Anxiety Disorders in Williams Syndrome Contrasted with Intellectual Disability and the General Population: A Systematic Review and Meta-Analysis

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Online Resource A

Complete list of papers based on the full text search for the systematic review

Included Articles

1. Cherniske EM, Carpenter TO, Klaiman C, et al. Multisystem study of 20 older adults with Williams syndrome. *American Journal of Medical Genetics Part A*. 2004; **131A** (3): 255-64.
2. Dodd HF, Porter MA. Psychopathology in Williams syndrome: The effect of individual differences across the life span. *Journal of Mental Health Research in Intellectual Disabilities*. 2009;**2**(2):89-109.
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4. Dodd HF, Porter MA. Interpretation of Ambiguous Situations : Evidence for a Dissociation Between Social and Physical Threat in Williams Syndrome. *Journal of Autism and Developmental Disorders*. 2011;**41, 3**:266-74.
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7. Green T, Avda S, Dotan I, et al. Phenotypic psychiatric characterization of children with Williams syndrome and response of those with ADHD to methylphenidate treatment. *Am J Med Genet, Part B-Neuropsychiatric Genetics*. 2011;**159B**(1):13-20.
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Velocardiofacial (22q11.2 deletion) and Williams (7q11.23 deletion) syndromes. *European Psychiatry*. 2014;**29**(4):203-10.

Excluded Studies

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2. Ashworth A, Hill CM, Karmiloff-Smith A, Dimitriou D. Cross syndrome comparison of sleep problems in children with Down syndrome and Williams syndrome. *Research in Developmental Disabilities*. 2013;**34**(5):1572-80.
3. Avery SN, Thornton-Wells TA, Anderson AW, Blackford JU. White matter integrity deficits in prefrontal-amygdala pathways in Williams syndrome. *Neuroimage*. 2012;**59**(2):887-94.
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Online Resource B

Supplemental Table 1. Quality Criteria used to rate the studies (adapted from Richards, Jones, Groves, Moss and Oliver 2015)

	Quality Rating			
	0 **Poor**	**1** **Adequate**	**2** **Good**	**3** **Excellent**
Sample Identification	Not specified/reported	Single restricted or non-random sample e.g., a specialist clinic or previous research study[a] Single regional sample e.g., a regional parent support group	Multiple restricted or non-random samples e.g., multi-region specialist clinics National non-random sampling e.g., national parent support groups	Random or total population sample
Confirmation of syndrome[b]	Not confirmed/reported Clinical diagnosis only suspected	Clinical diagnosis by 'generalist' e.g., General Practitioner or Paediatrician	Clinical diagnosis by 'expert' e.g., Clinical Geneticist or Specialist Paediatrician	Genetic confirmation of diagnosis/FISH tested
Anxiety assessment	Not specified/reported Clinician judgement only	Informant report/self-report instrument e.g., SCAS Screening instrument e.g. PAS-ADD Clinician judgement against specified diagnostic criteria e.g., DSM-IV or ICD-10	Diagnostic instrument/interviews e.g., K-SADS, ADIS	Consensus from multiple assessments, including at least one diagnostic instrument

[a] For individuals recruited as part of a larger *ongoing* study, if the recruitment strategy is described, it is coded. If not, it is coded as 1, indicating the sample has come from one source (i.e., the larger ongoing study).

[b] Studies can only be classified into a category if all of the participants were tested using the outlined method. For instance, if only 50% of participants were FISH tested, the study cannot receive a score of 3 and will receive a score of 2. For heterogeneous ID studies, a score of 1 is given to studies which include an IQ or adaptive behaviour assessment as part of the study design.

Online Resource C

Statistical Meta-Analytical models

There are various statistical meta-analytical models which can be used to estimate effect sizes. Each model makes different inferences and assumptions regarding the data in question (Hedges and Vevea 2000). The three models referenced in the study are the fixed-effects model, the random-effects model and the quality-effects model. Explanations of the models and justifications for the models used are provided below.

The Fixed Effects (FE) model

The FE model generates effect sizes based on the assumption that studies are homogenous and share common effect sizes (Hedges & Vevea 2000). This model only accounts for within study variability; however it is considered probable that there will also be some level of variation between studies that this model fails to consider. Variability may result from study methodological differences, as well as moderating variables which may act to influence outcomes (Hunter and Schmidt 2000). As a result, Type 1 bias may increase and inaccurate conclusions may be drawn using this model (Field 2003; Overton 1998).

The Random Effects (RE) Model

The RE model accounts for between study variance and is described as providing a more applicable model for real-world data (Borenstein, Hedges, Higgins and Rothstein 2010). The model assumes that effect sizes will vary due to random error and true variation between the studies and redistributes study weightings to account for this (Erez, Bloom and Wells 1996). As a result of the additional sources of variation, the confidence intervals generated in the RE model tend to be larger than those in the FE model (Egger, Smith and Phillips 1997) Even so, the RE model was considered a more appropriate alternative to the FE model for this review, as it considers both within and between study variability.

The Quality Effects (QE) Model

The QE model is a newer method which accounts for methodological differences between studies. This model provides more weight to studies which are of higher quality when estimating effect sizes and this is indicated to be more clinically relevant than the RE model (Doi and Thalib 2008). The redistribution of mathematical weightings corresponds to the parameters ‘0’indicating low quality and ‘1’ indicating high quality (Barendregt, Doi, Lee, Norman and Vos 2013). Quality assessment for this model is required and according to Doi and Thalib (2008), any criteria can be used, providing a Qi score (Quality of the ith score) is derived by dividing individual study quality scores by the maximum score.

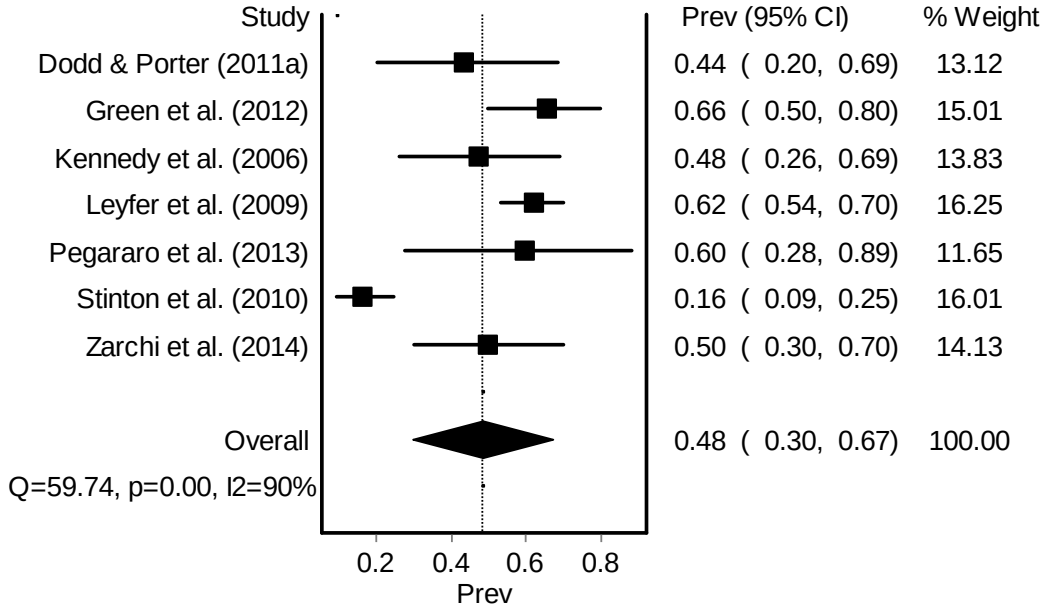
The Review

Both a RE model and a QE model were used in this review. These models were chosen for the meta-analysis as they were deemed the most suitable and appropriate for the study’s aims. Both models redistribute mathematical weight to prevent outliers from interfering with the effect size; with the RE model based on statistical heterogeneity and the QE model considering quality (Doi and Thalib, 2008), Usage of both models enabled us to demonstrate the utility of weighting the quality of studies when estimating effect sizes. It also provided some indication as to whether the model’s assumptions had an effect on the prevalence rates estimated.

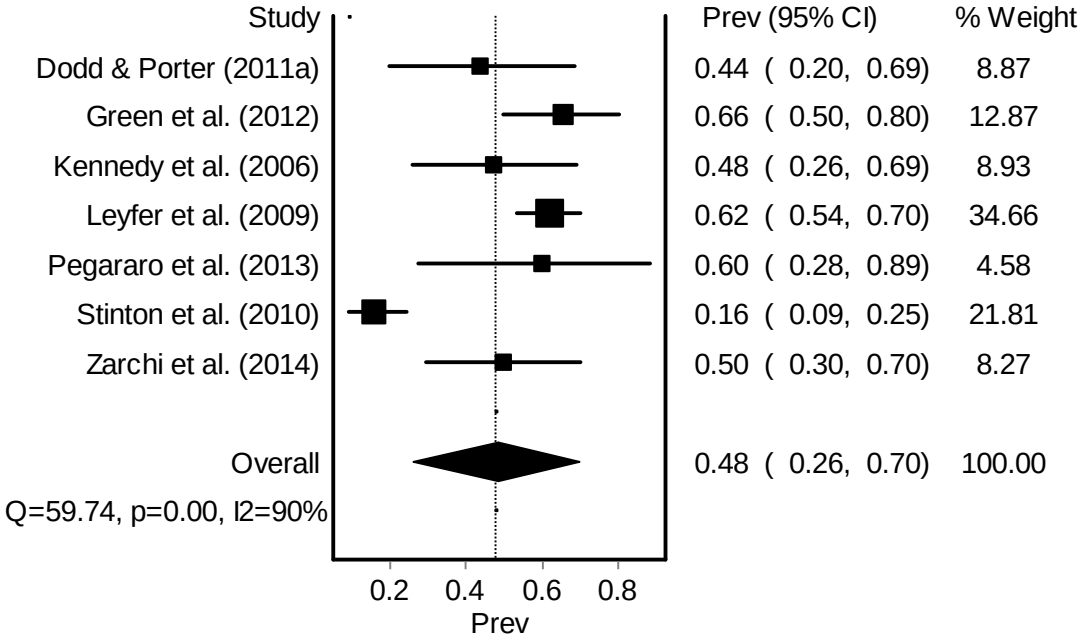
Models were generated using the statistical package MetaXL 2.0 (Barendregt and Doi 2011).

Online Resource D

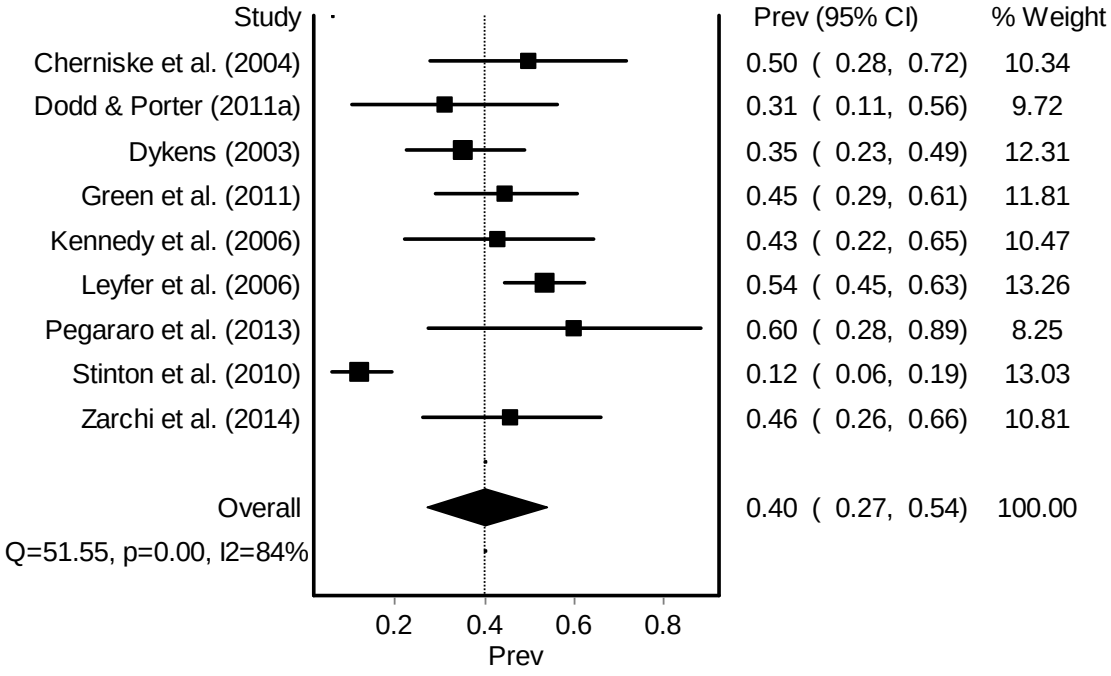
Random Effects Forest Plots and Quality Effects Forest Plots for Anxiety Disorders in Williams Syndrome



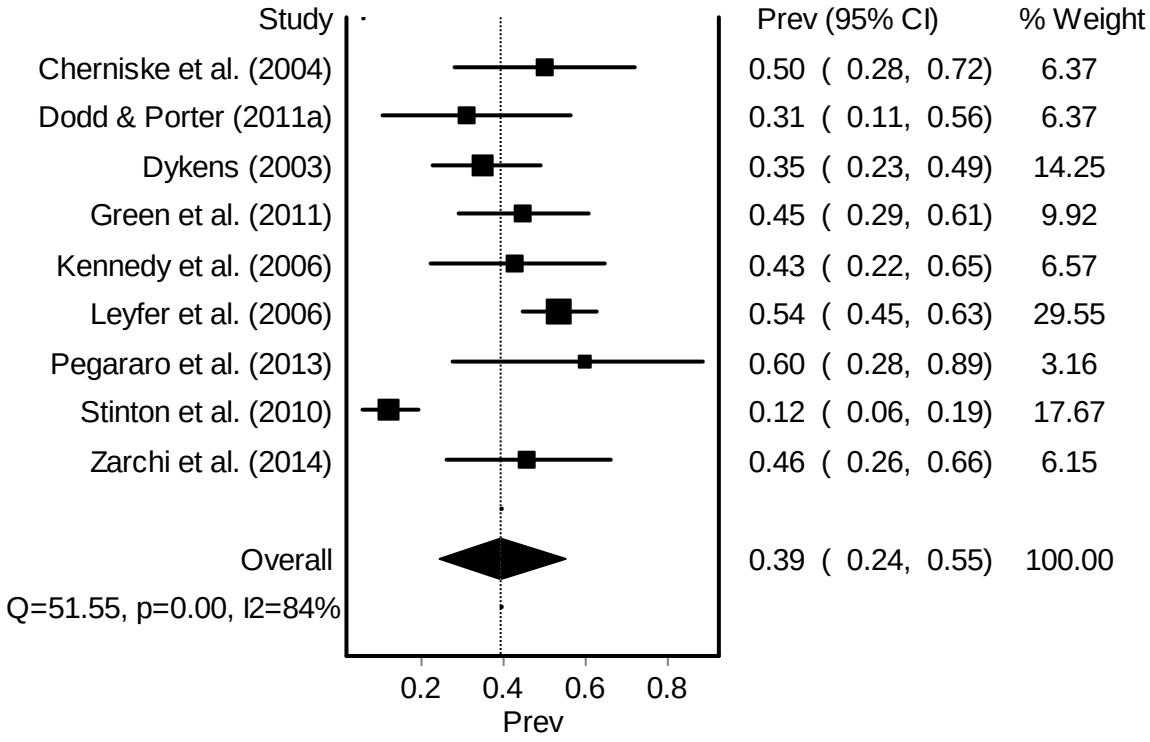
Supplemental Figure 1. Pooled Prevalence estimates for any anxiety disorder using the random effects model.



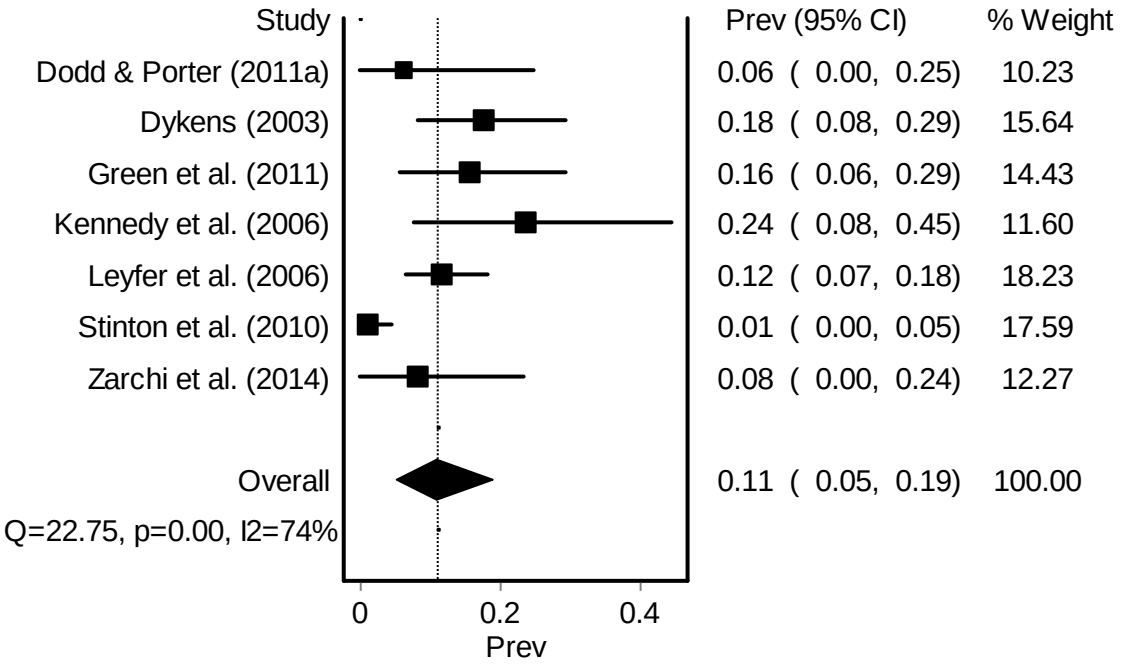
Supplemental Figure 2. Pooled Prevalence estimates for any anxiety disorder using the quality effects model.



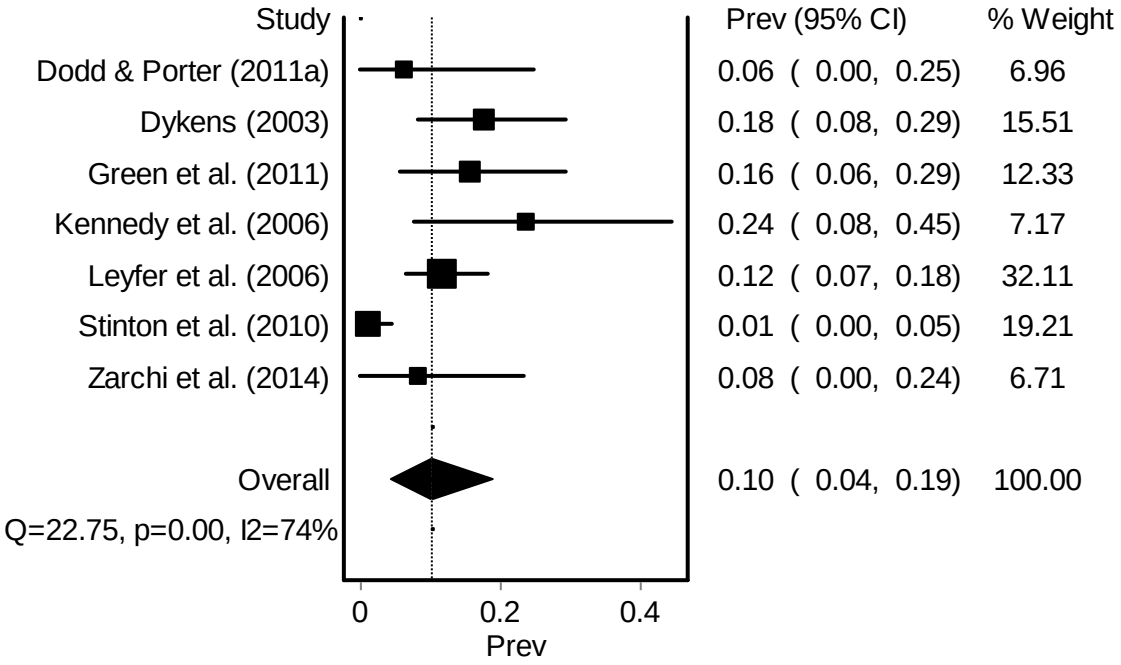
Supplemental Figure 3. Pooled Prevalence estimates for specific phobias using the random effects model.



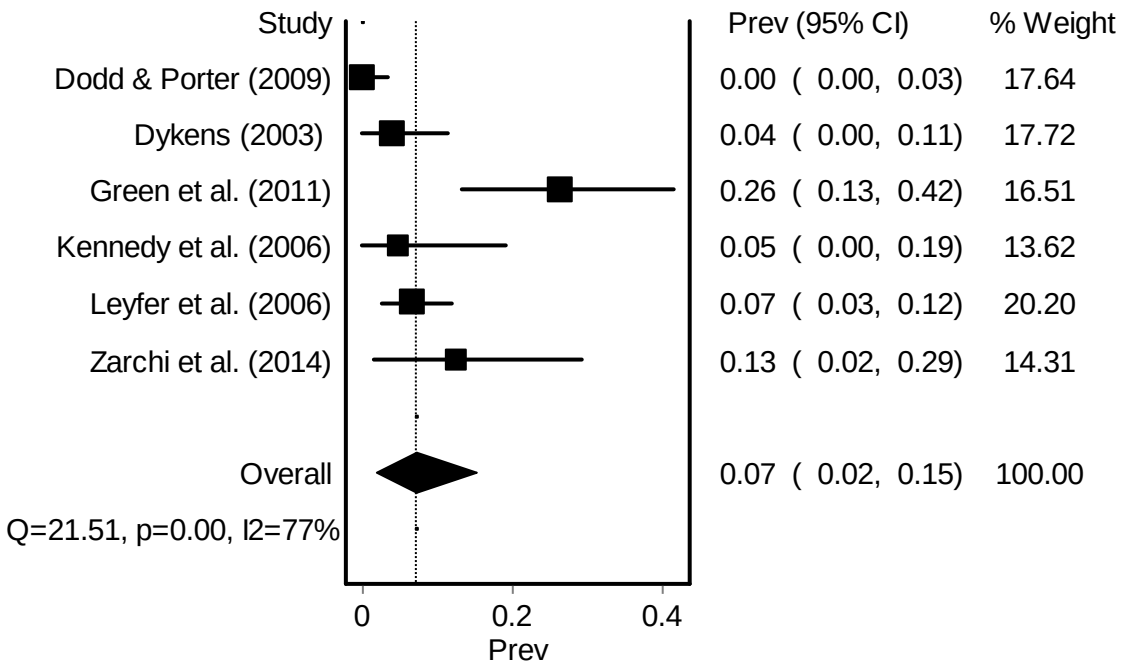
Supplemental Figure 4. Pooled Prevalence estimates for specific phobias using the quality effects model.



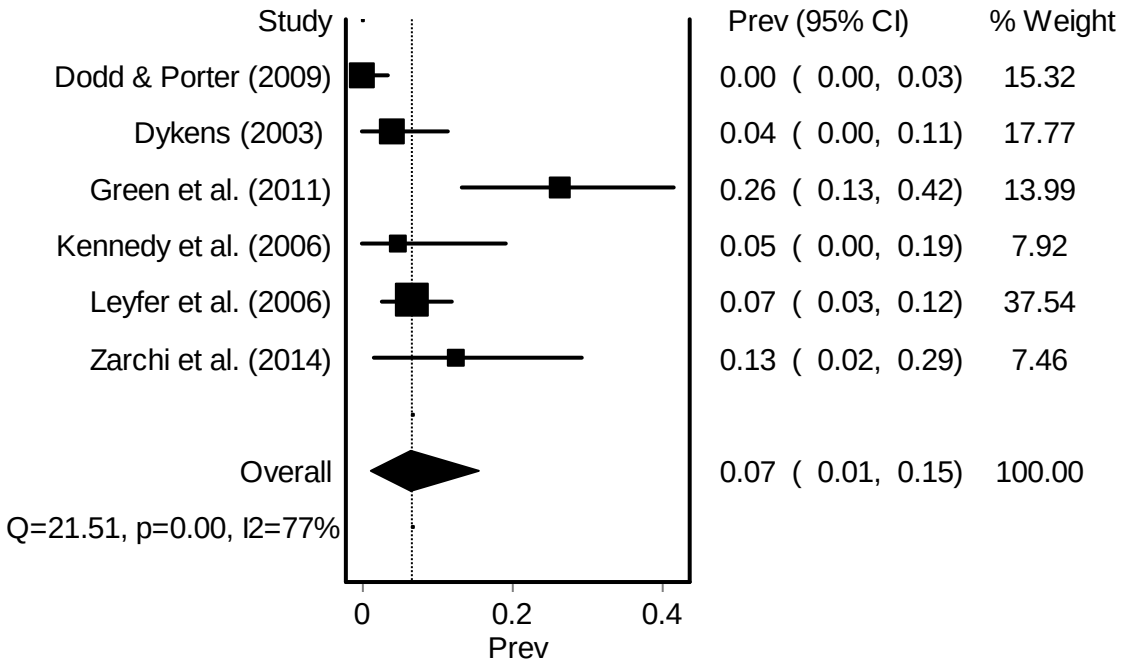
Supplemental Figure 5. Pooled Prevalence estimates for generalised anxiety disorder using the random effects model.



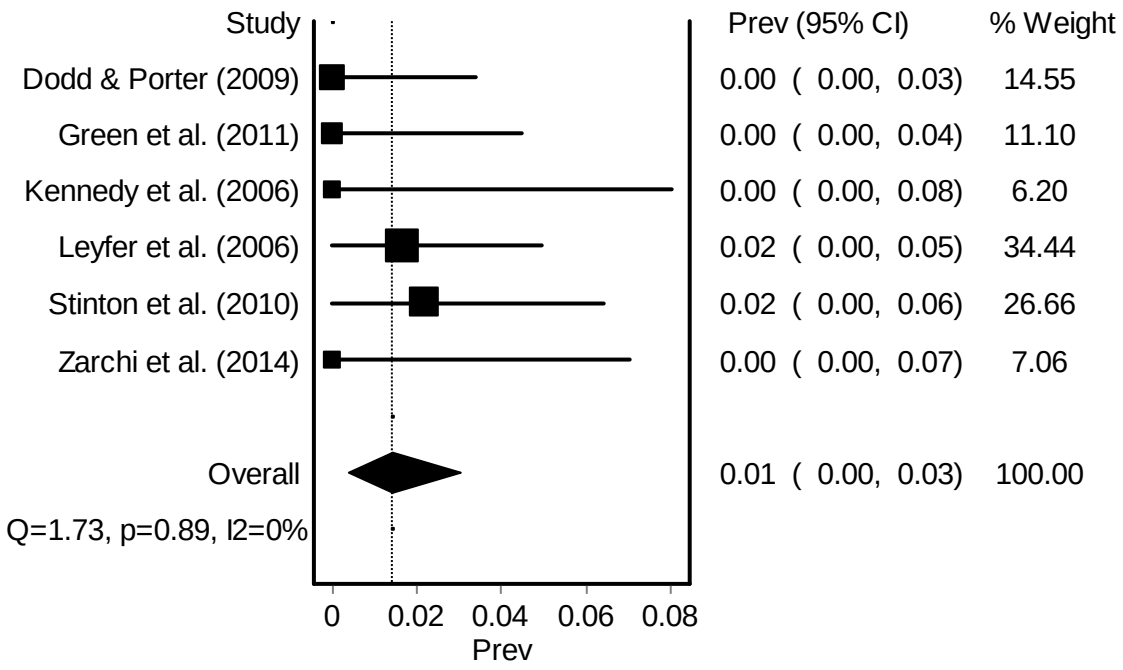
Supplemental Figure 6. Pooled Prevalence estimates for generalised anxiety disorder using the quality effects model.



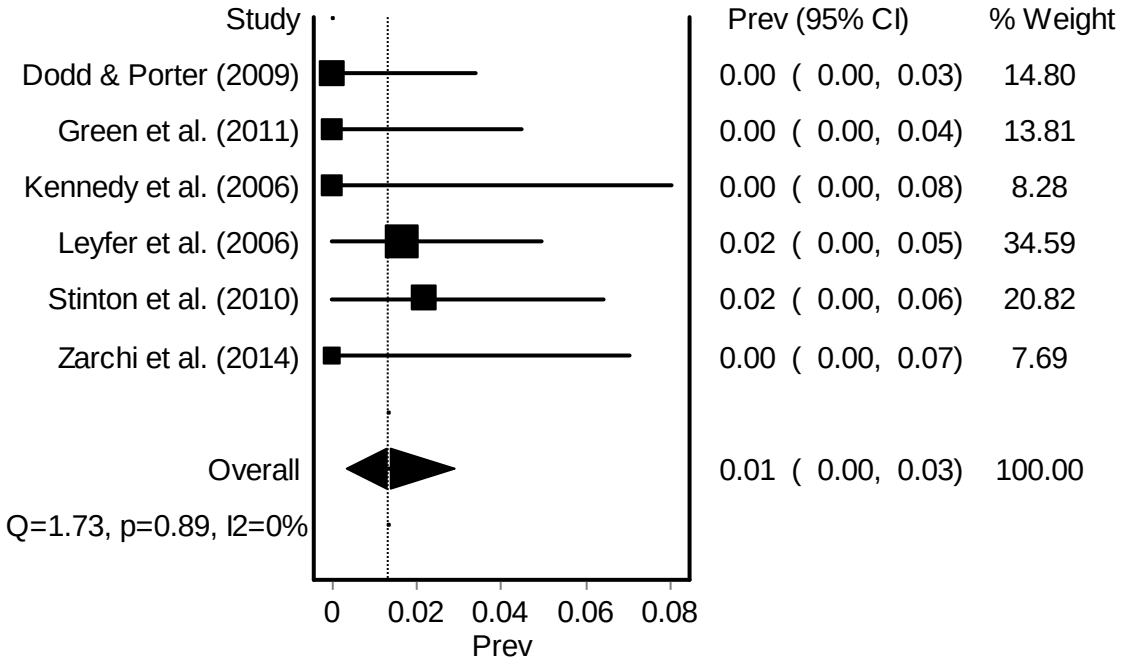
Supplemental Figure 7. Pooled Prevalence estimates for separation anxiety disorder using the random effects model.



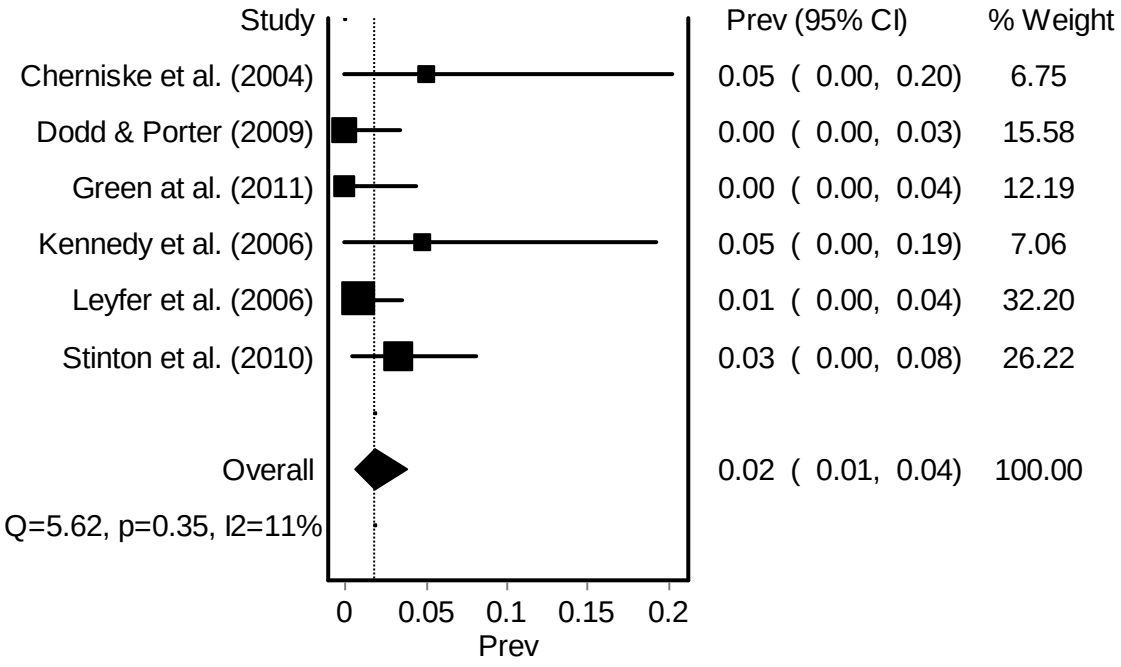
Supplemental Figure 8. Pooled Prevalence estimates for separation anxiety disorder using the quality effects model.



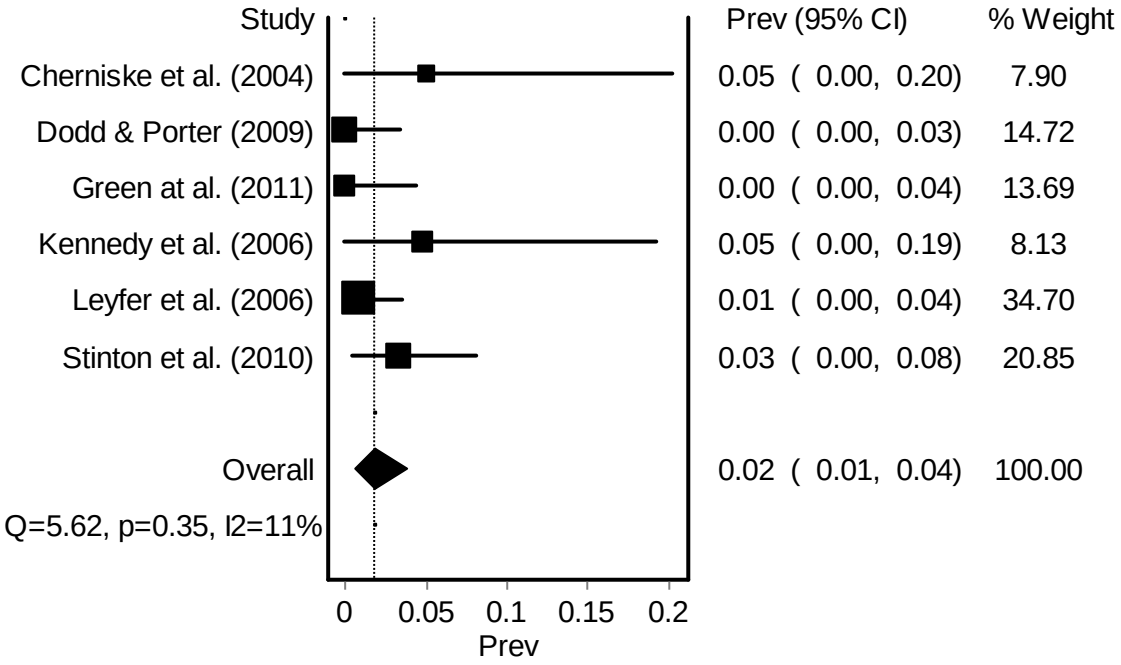
Supplemental Figure 9. Pooled Prevalence estimates for social anxiety disorder using the random effects model.



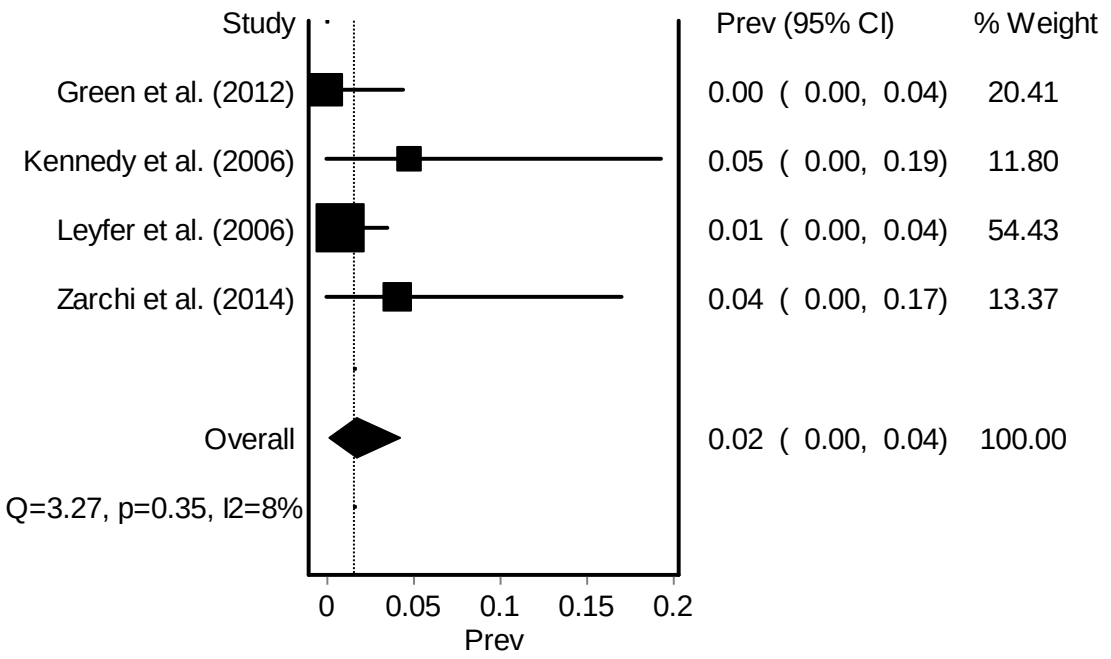
Supplemental Figure 10. Pooled Prevalence estimates for social anxiety disorder using the quality effects model.



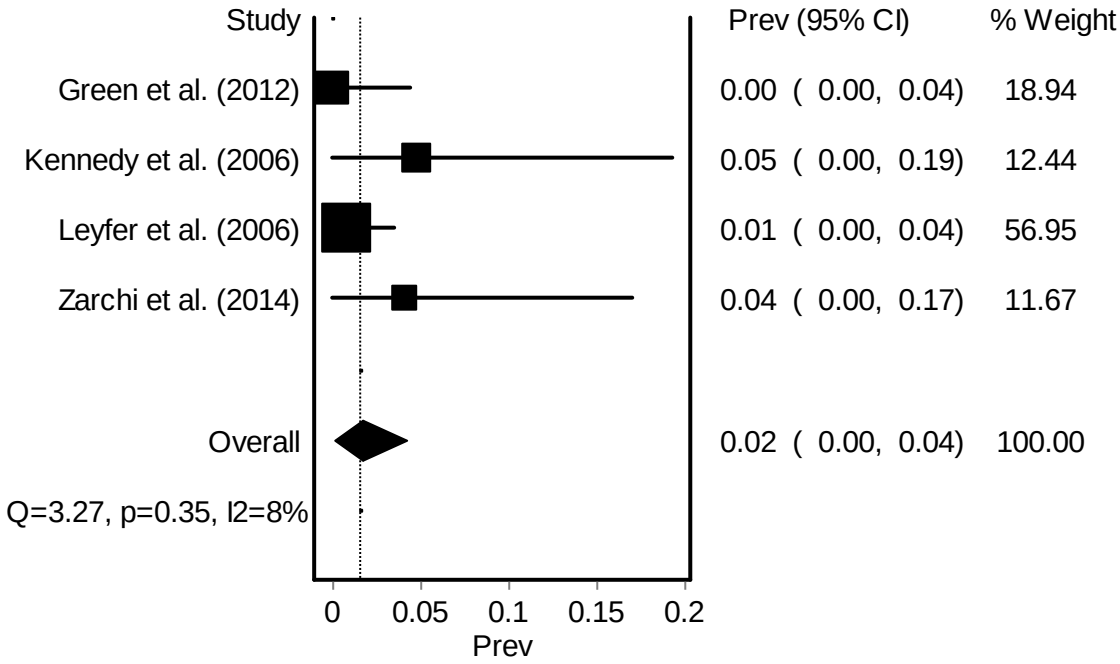
Supplemental Figure 11. Pooled Prevalence estimates for panic disorder using the random effects model.



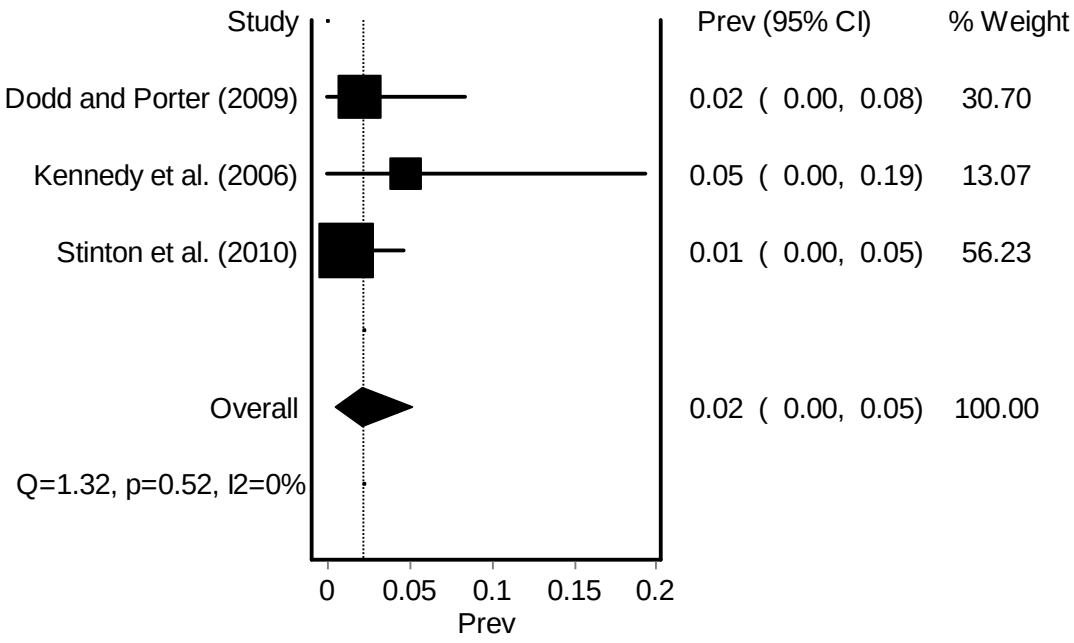
Supplemental Figure 12. Pooled Prevalence estimates for panic disorder using the quality effects model.



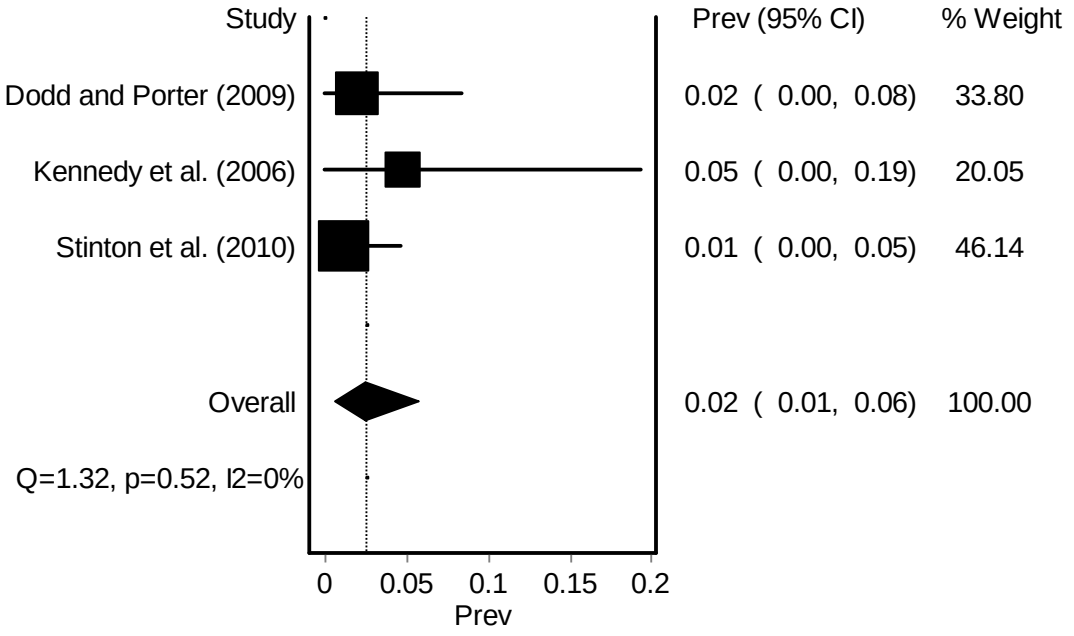
Supplemental Figure 13. Pooled Prevalence estimates for post-traumatic stress disorder using the random effects model.



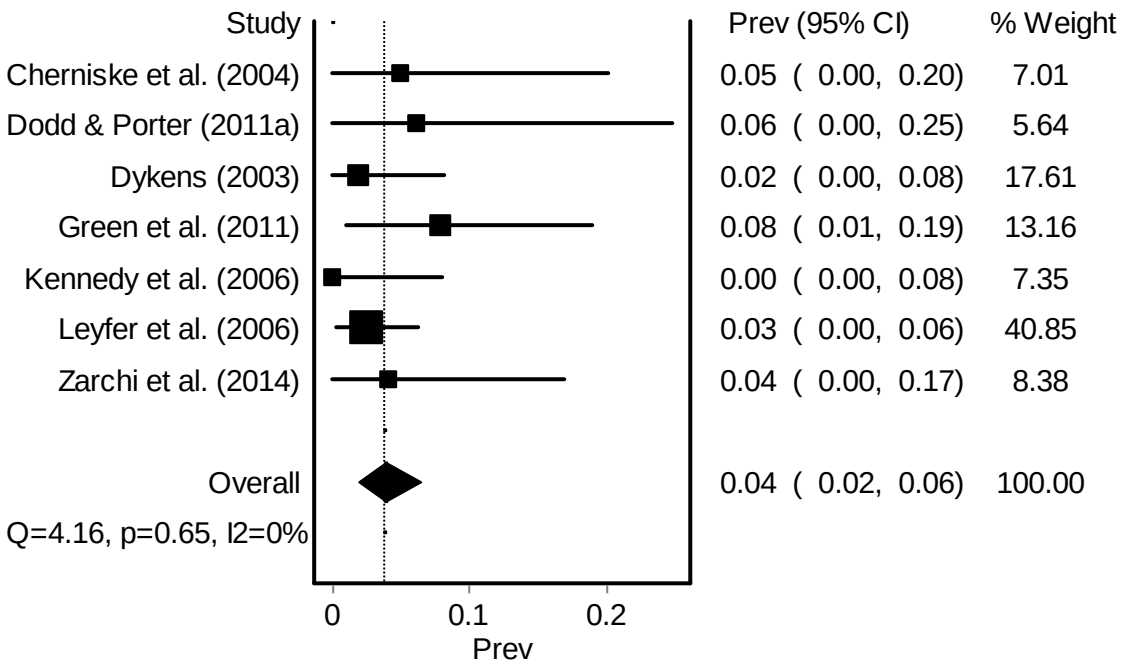
Supplemental Figure 14. Pooled Prevalence estimates for post-traumatic stress disorder using the quality effects model.



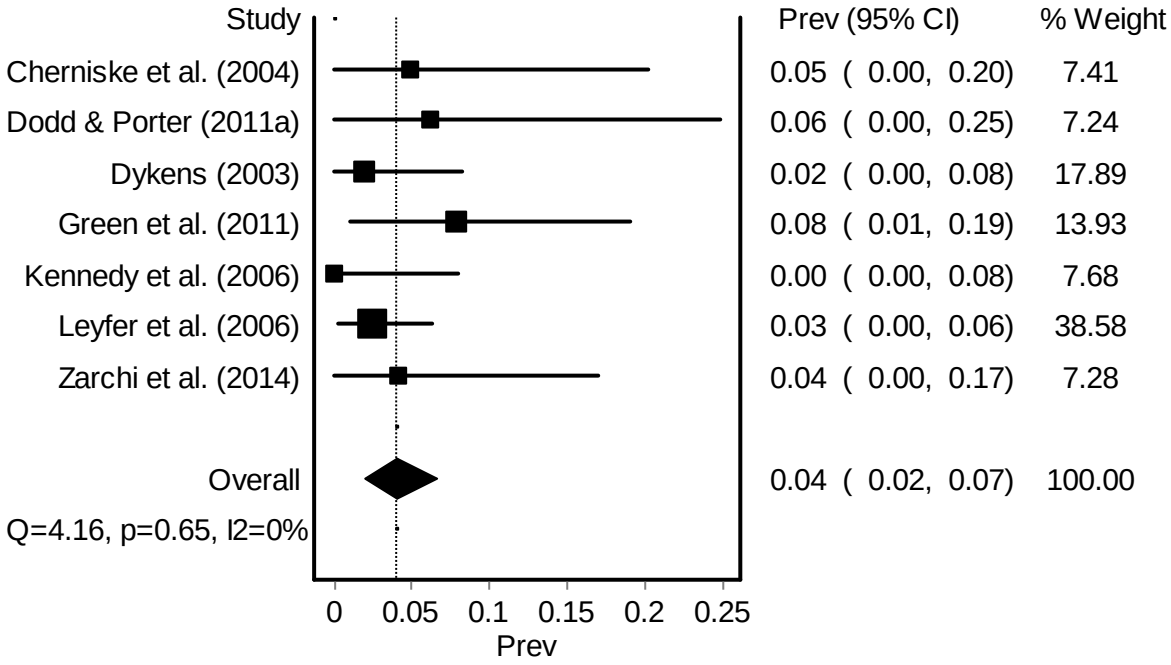
Supplemental Figure 15. Pooled Prevalence estimates for agoraphobia using the random effects model.



Supplemental Figure 16. Pooled Prevalence estimates for agoraphobia using the quality effects model.



Supplemental Figure 17. Pooled Prevalence estimates for obsessive-compulsive disorder using the random effects model.



Supplemental Figure 18. Pooled Prevalence estimates for obsessive-compulsive disorder using the quality effects model.

Online Resource E

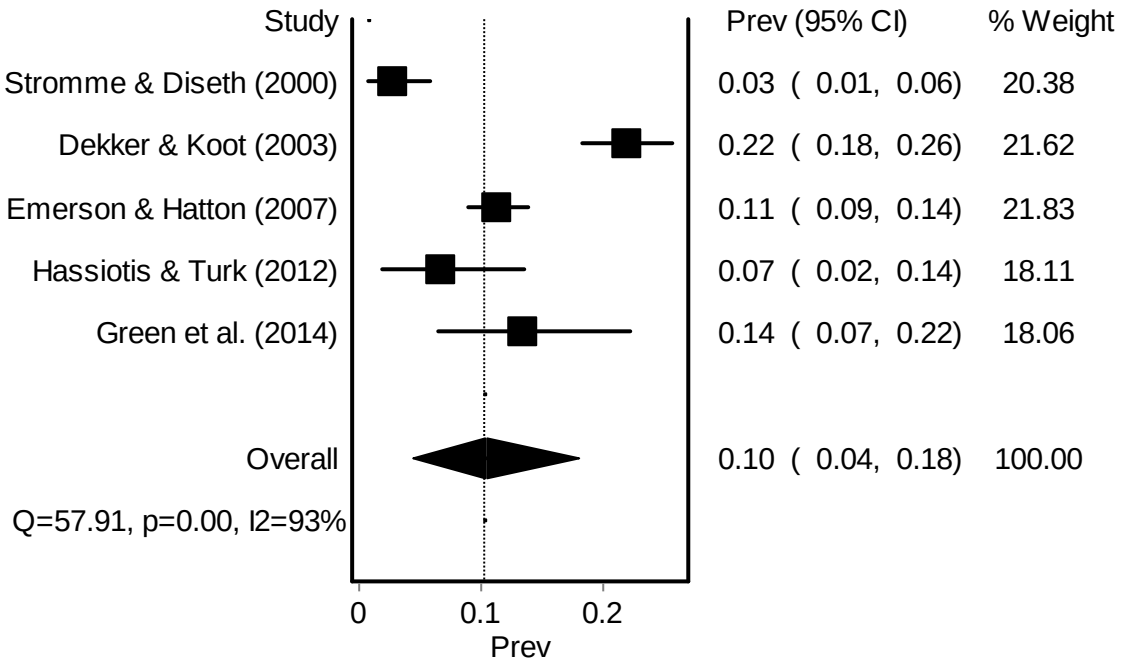
Pooled prevalence estimates, random effects forest plots and quality effects forest plots for anxiety disorders in individuals with intellectual disability of heterogeneous aetiology

Supplemental Table 2. Total number of included ID studies and participants, mean quality weightings; and random-effects/quality effects models with 95% confidence intervals. Data from Reardon, Gray and Melvin (2015).

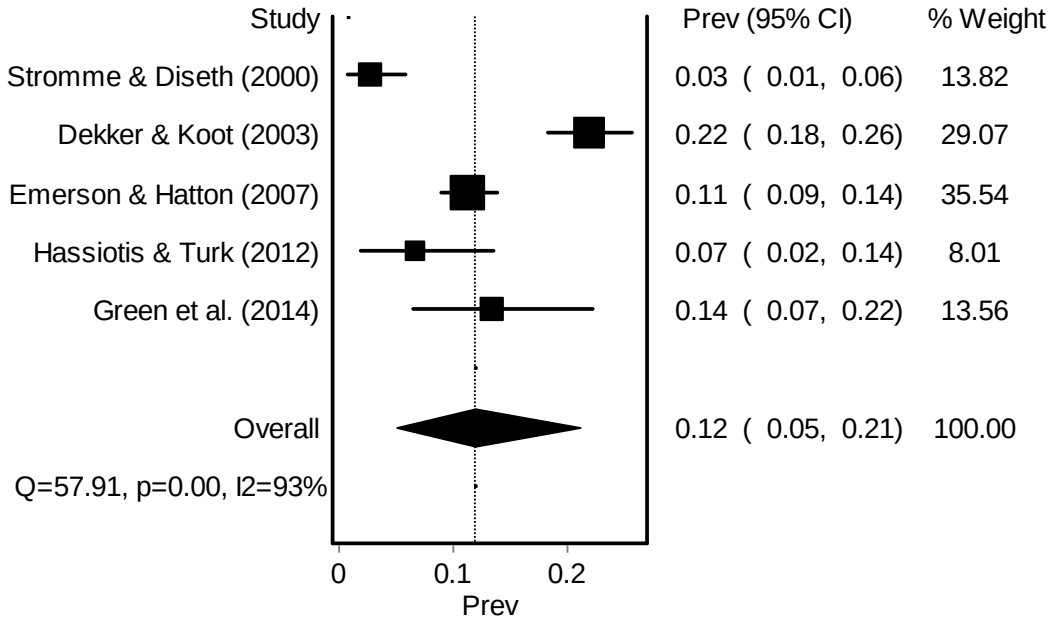
	Included Studies[a]	**Total Ppts**	**Mean QW**	**Random- Effects Pooled Prev.**	**Quality- Effects Pooled Prev.**
	(N)	***(N)***		***(CI)***	***(CI)***
Any anxiety disorder	5	1442	0.49	*10.0 (4.0-18.0)*	*12.0 (5.0-21.0)*
Specific phobias	2	1115	0.56	*8.0 (0.0-28.0)*	*7.0 (0.0-26.0)*
Generalised anxiety disorder	3	1189	0.56	*1.0 (0.0-3.0)*	*1.0 (0.0-3.0)*
Separation anxiety disorder	3	1210	0.56	*4.0 (1.0-9.0)*	*4.0 (1.0-8.0)*
Social anxiety disorder	4	1285	0.50	*2.0 (1.0-4.0)*	*2.0 (1.0-4.0)*
Panic disorder	2	1115	0.56	*0.0 (0.0-1.0)*	*0.0 (0.0-1.0)*
Agoraphobia	2	1115	0.56	*1.0 (0.0-2.0)*	*1.0 (0.0-2.0)*

Notes: QW, Quality Weighting

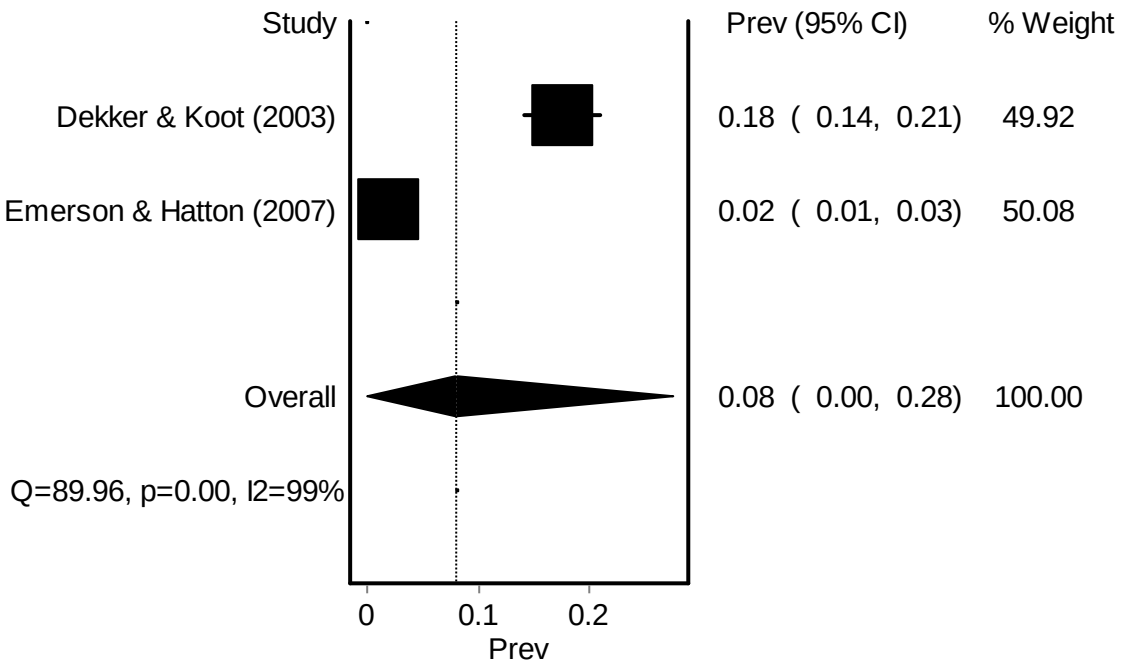
[a]Overlapping cohorts were removed from each analysis; the overlapping study with the highest quality rating was retained, whilst the others were excluded.



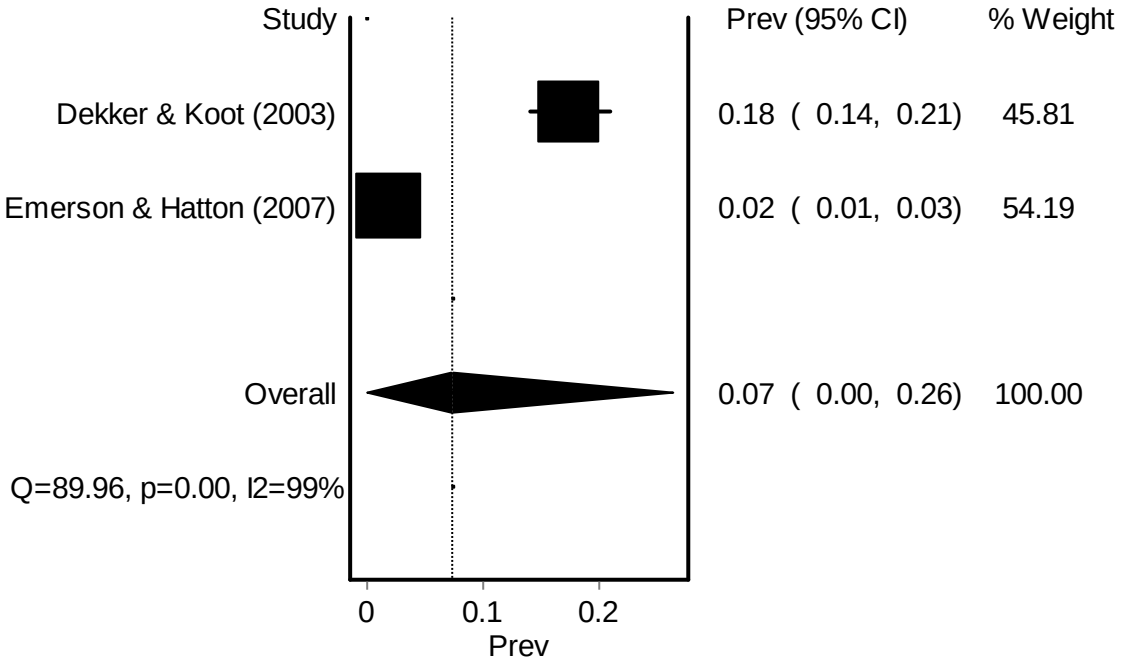
Supplemental Figure 19. Pooled prevalence estimates for any anxiety disorder using the random effects model.



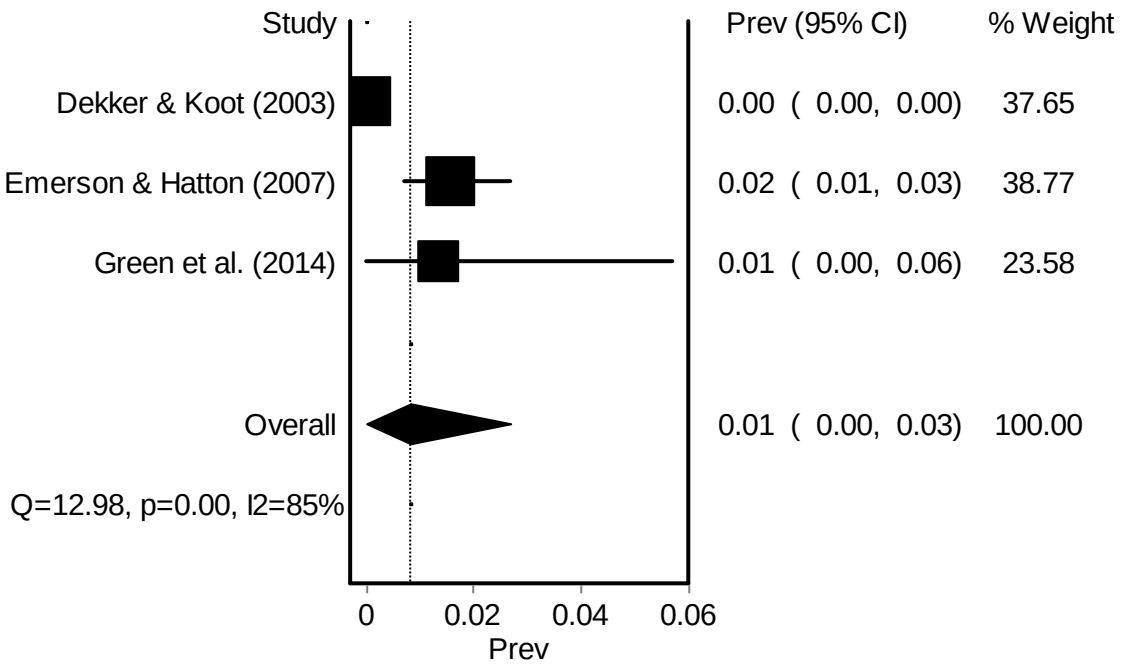
Supplemental Figure 20. Pooled prevalence estimates for any anxiety disorder using the quality effects model.



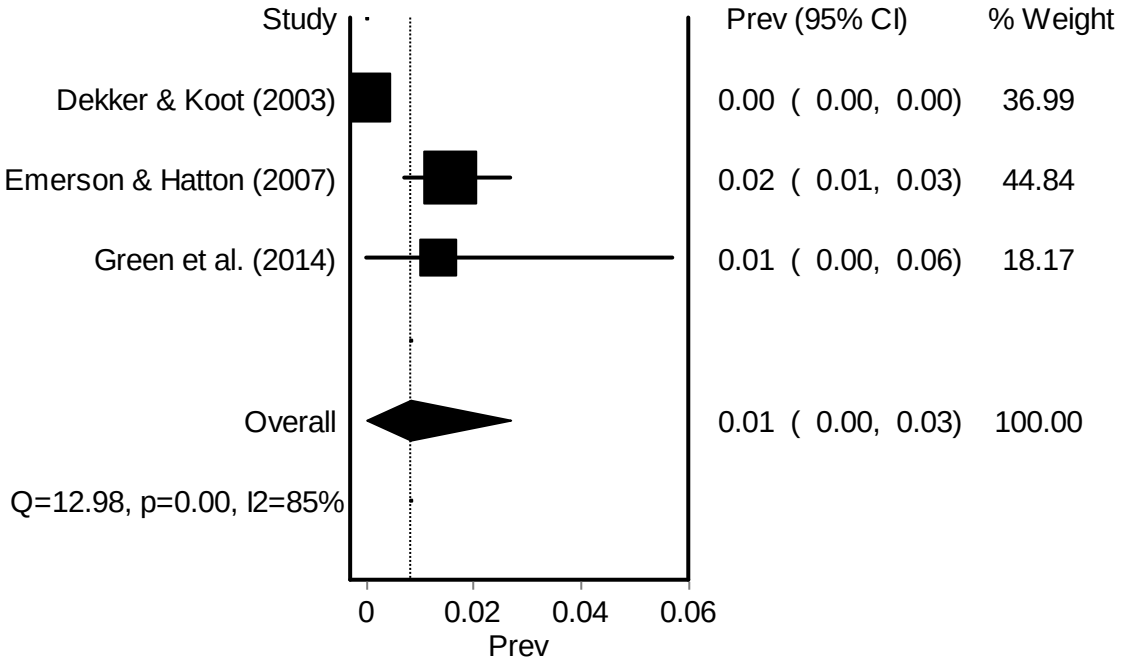
Supplemental Figure 21. Pooled prevalence estimates for specific phobias using the random effects model.



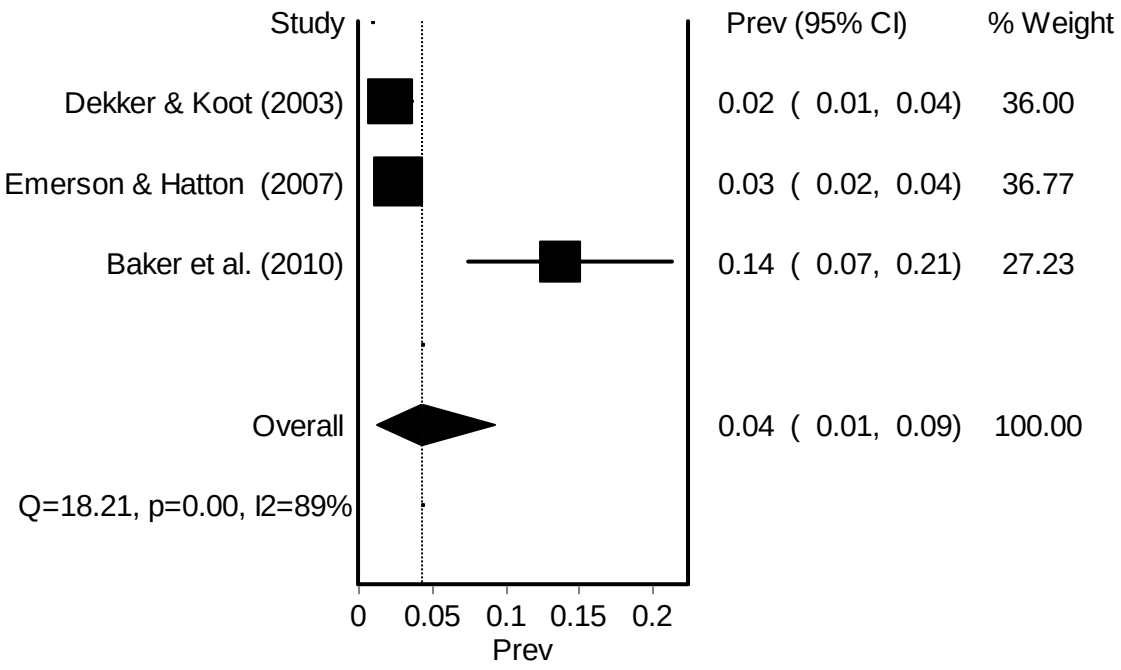
Supplemental Figure 22. Pooled prevalence estimates for specific phobias using the quality effects model.



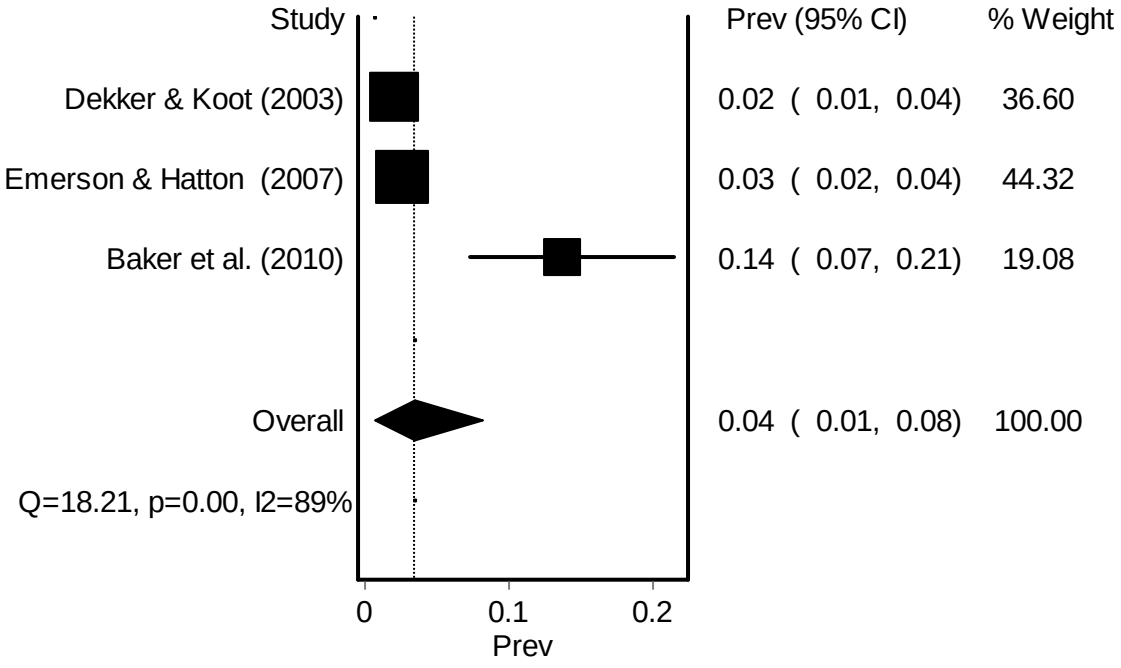
Supplemental Figure 23. Pooled prevalence estimates for generalised anxiety disorder using the random effects model.



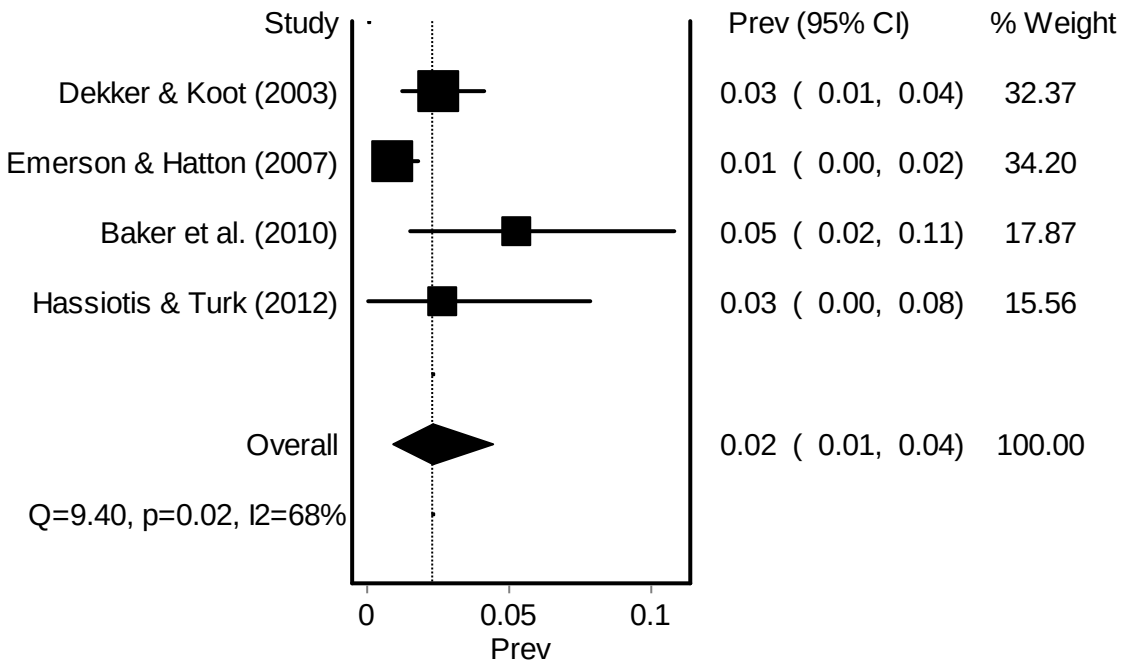
Supplemental Figure 24. Pooled prevalence estimates for generalised anxiety disorder using the quality effects model.



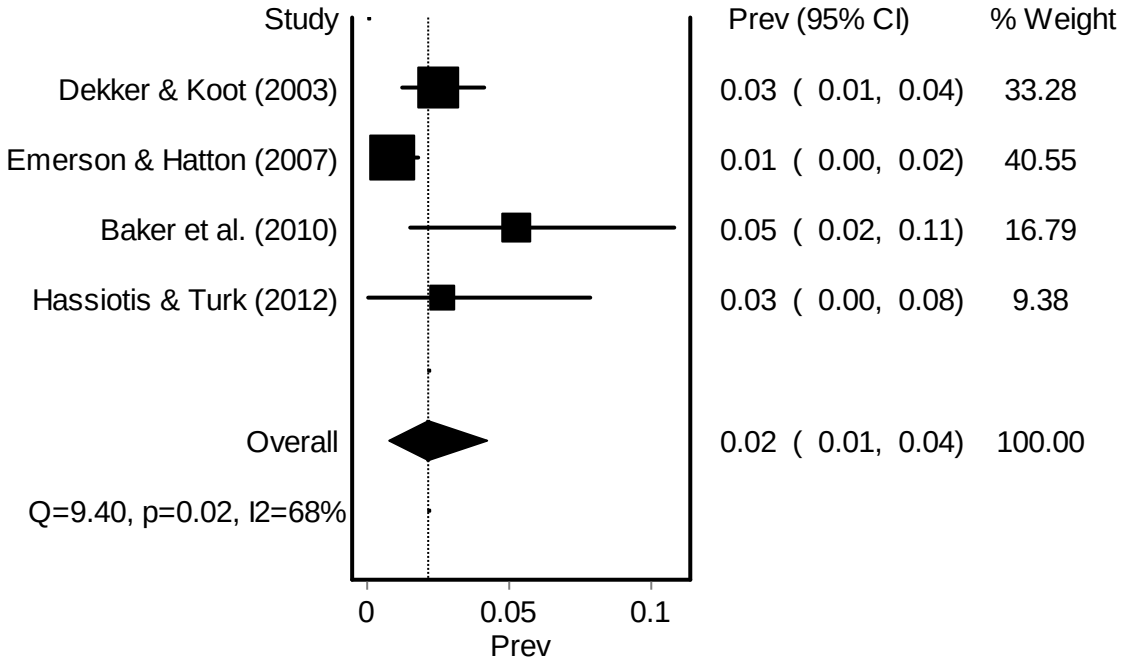
Supplemental Figure 25. Pooled prevalence estimates for separation anxiety disorder using the random effects model.



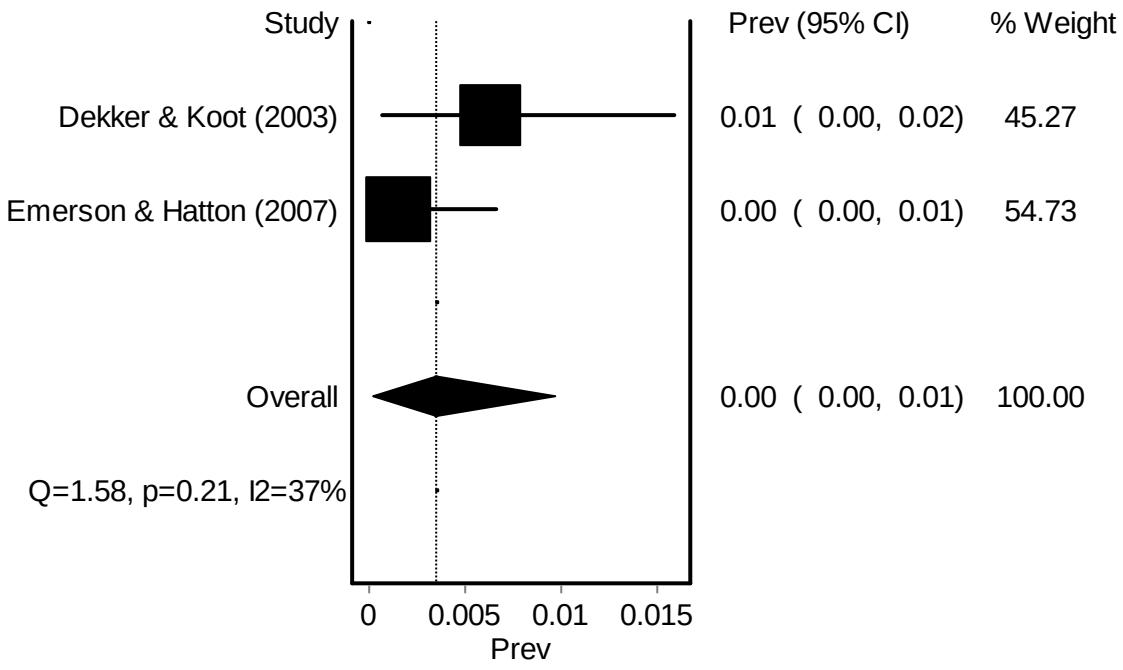
Supplemental Figure 26. Pooled prevalence estimates for separation anxiety disorder using the quality effects model.



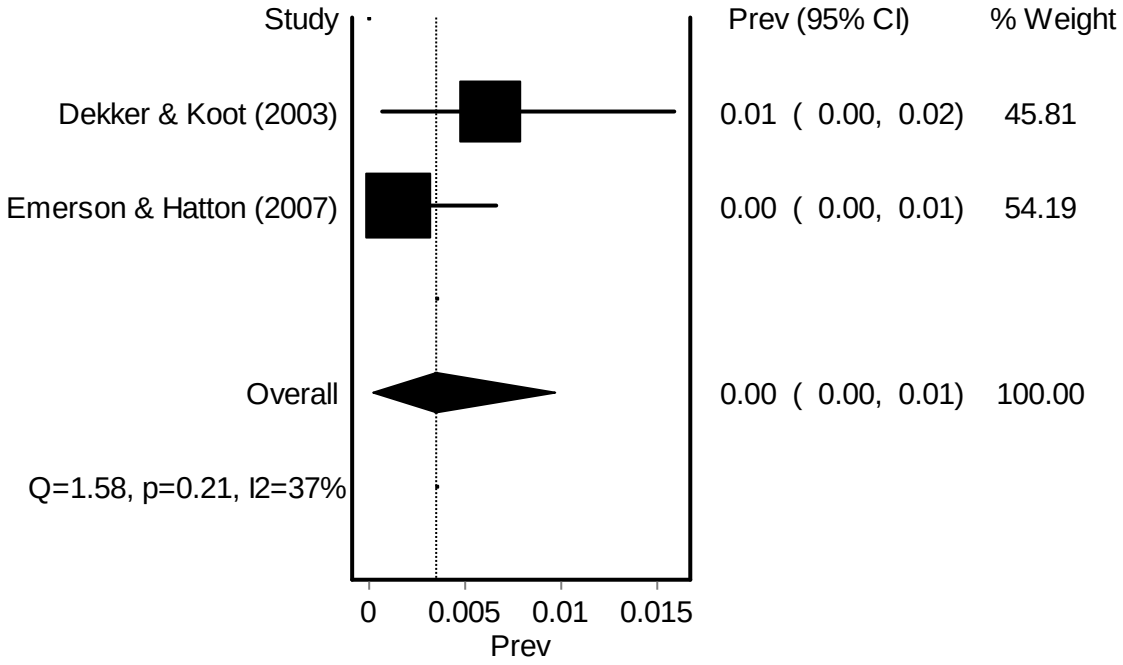
Supplemental Figure 27. Pooled prevalence estimates for social anxiety disorder using the random effects model.



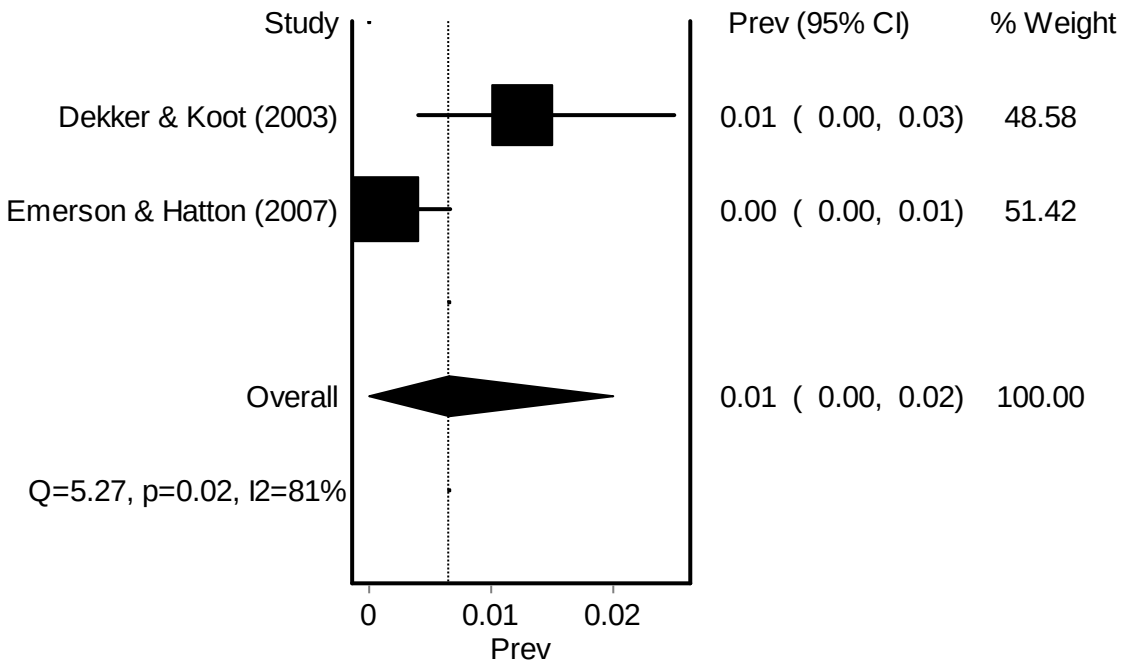
Supplemental Figure 28. Pooled prevalence estimates for social anxiety disorder using the quality effects model.



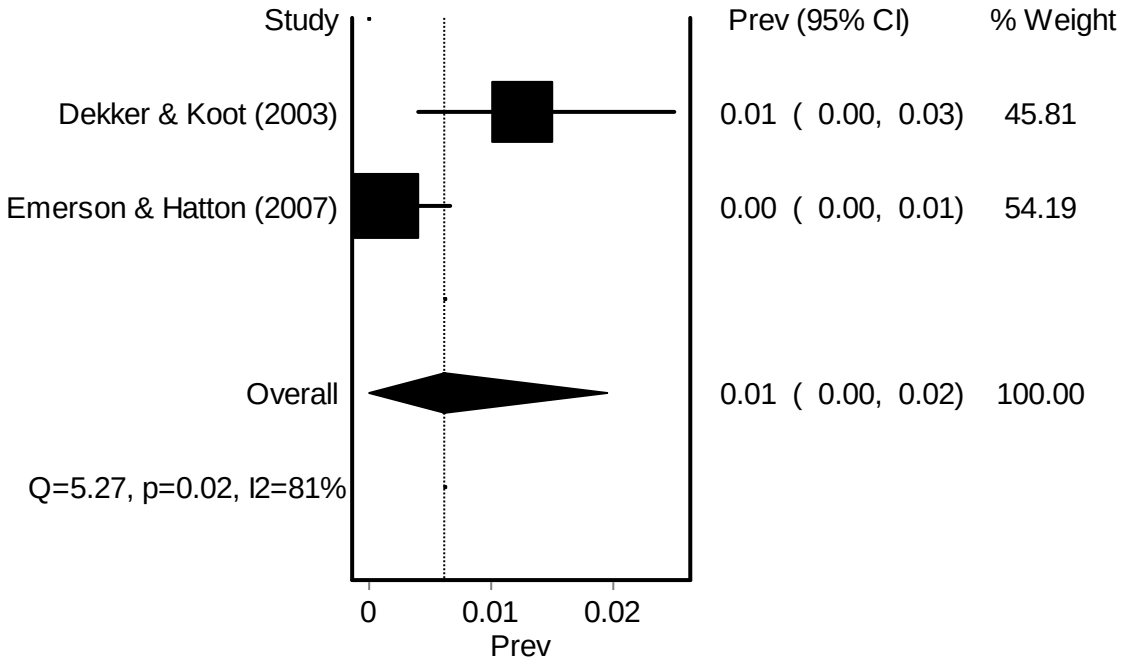
Supplemental Figure 29. Pooled prevalence estimates for panic disorder using the random effects model.



Supplemental Figure 30. Pooled prevalence estimates for panic disorder using the quality effects model.



Supplemental Figure 31. Pooled prevalence estimates for agoraphobia using the random effects model.



Supplemental Figure 32. Pooled prevalence estimates for agoraphobia using the quality effects model.

Online Resource F

Relative Risk and Odds Ratio statistics

Supplemental Table 3. Relative risk of having an anxiety disorder in individuals with WS compared to individuals with ID (95% confidence intervals).

Type of Disorder	Relative Risk
Any anxiety disorder	**4.00*** (2.27-7.06)**
Specific phobias	**5.57*** (2.62-11.86)**
Generalised anxiety disorder	**10.00* (1.30-76.67)**
Separation anxiety disorder	1.75 (0.53-5.79)
Social anxiety disorder	0.50 (0.05-5.43)
Panic disorder	5.00 (0.24-102.9)
Agoraphobia	2.00 (0.18-21.71)

Notes: ***significant at $p<0.0001$, *$p<0.05$

Supplemental Table 4. Odd ratios with 95% confidence intervals of rates of anxiety disorders in WS and ID compared to UK national population estimates (Green, McGinnity, Meltzer, Ford and Goodman 2004).

Type of disorder	Williams Syndrome	Heterogeneous intellectual disability
Any anxiety disorder	**27.05 (8.44-86.74)**	**4.00 (1.14-13.98)**
Specific phobias	**79.28 (8.47-742.13)**	9.33 (0.91-95.97)
Generalised anxiety disorder	**13.78 (1.39-136.75)**	1.25 (0.07-24.01)
Separation anxiety disorder	18.74 (0.76-459.26)	10.38 (0.40-270.90)
Social anxiety disorder	3.36 (0.06-200.45)	6.78 (0.14-317.95)
Panic disorder	10.18 (0.10-1018.2)	0.71 (0.01-83.68)
Agoraphobia	20.39 (0.04-11756.61)	10.09 (0.02-6755.82)
Post-traumatic stress disorder	10.18 (0.10-1018.25)	
Obsessive-compulsive disorder	20.79 (0.23-1870.96)	

Notes: bold=significant

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