (50-83) mUPD 68.7 (56-105)
Soni et al. (2007)	Cohort	119	119 participants with confirmed PWS on genetic testing. Multi-regional recruitment via PWS Association (UK) and ID services.	ICD-10	Confidence interval	**6**	Over study period (12 weeks – 2.5 years following original data collection) there were 3 new cases.	delPWS 31.8 (17-51) mUPD 30.6 (12-50)	Mean IQ (range): delPWS 64.5 (50-83) mUPD 68.7 (56-105)
Sinnema et al. (2011)	Cross-sectional	97	97 Participants with confirmed genetic diagnosis of PWS from Dutch Prader-Will Parent Association and ID services.	ICD-10	-	**5**	delPWS 7/53 (13%) mUPD 11/44 (25%) Total 18/97 (18%)	36.2 years (SD =12.4, 18-66)	Not differentiated
Haraiwa et al. (2007)	Retrospective cohort	165	116 participants from Japanese PWS	Questionnaire	-	**3**	6/165 (4%)	Age range 2-31 years	Borderline 4.2%

			Association						Mild 33.3% Moderate 62.5%
Reddy & Pfeiffer (2007)	Cross-sectional	73	13 PWS confirmed on genetic testing, 30 with ID, and 30 with ID and co-existing psychiatric disorder. Recruited from residential facilities for the treatment and education of children with ID	Devereux Scale	Standard deviation	**4**	No clinically significant scores for depression	17.36 years (11.25-20.25)	Mild 46% Moderate 54%
Skokauskas et al (2012)	Cross-sectional	48	Confirmed genetic diagnosis PWS Participants in National Irish PWS study, unclear how identified.	Child behaviour checklist 6-18 – used DSM orientated subscales	Standard deviation	**5**	Children with PWS scored significantly higher on CBCL subscales for anxious/depressed and withdrawn/depressed than children with ID. This was not found to be clinically significant on CBCL DSM-orientated subscales.	9.9 years (SD 3.6)	Mean IQ 64 (SD 3.1)
Beardsmore et al (1998)	Cross-sectional	96	23 clinically diagnosed PWS (87% had genetic testing) and 73 controls with ID. Subjects identified from health records of ID services of 2	DCR-ICD10 DSM-IV	-	**5**	4/24 (17.4%)	29.3 years (SD +/- 8.2 years)	Range: borderline-severe (not quantified)

			NHS trusts, and from 2 specialist residential units for PWS						

Quality assessment (modified version) based on Hermans, H. & Evenhuis, H.M. (2010)

APPENDICES

Appendix 1: Rationale for the exclusion of challenging behaviour

The observation of an individual for changes in behaviour is an essential requirement for the diagnosis of depression. There is a difference between behavioural changes (how an individual perceives, and interacts with their environment plus eating and sleeping) and challenging behaviour (Walton & Kerr, 2015). In the general intellectual disability (ID) population, Meins (1995) concluded that new behaviour problems were observed to start equally in both mild-moderate ID and severe ID when the groups were compared. It was noted that an increase in pre-existing behaviour issues was observed in the severely disabled group. Studies that have concluded that there is a demonstrable link have been small-scale and under-powered (Hayes et al, 2011). Conversely, Holden & Gitleson (2002) found no association between the emergence of depression and the onset of challenging behavior. This was supported by Sturmey et al (2010). It is apparent that the debate continues, and it is beyond the scope of this review to assess for psychiatric morbidity presenting as new challenging behaviour.

Appendix 2: Evaluation of Study Quality

Table 1: Evaluating methodological quality of studies

Item	Criteria	Score
Number of participants	>100 >30-100 <30	2 1 0
Characteristics of participants	Group representing target population of the instrument (screening for depression)	0/1
Psychopathology of the	>20-50% of participants had depression	2

participants	10-20% or >50-90% had depression <10% or >90% of the participants had depression Unclear	1 1 0
Gold standard	Clinical diagnosis by a psychiatrist or psychologist based on standard diagnostic system Clinical diagnosis by a psychiatrist or psychologist Other depression screening instrument used as reference standard All other Not applicable	2 1 1 0 0
Report on measures of validity	Standard deviation or standard error, or confidence interval is reported.	0/1

Hermans, H. & Evenhuis, H.M. (2010)

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