Schizophrenia Research 213 (2019) 23–31

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Pituitary volume in individuals at elevated risk for psychosis: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 4 October 2018
Received in revised form 13 December 2018
Accepted 16 December 2018
Available online 29 December 2018

Keywords:
Hypothalamic-pituitary-adrenal (HPA) axis
Stress
Schizophrenia
Prodrome
Cortisol
Review

ABSTRACT

Background: Pituitary volume (PV) abnormalities, representing one of several markers of hypothalamic-pituitary-adrenal (HPA) axis dysregulation, have been observed in psychosis, with variable patterns across illness stages. Typically, enlargements characterise first-episode patients, with reductions observed in those with chronic illness relative to healthy controls. Findings in high-risk populations have been inconsistent, highlighting the need for an updated review of the evidence.

Methods: We searched PubMed, PsycINFO, and EMBASE for studies examining PV in high-risk [clinical high-risk (CHR), family history of psychosis (FHx), schizotypal personality disorder (SPD), and psychotic-experiences (PEs)] and healthy individuals. Random effects models were used to examine group differences in PV (Hedges g) with stratified analyses and meta-regression employed to investigate the effect of high-risk category, transition status, age, sex, and antipsychotic medication.

Results: Ten studies, yielding 11 effect sizes, were eligible for inclusion. Overall, high-risk individuals had significantly larger PV relative to healthy controls ($g = 0.16$ [95% CI: 0.01 to 0.32] $p = 0.04$), despite showing a reduction in whole brain volume ($g = -0.17$, [95% CI. −0.30 to −0.03] $p = 0.020$). Individual sub-group analyses for CHR and FHx groups showed no significant differences relative to controls; however, larger PV increases characterised those who later transitioned to psychosis ($g = 0.55$, [95% CI. 0.06 to 1.04] $p = 0.028$). Larger effect sizes were positively associated with the proportion of high-risk individuals receiving antipsychotic medication.

Conclusions: PV enlargements characterise high-risk individuals and are more pronounced among those who later develop psychosis. We provide recommendations for future studies.

1. Introduction

The neural diathesis-stress model of schizophrenia posits that psychosocial and biological stressors, acting via the hypothalamic-pituitary-adrenal (HPA) axis, may further elevate the risk of psychosis in those with a pre-existing vulnerability (Walker et al., 2008; Walker and Diforio, 1997). Whilst the presence of abnormal cortisol profiles among individuals with, and at elevated risk for, psychosis provides evidence to support the model, methodological complexities (including, psychotropic medications, sex differences, cross-sectional designs, and heterogeneity in cortisol measurements) lead to inconsistent findings (Pruessner et al., 2017). Pituitary gland volume (PV) provides an alternative marker of HPA axis function, with enlargements thought to indicate HPA axis hyperactivity through an increase in the size and number of corticotroph cells producing adrenocorticotropic hormone (Pariante, 2008). Consistent with the elevated basal cortisol levels observed in this population, previous meta-analyses indicate increased PV in those with first-episode psychosis (FEP) relative to healthy individuals (Borges et al., 2013; Nordholm et al., 2013) In contrast, reduced PV has been observed in chronic schizophrenia (Pariante et al., 2004; Upadhyaya et al., 2007), perhaps reflecting pituitary hypoplasia caused by repeated episodes of HPA axis hyperactivity. The extent to which these abnormalities are present among individuals at high-risk for psychosis, however, is currently unclear.

High-risk studies typically examine one of four main groups: (1) clinical high-risk (CHR), also known as ultra high-risk (UHR) or the at-risk mental state (ARMS), predominately characterised by attenuated psychotic symptoms (Fusar-Poli et al., 2013; Yung et al., 2005); (2) family history of psychosis (FHx), typically defined as the presence of a first-degree relative with psychosis [i.e., offspring or siblings of those with psychosis (Niemi et al., 2003)]; (3) schizotypal personality disorder (SPD), characterised by perceptual distortions and eccentric behaviour (American Psychiatric Association, 2013; World Health

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https://doi.org/10.1016/j.schres.2018.12.026
0920-9964/

Organization, 1992); and (4) psychotic experiences (PEs), also known as psychotic-like experiences or subclinical psychotic symptoms (Nelson et al., 2012). Transition rates among these groups are varied. Meta-analytic evidence shows that 36% of individuals at CHR transition to psychosis within the first three years of clinical presentation (Fusar-Poli et al., 2012). Although less extensively studied, similar transition rates (25–40%) have been reported in longitudinal studies of individuals with SPD (Fenton and McGlashan, 1989; Nordentoft et al., 2006; Woods et al., 2009). Lower transition rates have been observed in those with a FHx of illness, with a recent meta-analysis reporting that 12% of individuals with a parent with schizophrenia develop the same illness in adulthood (Rasic et al., 2014). Similarly, whilst longitudinal studies indicate that individuals experiencing PEs (e.g., hallucination- and delusion-like symptoms) are at an increased risk of developing psychosis relative to the general population (Kaymaz et al., 2012), the transition rate is notably lower (0.56%). Establishing whether PV abnormalities characterise some, or all, of these groups is an important step to understanding the role of HPA axis dysregulation in the onset of psychosis.

Previous reviews have provided preliminary evidence for PV abnormalities in high-risk groups. Aiello and colleagues conducted a systematic review of CHR and FHx populations, reporting enlarged PV in both groups (Aiello et al., 2012). Similarly, a subsequent systematic review and meta-analysis reported a trend for larger PV in CHR individuals who later transitioned to psychosis compared to healthy controls (Nordholm et al., 2013); however, FHx and PE groups were not examined. An updated review reported heterogenous findings in CHR, FHx, and SPD groups, with studies reporting that PV was enlarged, reduced, or no different relative to healthy controls (Pruessner et al., 2017). However, studies were not obtained systematically, and no meta-analysis was conducted; thus, the magnitude and consistency of any effects remains unclear. Moreover, important potential confounds such as sex, antipsychotic medication, and transition status were not statistically examined.

Pituitary volume is not the only indicator of HPA axis activity. Meta-analytic evidence shows that basal cortisol levels (one of the most widely-studied indictors of HPA axis function) are elevated among those at CHR (Chaumette et al., 2016), with similar elevations also reported in those with SPD (Mittal et al., 2007; Walker et al., 2001; Weinstein et al., 1999). However, there is less consistent evidence for the cortisol awakening response (CAR), thought to represent the response to a mild, natural stressor (i.e., awakening), independent from basal cortisol. A recent meta-analysis reported that individuals with psychosis and schizophrenia, but not those at CHR, were characterised by a blunted CAR relative to controls (Berger et al., 2016), tentatively suggesting that this aspect of HPA axis dysregulation does not emerge till later in illness. Such findings are consistent with the tonic/phasic model of HPA axis dysfunction (Shah and Malla, 2015) which proposes that the HPA axis may become overwhelmed by chronic hyperactivation (represented by basal cortisol) eventually leading to a maladaptive response to stressors.

Perhaps unsurprisingly, given the contribution of stress to multiple psychiatric disorders, HPA axis dysregulation is not specific to psychosis. Indeed, PV abnormalities have also been reported in bipolar disorder (Delvecchio et al., 2018; Takahashi et al., 2009a), major depression (Kessing et al., 2011), panic disorder (Kartalci et al., 2011), and obsessive-compulsive disorder (Atmaca et al., 2009). Whilst it may be possible to differentiate psychosis from other neuropsychiatric disorders using a combination of PV and other stress-response biomarkers, a psychosis-specific 'stress-signature' has not yet been identified. Determining the extent and nature of pituitary volume abnormalities among individuals at elevated risk for psychosis may help with this endeavour.

Given that research in high-risk groups has burgeoned in recent years, there is a need for an updated review of the evidence in this population. We therefore conducted a systematic review and meta-analysis which aimed to (1) systematically appraise studies examining PV in high-risk individuals and controls; (2) determine the magnitude and consistency of effects using meta-analytic techniques; and (3) formally examine sources of heterogeneity (high-risk definition, transition status, age, sex, and antipsychotic medication exposure) on effect sizes by means of stratified analyses and meta-regression.

2. Method

The protocol for this systematic review and meta-analysis was prospectively registered on PROSPERO (CRD42018108098), our search strategy and reporting complied with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000).

2.1. Search strategy

The search was conducted independently in August 2018 by two researchers (T.S.S. and A.E.C.) within PubMed, PsycINFO, and EMBASE using the following terms: [(((pituitary gland) OR pituitary volume)) AND (((((((((schizotypal personality disorder) OR schizotypy) OR psychotic experiences) OR psychotic-like experiences) OR subclinical psychotic symptoms) OR subclinical psychosis) OR non-clinical psychosis)) OR ((((schizophrenia) OR psychosis)) AND ((((((((((relatives) OR offspring) OR sibling) OR family history) OR genetic risk) OR at risk mental state) OR ultra high risk) OR clinical high risk) OR prodrome) OR high risk)))]. No restrictions were applied for year of publication or language. Reference lists of studies and reviews were manually searched to identify additional studies. Only studies published in peer review journals were included, conference abstracts were excluded.

2.2. Study selection

We included observational studies (case-control) which compared pituitary gland volumes in those at high-risk for psychosis and controls. We defined "high-risk" participants as those who met criteria for "clinical high-risk" for psychosis [also known as "ultra high-risk" or individuals with an "at-risk mental state"; (Yung et al., 2005)], individuals at familial risk for psychosis (defined by a family history of the illness; FHx), those who met diagnostic criteria for schizotypal personality disorder (SPD), or youth who presented with psychotic-experiences (also known as psychotic-like experiences or non-clinical psychotic symptoms). Studies with no control group or overlapping samples were excluded (where we included the larger study sample). A.E.C and T.S.S double rated studies for inclusion/exclusion, study authors were contacted where necessary to resolve disagreements.

2.3. Data extraction

Two researchers (T.S.S and A.E.C.) independently extracted data from eligible studies. This included: year of publication, sample size, mean age of participants, participant sex, percentage of participants who received antipsychotic medication, recruitment method, high-risk definition, pituitary gland tracing software, PV mean and standard deviation (SD) per group, and mean and SD for whole brain volume (WBV) or total intracranial volume (TIV). The researchers were not blind to the names of authors, journals, or institutions. To pool data within studies reporting effect sizes separately for males and females, we extracted raw data and computed a combined mean and pooled SD using the Hedge's method for calculating SDs (Hedges, 1981). We contacted authors via email where information was missing (Habets et al., 2012; Mondelli et al., 2008; Nordholm et al., 2018; Romo-Nava et al., 2013; Takahashi et al., 2009b, 2013) and all but one responded and provided the necessary information. Any

discrepancies in data extraction were resolved by discussion and joint data extraction/computation.

2.4. Assessment of studies

Eligible studies were assessed for quality independently by both researchers (T.S.S. and A.E.C.) using a modified version of the Newcastle-Ottawa scale [NOS (Wells et al., 2011)]. with discrepancies resolved by discussion. The NOS is a quality appraisal tool for case-control and cohort studies. The NOS covers eight domains including participant selection, case definition, matching factors, and exposure ascertainment. Items were modified assess domains pertinent to the meta-analysis (see Table 2), each item was rated as 0 or 1 yielding a maximum score of eight for each study.

2.5. Statistical analyses

Meta-analyses and meta-regression analyses were conducted using Stata version 15 (metan and metareg commands, respectively). Random-effects models were used for all analyses as we assumed the 'true effect' would differ across studies owing to the fact that studies examined different high-risk groups of varying ages. Inverse weighting was applied for all analyses (DerSimonian and Laird, 1986). Standardised mean differences (SMD) in PV and WBV/TIV between high-risk individuals and healthy controls were derived with Hedges' *g* adjustment (Hedges, 1981). Statistical significance for all analyses was set at $p < 0.05$ (two-tailed). Heterogeneity was assessed via the Cochran Q statistic (to identify statistically significant heterogeneity) and the I^2 statistic (to estimate the percentage of the variability in effect sizes owing to heterogeneity) where classification of the latter as likely unimportant (0–40%), moderate (30%–60%), substantial (50%–90%), or considerable (75%–100%) was dependent on the magnitude and/or direction of effects and statistical significance of heterogeneity (Higgins et al., 2008). Small sample bias was assessed visually by means of a funnel plot.

In our primary analyses, we compared PV in all high-risk groups and healthy controls. Sub-group analyses were then conducted for individual high-risk groups where more than three effect sizes were available. We additionally examined PV differences between high-risk participants who later transitioned to psychosis and healthy controls. Univariable meta-regression analyses were then performed to examine the effect of demographic variables (age, sex, and antipsychotic medication exposure) on the SMDs for PV. For whole brain volume, we first examined SMDs in WBV/TIV between all high-risk groups and healthy controls. For each study, we then extracted all data-points (i.e., data for both the high-risk and healthy control group, which were treated as separate rows) to conduct meta-regression analyses examining the effect of WBV/TIV on PV.

3. Results

3.1. Search strategy

Sixty-nine studies were identified in the initial search. After screening studies for eligibility (see Fig. 1), 10 met criteria for inclusion in the meta-analysis (Büschlen et al., 2011; Cullen et al., 2015; Garner et al., 2005; Habets et al., 2012; Mondelli et al., 2008; Nordholm et al., 2018; Romo-Nava et al., 2013; Shah et al., 2015; Takahashi et al., 2009b, 2013), yielding 11 effect sizes. Study details are provided in Table 1.

3.2. Study characteristics

3.2.1. Sample size and demographic factors

Sample sizes of included studies ranged from 44 to 143; the total number of high-risk and healthy individuals was 449 and 464

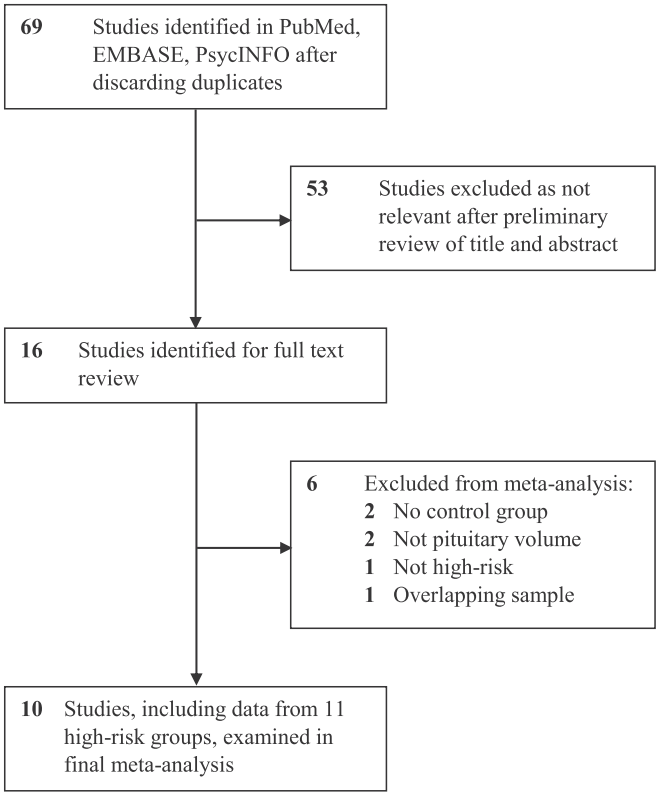

Fig. 1. Search process.

respectively. Only one study conducted a power analysis (Habets et al., 2012). Most studies included a mix of males and females.

3.2.2. Group status and high-risk definitions

Four studies examined participants at CHR (Büschlen et al., 2011; Garner et al., 2005; Nordholm et al., 2018; Takahashi et al., 2013), four included individuals with a FHx of psychosis (Cullen et al., 2015; Habets et al., 2012; Mondelli et al., 2008; Shah et al., 2015), two examined participants with SPD (Romo-Nava et al., 2013; Takahashi et al., 2009b), and one included a high-risk group of youth reporting psychotic-like experiences in combination with other well-established antecedents of schizophrenia (Cullen et al., 2015).

All four studies of CHR individuals used the Personal Assessment and Crisis Evaluation [PACE (Yung et al., 2007)] criteria to define the high-risk group, employing tools such as the Comprehensive Assessment of the At-Risk Mental States (Yung et al., 2005) or The Basel Screening Instrument for Psychosis (Riecher-Rossler et al., 2008). The PACE criteria define an individual at-risk for psychosis if they meet one or more of the following criteria: (a) attenuated psychotic symptoms; (b) brief limited intermitted psychotic symptoms; or(c) trait and state risk factor (those with SPD or a first-degree relative with a psychotic disorder and a significant decrease in functioning in the past year). All CHR participants in these studies were help-seeking individuals recruited from specialist early intervention services which provided treatments aimed at reducing the risk of psychosis in this population.

Three FHx studies examined individuals with a first-degree relative with a psychotic disorder (Habets et al., 2012; Mondelli et al., 2008) or schizophrenia/schizoaffective disorder (Shah et al., 2015) and one study included children who had either a first- or second-degree relative with schizophrenia/schizoaffective disorder (Cullen et al., 2015). Individuals with a FHx of illness were recruited using a variety of methods, including advertisements placed in inpatient units/outpatient clinics, online advertisement, support

Table 1
Characteristics of studies examined in the systematic review and meta-analysis.

Study	N and risk group	% Male	Age (years)	Recruitment method	% Treated antipsychotics	Adjustment factors	Mean PV (SD), mm3	Software
Büschlen et al., 2011	20 HC	65%	22.9	Outpatient clinic for UHR	0%	Sex	470 (83)	Manually traced in AMIRA.
	36 CHR	58%	24.9		11%		505 (74)	
Cullen et al., 2015	32 HC	47%	13.0	Community-screening procedure from schools at ages 9–12	0%	IQ, sex, ethnicity, SES, pubertal status, weight	441 (200)	Manually traced in Measure (v0.08).
	30 ASz	67%	13.1		0%		419 (160)	
	22 FHx	50%	13.3		0%		448 (189)	
Garner et al., 2005	49 HC	65%	20.2	Admissions to PACE clinic	0%	Sex	542 (98)	Manually traced using ANALYZE 7.5.
	94 CHR	62%	19.8		0%		527 (147)	
Habets et al., 2012	32 HC	31%	32.9	Outpatient clinics and inpatient units	0%	Age, Sex, intracranial volume, oestrogen exposure, scan type	624 (102)	Manually traced using GIANT.
	37 FHx	38%	28.3		0%		625 (106)	
Mondelli et al., 2008	46 HC	48%	39.7	Support groups, internet, and referral from mental health services	0%	Age, sex	611 (138)	Manually traced using ANALYZE 7.5.
	44 FHx	41%	49.7		0%		661 (123)	
Nordholm et al., 2018	43 HC	58%	24.7	Mental health centre and online advertisements	0%	Age, sex	731 (134)	Manually traced in Measure (v. 0.08).
	39 CHR	43%	23.9		17%		753 (183)	
Romo-Nava et al., 2013	67 HC	73%	30.2	Newspaper advertisements	0%	Age, years of education, SES, whole brain volume	718 (171)	Manually traced using 3D Slicer.
	40 SPD	50%	29.4		0%		696 (159)	
Shah et al., 2015	40 HC	35%	16.6	Inpatient units and outpatient clinics	0%	Age, sex, intracranial volume	623 (118)	Images analysed using 3D Slicer.
	38 FHx	47%	16.6		0%		655 (96)	
Takahashi et al., 2009b	81 HC	57%	24.5	Neuropsychiatry clinics	0%	Age, sex, height, parental education	706 (128)	Manually traced using Dr View 5.3.
	47 SPD	62%	25.0		85%		775 (129)	
Takahashi et al., 2013	22 HC	50%	19.4	Clinic for young people at-risk for psychosis	0%	Age, sex	697 (143)	Manually traced using Dr View 5.3.
	22 CHR	50%	19.1		18%		763 (124)	

Note. HC: healthy control; CHR: clinical high-risk; FHx: family history; ASz: antecedents of schizophrenia; PV: pituitary volume; SD: standard deviation; PACE: Personal Assessment and Crisis Evaluation; SES: socioeconomic status.

groups, and referrals from mental health services (Mondelli et al., 2008; Habets et al., 2012; Shah et al., 2015). One study (Cullen et al., 2015) recruited FHx participants using a novel, community screening method in which caregivers of children aged 9–12 years completed a questionnaire which included items assessing child and family mental health difficulties, subsequently confirmed at interview. This approach was coupled with reviewing medical records of mental health service users with schizophrenia or schizoaffective disorder to identify patients with a child relative aged 9–12 years.

SPD studies either used the Diagnostic and Statistical Manual of Mental Disorders [5th ed.; DSM-5 (American Psychiatric Association, 2013)] criteria for SPD (Romo-Nava et al., 2013) or the International Classification of Diseases and Related Health Problems [10th ed.; ICD-10; (World Health Organization, 1992)] research criteria (Takahashi et al., 2009b). The recruitment methods employed in the two studies of SPD individuals varied greatly; whilst Romo-Nava and colleagues recruited participants from the general population via newspaper advertisements, participants in the study by Takahashi et al. were patients visiting a hospital-based neuropsychiatric clinic. As such, these help-seeking SPD individuals requiring clinical care were likely more impaired and unwell compared to those examined in the former study. One study also defined high-risk as participants who report PEs and other antecedents of schizophrenia [ASz; (Cullen et al., 2015)]. Whilst this study used a novel, community screening method (questionnaires completed by the child at school and the caregiver at home) to recruit children who presented well-replicated antecedents of illness (Laurens and Cullen, 2016), in the absence of longitudinal follow-up data, the degree of risk conferred by the antecedent triad is unclear.

3.2.3. Matching

As shown in Table 1, only half of the studies included in the review matched high-risk and healthy individuals on demographic factors likely to influence PV. Two CHR studies (Nordholm et al., 2018; Takahashi et al., 2013), two FHx (Habets et al., 2012; Shah et al., 2015) and one SPD study (Takahashi et al., 2009b) matched participants on age and sex, whilst Habets and colleagues additionally matched FHx and healthy control groups on level of education. The remaining studies did not match high-risk participants and controls on any variables, but nonetheless adjusted for demographic factors such as sex in analyses comparing PV.

3.2.4. Age

The majority of studies examined a wide age range of at-risk adolescents and young adults (up to a mean age of 29.4); however, one study examined adolescents within a narrower age range (mean age of 13 years old; Cullen et al., 2015), and one study used participants with the mean ages of 39.7 and 49.7 for the controls and FHx groups respectively (Mondelli et al., 2008). Given that the peak age of psychosis risk is in late adolescence/early adulthood, the extent to which participants in the study by Mondelli and colleagues remained at risk is unclear.

3.2.5. Adjustment for whole brain volume or intracranial volume

All ten studies included in the review included a measurement of whole brain volume (WBV = 5) or total intracranial volume (TIV = 6) and all adjusted for these measures in analyses examining PV.

3.2.6. Pituitary gland volume measurement

Investigators measuring pituitary gland volumes were blind to group status in all studies. As reported in Table 1, there was variation in the software used to measure PV; two studies used the Measure v0.08 software, which implements a point-counting method to ascertain volume, two studies used ANALYZE 7.5, two used 3D, two used Dr View 5.3, one used AMIRA, and one used GIANT. All studies used the same protocol when tracing pituitary glands which excludes the pituitary stalk but includes the posterior pituitary gland and the borders of the anterior and posterior pituitary (Sassi et al., 2001). Only one study reported the training procedures of the researcher tracing pituitary glands (Cullen et al., 2015). All studies, except for one (Mondelli et al., 2008), reported intra-rater reliability and all bar two reported inter-rater reliability (Cullen et al., 2015; Habets et al., 2012).

3.2.7. Transition to psychosis and follow-up

Three CHR studies (Büschlen et al., 2011; Garner et al., 2005; Takahashi et al., 2013) and one FHx study (Shah et al., 2015) followed participants to examine transition to psychosis. Reported mean follow-up periods were 1.1 years (Garner et al., 2005), 1 to 3 years (Shah et al., 2015), and 1.3 years (Takahashi et al., 2013). Büschlen

and colleagues reported the mean follow-up time for participants who transitioned to psychosis only at 12.3 months. Given that meta-analytic evidence suggests transition rates among CHR individuals are 22% within one year, 29% after 2 years, and 36% after three years (Fusar-Poli et al., 2012), these follow-up periods are unlikely to capture all individuals who may have transitioned to psychosis.

3.2.8. Study quality assessment

Study quality ratings are provided in Table 2; the mean rating for all 10 studies was 4.9 (with the maximum possible rating being 8). The mean rating was 4.8 for CHR studies, 4.8 for FHx studies, and 5.5. for SPD studies. In terms of group selection, all studies adequately defined cases using validated tools; however, no studies assessed the representativeness of the high-risk group (i.e., whether those recruited were representative of the target population). Few studies ensured controls were representative, for example, three studies included hospital staff or university students in their control groups (Garner et al., 2005; Takahashi et al., 2009b, 2013). In terms of group comparability, as previously mentioned above, only half of the included studies matched participants on demographic factors. Four studies also failed to confirm that controls did not have the outcome of interest as either a full diagnostic interview was not performed (Nordholm et al., 2018; Takahashi et al., 2013), or family history was not recorded (Habets et al., 2012; Shah et al., 2015). For ascertainment of exposure, all studies used a robust method for measuring pituitary volume (i.e., MRI scans with PV manually traced by a blinded researcher) and all but one study used the same method of ascertaining exposure in both cases and controls. Specifically, Romo-Nava and colleagues reported using a different scanner for some controls, with no assessment of comparability (Romo-Nava et al., 2013). With regards to response rate, this refers to the proportion of individuals who were invited to participate in the study and subsequently agreed to. Only one study partially reported response rates (Cullen et al., 2015). The authors provided information on the number of people approached who subsequently participated in the overarching longitudinal study but did not provide information on the proportion of people approached who subsequently completed MRI scanning.

3.3. Meta-analysis of pituitary gland volume

3.3.1. Comparison of pituitary gland volume in high-risk individuals and healthy controls

A random-effects model indicated a significant overall difference in PV between high-risk and healthy individuals ($g = 0.16$ [95% CI: 0.01 to 0.32] $p = 0.04$), representing a small increase in PV in the former (see Fig. 2 and Table 3). Between-study heterogeneity was small ($I^2 = 28\%$) and not statistically significant ($p = 0.18$ for Cochran's Q). Visual inspection of the funnel plot showed no evidence of asymmetry, indicating that the results were not influenced by small sample bias (see Supplementary Fig. 1).

3.3.2. Comparison of pituitary gland volume in high-risk subgroups and healthy controls

Subgroup analyses were performed for individual high-risk groups where more than three studies were available (see Table 3). Random effects models indicated that when examined in isolation, there were no significant differences in PV between CHR participants ($g = 0.17$ [95% CI = −0.12 to 0.45] $p = 0.25$), or FHx participants ($g = 0.20$ [95% CI. −0.03 to 0.43] $p = 0.09$), relative to healthy controls. For both sub-group analyses, heterogeneity estimates were small ($I^2 = 32.5\%$ and 0%, respectively) and not statistically significant (p for Cochran's Q > 0.05 for both).

3.3.3. Comparison of pituitary gland volume in high-risk individuals who transitioned to psychosis and healthy controls

Four studies (Büschlen et al., 2011; Garner et al., 2005; Shah et al., 2015; Takahashi et al., 2013) provided baseline PV data for high-risk individuals who later transitioned to psychosis; random effects models were used to compare mean PV among those who transitioned to psychosis and healthy controls (Table 3). As shown in Fig. 3, baseline PV was significantly increased in the group who later transitioned to psychosis relative to healthy controls ($g = 0.55$, [95% CI. 0.06 to 1.04] $p = 0.028$). Whilst moderate between-study heterogeneity was detected ($I^2 = 48.4\%$), estimates were not statistically significant (p for Cochran's Q = 0.12).

3.3.4. Effect of demographic factors on pituitary volume differences

Individual meta-regression analyses were conducted to examine the effects of demographic variables (age, sex and antipsychotic medication) on SMDs (Hedges' g) for PV. For each study, we calculated the mean age (years) for the total sample, proportion male for the total sample, ratio of the proportion male in high-risk individuals vs. controls, and the proportion of the high-risk group prescribed antipsychotic medication.

Analyses indicated that SMDs were not significantly associated with mean age in the total sample ($B = 0.01$, [95% CI: −0.02 to 0.03], $p = 0.52$), proportion male in the total sample ($B = -0.57$, [95% CI: −2.63 to 1.49], $p = 0.55$), or the ratio of the proportion of males in the high-risk group relative to healthy controls ($B = -0.15$, [95% CI: −0.98 to 0.68], $p = 0.70$). In contrast, there was a significant association between medication status and the SMD for pituitary gland volume ($B = 0.58$, [95% CI: 0.04 to 1.12], $p = 0.038$). Results indicated that as the proportion of high-risk individuals with antipsychotic medication exposure increased, the larger the difference in PV between high-risk individuals and healthy controls. Visual inspection of the regression plot (see Supplementary Fig. 2) indicated the presence of one extreme outlier (Takahashi et al., 2009b) in which 85% of individuals with SPD were treated with antipsychotic medication. After excluding this study, there was no longer a significant association between medication status and PV SMD ($B = 1.56$, [95% CI: −0.95 to 4.07], $p = 0.19$).

Table 2
Study quality ratings.

Author	Adequate HR definition (Max 1)	HR group representative (Max 1)	Selection of HC unbiased (Max 1)	HC status confirmed (Max 1)	HR and HC matched (Max 1)	PV measure blinded (Max 1)	PV method same in HR and HC (Max 1)	Response rate reported (Max 1)	Total quality score (Max 8)
Büschlen et al., 2011	1	0	1	1	0	1	1	0	5
Cullen et al., 2015	1	0	0	1	0	1	1	1	5
Garner et al., 2005	1	0	0	1	0	1	1	0	4
Habets et al., 2012	1	0	0	0	1	1	1	0	4
Mondelli et al., 2008	1	0	1	0	1	1	1	0	5
Nordholm et al., 2018	1	0	1	0	1	1	1	0	6
Romo-Nava et al., 2013	1	1	1	1	0	1	0	0	5
Shah et al., 2015	1	0	1	0	1	1	1	0	5
Takahashi et al., 2009b	1	1	0	1	1	1	1	0	6
Takahashi et al., 2013	1	0	0	0	1	1	1	0	4

Note. HR: high-risk; HC: healthy control; PV: pituitary volume.

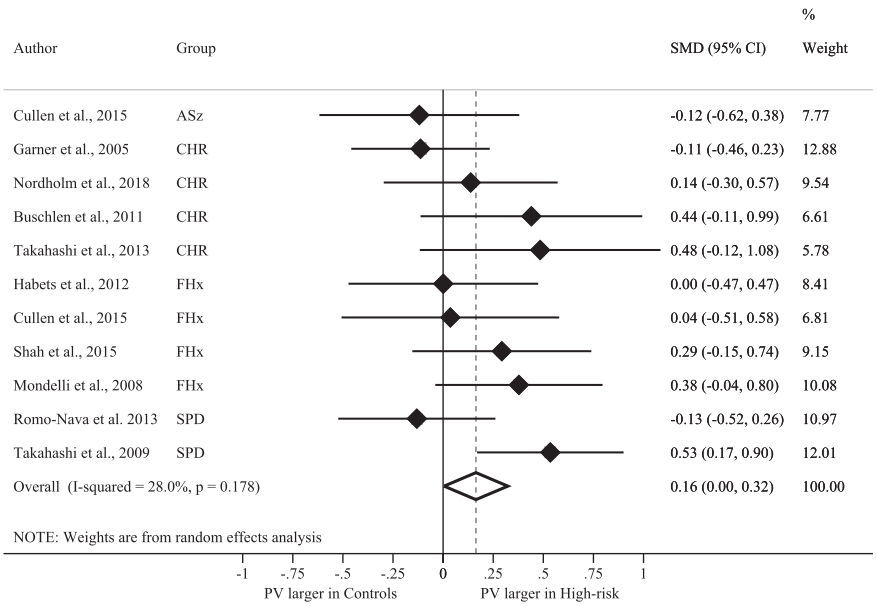

Fig. 2. Forest plot results of primary meta-analysis examining pituitary gland volume in all high-risk individuals versus healthy controls.
Abbreviations: ASz; antecedents of schizophrenia; CHR: clinical high-risk; FHx: family history of psychosis; SPD: schizotypal personality disorder; SMD: standardised mean difference; CI: confidence interval; PV: pituitary volume.

3.4. Meta-analysis of whole brain volume

3.4.1. Comparison of whole brain volume in high-risk individuals and healthy controls

Mean WBV/TIV values were obtained for high-risk individuals and healthy controls from all studies bar one (Habets et al., 2012); this study measured TIV but did not provide raw data which could be used in analyses. A random-effects meta-analysis (see Fig. 4) performed on SMDs indicated a significant decrease in WBV/TIV among the high-risk group relative to healthy controls ($g = -0.17$, [95% CI. -0.30 to -0.03] $p = 0.020$) where there was no evidence of between study heterogeneity ($I^2 = 0.0\%$, p for Cochran's Q = 0.49).

3.4.2. Meta-regression of whole brain volume on pituitary volume

Meta-regression analyses were conducted using all group-level data (i.e., for each study, we used the mean WBV/TIV for both the high-risk and healthy control group such that each study contributed two rows of data) to examine the effect of WBV/TIV on PV. Across the total sample (20 observations), WBV/TIV was negatively associated with PV ($B = -0.20$, [95% CI. −0.37 to −0.05] $p = 0.015$) indicating that larger WBV/TIV was correlated with smaller PV (see Supplementary Fig. 3). There was no change to the pattern of results (i.e., the negative correlation observed) when analyses were conducted in high-risk and healthy control groups separately (data not shown).

4. Discussion

This is the first meta-analysis to examine pituitary volume in all high-risk groups (CHR, FHx, SPD, and PEs), and the first to systematically examine potential confounders such as sex, transition status, and medication. Overall, high-risk individuals showed enlarged PV relative to healthy controls ($g = 0.16$), with even larger increases observed among high-risk individuals who later transitioned to psychosis ($g = 0.55$). This pattern emerged despite high-risk individuals being characterised by reduced WBV ($g = -0.17$). Meta-regression indicated no significant effect of age or sex on PV differences; antipsychotic medication was associated with larger effect sizes although this finding was driven by one study of SPD individuals in which a high proportion had received treatment.

4.1. Findings from the meta-analysis

Our findings are broadly in line with earlier systematic reviews (Aiello et al., 2012) and meta-analyses (Nordholm et al., 2013) examining PV in high-risk populations. Our finding of increased PV in individuals at high-risk for psychosis is also consistent with that observed in FEP patients in the meta-analysis by Nordholm and colleagues, although our effect size is considerably smaller (SMD = 0.16 vs. 0.39, respectively). This pattern contrasts with the reduced PV found in those with established illness (Pariante et al., 2004; Upadhyaya et al., 2007). Taken together, these results tentatively suggest that PV enlargements (implying hyperactivity of the HPA axis) precede the onset of psychosis, increase in magnitude during the first episode of the illness, then reduce following multiple psychotic episodes, perhaps via a process of negative feedback driven by hyperproduction of cortisol (Pariante, 2008). Importantly, our analyses demonstrate that this increase in PV in high-risk individuals occurs despite a corresponding decrease in WBV, which was itself, negatively associated with PV. Moreover, there was no evidence of significant or substantial heterogeneity or any indication that the results were influenced by small sample bias.

Table 3
Results of meta-analyses examining mean differences in pituitary volume in high-risk individuals and healthy controls.

	No. ES	HR (N)	HC (N)	SMD	(95% CI)	*P*	Q (*p*)	I^2
HR vs. HC	11	449	464	0.16	−0.01 to 0.32	0.04	0.18	28.0%
Subgroup analyses								
CHR vs. HC	4	191	134	0.17	(−0.12 to 0.45)	0.25	0.22	32.5%
FHx vs. HC	4	141	150	0.20	(−0.03 to 0.43)	0.09	0.59	0.0%
Transitioned vs. HC	4	59	131	0.55	(0.06 to 1.04)	0.03	0.12	48.4%

Note. HR: high-risk; HC: healthy control; CHR: clinical high-risk; FHx: family history; ES: effect-sizes; N: total N; CI: confidence interval; Q Cochran's Q.

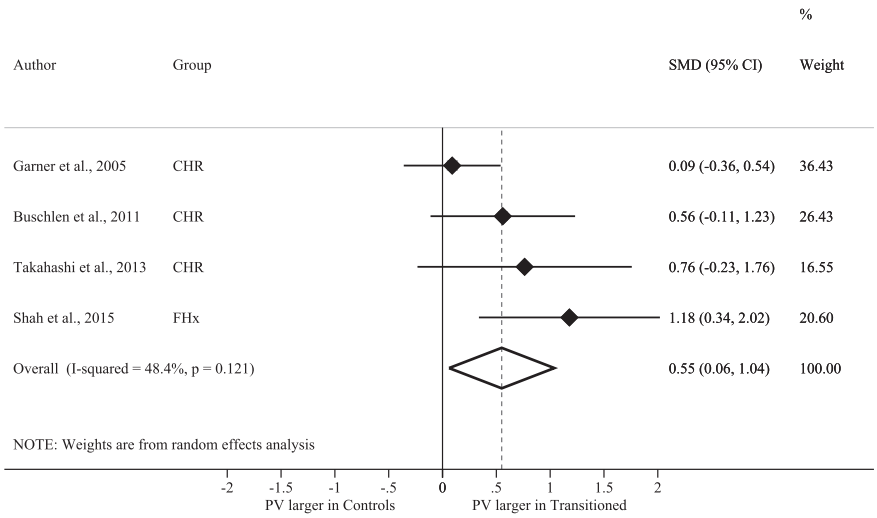

Fig. 3. Forest plot of sub-group meta-analysis examining pituitary gland volume in high-risk individuals who subsequently transitioned to psychosis versus healthy controls.
Abbreviations: CHR: clinical high-risk; FHx: family history of psychosis; SMD: standardised mean difference; CI: confidence interval; PV: pituitary volume.

When examining high-risk groups individually, we found no significant difference in PV between healthy controls and CHR or FHx groups, even though effect sizes in these subgroups were larger (SMD: 0.17 and 0.20, respectively) than the overall effect size that we derived. This perhaps reflects reduced statistical power given the small number of studies included in these sub-analyses. Alternatively, the lack of differences across subgroups could imply a pluripotent mechanism, whereby PV enlargement among high-risk individuals is independent of the criteria used to define high-risk status. In contrast, transition status appears to be an important determinant of PV. Consistent with a previous meta-analysis, high-risk individuals who later transitioned to psychosis had significantly increased PV relative to controls, equating to a moderate effect size (SMD: 0.55). This difference in magnitude likely reflects the fact that high-risk strategies inevitably capture many individuals who will not go on to develop psychosis, leading to an attenuated effect size. It is important to note that the 'transitioned' group includes a broad range of psychotic disorder outcomes. In the study by Takahashi et al. (2013), all individuals in the transitioned group (among whom increased PV was observed) developed schizophrenia at follow-up. In contrast, Garner et al. (2005) reported that the PV enlargements observed among those who transitioned to psychosis were specific to those who developed affective psychosis, which is consistent with previous studies showing PV enlargements in affective disorders (Kessing et al., 2011; Takahashi et al., 2009a). Taken together, these findings suggest that PV enlargement may be a marker of illness severity rather than psychosis per se.

A previous meta-analysis employing meta-regression techniques observed that the SMD for PV was significantly associated with the percentage difference in females across patients and controls and the percentage of subjects receiving antipsychotic medication (Nordholm et al., 2013). In contrast, we found no effect of age or sex (regardless of whether we examined the proportion male in the total sample or the ratio of males in high-risk vs. controls) on the pooled SMD. Moreover, the significant effect we observed for antipsychotic medication was attributable to one study (Takahashi et al., 2009b) where 85% of SPD patients were treated with antipsychotics. It is possible that the statistically significant effect of antipsychotic medication that we initially observed (prior to excluding the study by Takahashi and colleagues) is confounded by transition status. Unfortunately we were unable to assess this as only one study reported information on medication rates among those who did and

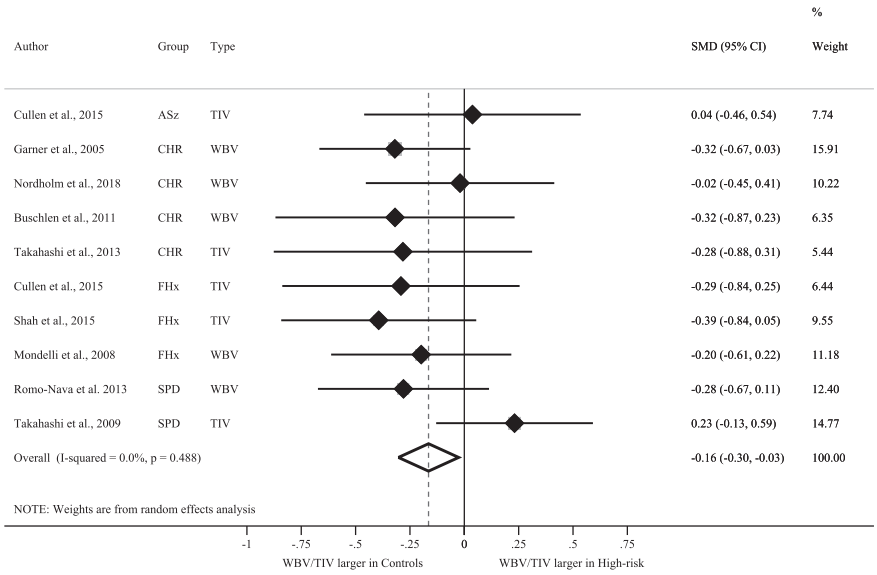

Fig. 4. Forest plot of meta-analysis examining whole brain volume in all high-risk individuals versus healthy controls.
Abbreviations: ASz; antecedents of schizophrenia; CHR: clinical high-risk; FHx: family history of psychosis; SPD: schizotypal personality disorder; TIV: total intracranial volume; WBV: whole brain volume; SMD: standardised mean difference; CI: confidence interval.

did not transition to psychosis (Büschlen et al., 2011), where of the four CHR individuals who were treated with antipsychotics, only two subsequently transitioned.

The fact that our meta-regression analyses (in contrast to those performed by Nordholm and colleagues for FEP studies) showed that age, sex, and medication status were not robustly associated with effect sizes, may reflect the fact that our estimate of heterogeneity was far lower ($I^2 = 28\%$ vs. 77%, respectively). The reduced between-study variability in effect sizes may have impacted on our ability to detect meaningful relationships with confounding factors.

4.2. Findings from the systematic review

Whilst heterogeneity estimates were small and not statistically significant, our systematic review indicated substantial variability in methodology across studies. Only half of the studies matched groups on demographic factors, although all remaining studies adjusted for participant sex. There were also considerable differences in the definitions and methods used to estimate of WBV, with a greater proportion instead measuring TIV. The overall quality of studies included in this meta-analysis was moderate, with a mean rating of just 4.9 (8 representing the total maximum score).

Most studies failed to ensure the representativeness of their samples. This limits the extent to which sampling bias can be assessed, and it is possible that high-risk individuals who complete MRI scans are less symptomatic and functionally impaired than those who do not. As such, the extent to which studies of PV are generalisable to all high-risk individuals may be limited. Four studies did not conduct a full diagnostic interview or obtain family history of psychosis in controls and so the presence of risk factors (i.e., psychotic experiences or genetic liability) cannot be ruled out in these groups.

With regards to high-risk definitions, there was greater consistency in CHR studies compared to FHx and SPD studies. All CHR studies used the PACE criteria to define a high-risk group. In contrast, FHx studies varied on the degree of relatedness and extent to which they were truly 'at-risk' for psychosis; for example, Cullen et al. (2015) included children with both first- and second-degree relatives (Cullen et al., 2015), whilst Mondelli and colleagues (Mondelli et al., 2008) examined first-degree relatives, the majority of whom were parents of patients (and therefore unlikely to develop psychosis as they had passed the peak age of psychosis risk). Similarly, SPD studies employed both clinical (Takahashi et al., 2009b) and non-clinical (Romo-Nava et al., 2013) populations. The software used to measure PV also varied substantially, with six different packages used across the 10 studies. However, one major strength, was that all studies specified the protocol used and ensured that all raters were blinded to group status.

4.3. Limitations and recommendations

Whilst this is the largest review of PV in individuals at high-risk for psychosis, there were insufficient numbers of studies for each high-risk group to permit more robust analyses comparing effect sizes across individual groups. A further limitation is that effect sizes were calculated from raw means and standard deviations, with no adjustment made for potentially important confounding variables. Nevertheless, we investigated the effect of these variables using meta-regression techniques Additionally, all studies used manual tracing of pituitary volume which can be open to human error. Although methods for ascertaining pituitary volume using automated techniques are beginning to be developed (Wong et al., 2014), these techniques are in their infancy and have not yet been validated or implemented in research settings. A final limitation is that an independent academic librarian was not included to validate search terms and overall search strategy. However, we took several steps to ensure that the search procedure was robust, such as using the same search terms employed in previous systematic reviews of pituitary volume in high-risk individuals plus additional terms (e.g., subclinical psychotic symptoms) to capture other high-risk groups. The search was also conducted independently by both the senior and first author, and all eligible studies as well as previous reviews/meta-analyses were manually reviewed to ensure all relevant studies were obtained.

To improve study quality and reduce the risk of bias, we recommend that future studies (1) adopt more consistency in defining high-risk groups, (2) report non-response rates for all groups, (3) match groups on, or adjust for, potential confounders including age, sex, and antipsychotic medication, (4) report both WBV and TIV to facilitate pooling of data across studies, (5) identify a gold-standard software and procedure for measurement of pituitary volume, and (6) conduct longitudinal follow-ups with repeated measurements of pituitary volume as such studies have indicated an increase in PV over time among high-risk individuals (Takahashi et al., 2011). We also suggest that studies should consider other potentially important confounders, such as trauma and substance use. Whilst both have a higher prevalence in high-risk individuals relative to controls (Buchy et al., 2015; Fusar-Poli et al., 2017), these factors are often not reported in studies examining PV. Finally, future research could benefit from examining the correspondence between PV and cortisol. Few studies currently have measured both concurrently (Nordholm et al., 2018; Thompson et al., 2007), but this may help to fully understand the importance of PV and its impact on HPA axis functioning.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.12.026.

Conflicts of interest

All authors declare that they have no financial relationships with commercial interests.

Funding

Dr. Cullen is funded by a Sir Henry Wellcome Postdoctoral Fellowship (107395/Z/15/Z). All authors are affiliated with the NIHR Specialist Biomedical Research Centre (BRC) for Mental Health at the South London and Maudsley National Health Service Foundation Trust and Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom.

Acknowledgements

The authors are grateful to Drs Nordhom, Romo-Nava, Takahashi, and Shah for providing additional data for inclusion in the review.

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