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REVIEW

# Pituitary gland volume in patients with schizophrenia, subjects at ultra high-risk of developing psychosis and healthy controls: A systematic review and meta-analysis



Dorte Nordholm<sup>a,b,\*</sup>, Jesper Krogh<sup>a</sup>, Valeria Mondelli<sup>c</sup>,  
Paola Dazzan<sup>c</sup>, Carmine Pariante<sup>c</sup>, Merete Nordentoft<sup>a</sup>

<sup>a</sup> Mental Health Center Copenhagen, Faculty of Health Science, University of Copenhagen, Denmark

<sup>b</sup> Lundbeck Foundation Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Mental Health Center Glostrup, Denmark

<sup>c</sup> Institute of Psychiatry, Kings College London, London, UK

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## KEYWORDS

Pituitary;  
HPA axis;  
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MRI;  
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Meta-analysis

## Summary

**Background:** A larger pituitary size is thought to reflect a greater activation of the hypothalamic–pituitary–adrenal (HPA) axis, which may be related to an increase in the number and size of corticotroph cells. Some studies, but not all, indicate that pituitary volume increases before or at the onset of psychosis. There is a need for a critical appraisal of the literature on this topic accompanied by a meta-analytical evaluation of the data.

**Methods:** We included studies comparing the volume of the pituitary gland in healthy controls and patients with schizophrenia, first episode of psychosis (FEP), schizotypal disorder or ultra high-risk (UHR) subjects. We defined three groups of subjects for the analyses: healthy controls; UHR and schizotypal patients; and patients diagnosed with first episode of psychosis, schizophrenia or schizoaffective disorder.

**Results:** Ten studies were included in the meta-analysis. We found a trend of a larger pituitary volume in both UHR subject who had transition to psychosis ( $p = 0.05$ ) and in FEP subjects ( $p = 0.09$ ) compared to healthy controls. There was no difference in pituitary volume between patients with schizophrenia combined with FEP versus healthy controls ( $p = 0.52$ ) or between UHR (with and without transition) and healthy controls ( $p = 0.24$ ). In a regression analysis, we demonstrated that the number of subjects receiving antipsychotics and pituitary volume were positively correlated. As previously reported in other samples, gender also had an impact on pituitary volume with females presenting with a larger mean volume.

\* Corresponding author at: Mental Health Center Copenhagen, Research Unit, Bispebjerg Bakke 23, 13A, 2400 Copenhagen NV, Denmark. Tel.: +45 60 40 78 30.

E-mail address: [dorte.nordholm@regionh.dk](mailto:dorte.nordholm@regionh.dk) (D. Nordholm).

*Conclusion:* Results from this meta-analysis suggest that the pituitary gland could be increasing before the onset of psychosis. Both gender and use of antipsychotics have a major impact on the pituitary volume.

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## Contents

1. Introduction . . . . .	2395
2. Method . . . . .	2396
2.1. Data sources . . . . .	2396
2.2. Study selection . . . . .	2396
2.3. Data extraction . . . . .	2396
2.4. Assessment of studies . . . . .	2396
2.5. Contact with authors . . . . .	2396
2.6. Statistical analyses . . . . .	2396
3. Results . . . . .	2397
3.1. Inclusion of the studies . . . . .	2397
3.2. Study population . . . . .	2397
3.2.1. Diagnosis, matching, duration of illness and substance abuse . . . . .	2397
3.2.2. Structural magnetic resonance imaging (MRI) . . . . .	2399
3.2.3. The standard mean difference (SMD) of the pituitary gland volume . . . . .	2399
4. Discussion . . . . .	2401
4.1. Gender, hormones and pituitary volume . . . . .	2401
4.2. Antipsychotics and pituitary volume . . . . .	2401
4.3. Duration of untreated psychosis and pituitary volume . . . . .	2401
4.4. Age and pituitary volume . . . . .	2402
4.5. Ultra-high risk and schizotypal subjects versus healthy controls . . . . .	2402
4.6. Schizophrenia and FEP versus healthy controls . . . . .	2402
4.7. Ultra-high risk versus schizophrenia . . . . .	2402
4.8. Potential confounders . . . . .	2402
Acknowledgements . . . . .	2403
References . . . . .	2403

## 1. Introduction

For decades researchers have been studying the structural changes of the brain during the early phases of psychosis and in established schizophrenia (Nenadic et al., 2012; Shepherd et al., 2012). The pituitary gland is one of the structures that has been studied, and some researchers have found that the pituitary gland volume could be increasing before the onset of psychosis (Garner et al., 2005) and during the early stages of psychosis (Pariante et al., 2005; Takahashi et al., 2009). A larger pituitary size is thought to reflect a greater activation of the hypothalamic–pituitary–adrenal (HPA) axis, related to an increase in the number and size of corticotroph cells (Axelson et al., 1992; Pariante et al., 2004b). This is supported by animal studies showing that the corticotroph cells increase in size and number when stimulated by corticotrophin releasing hormone (Westlund et al., 1985; Gertz et al., 1987). Some studies indicate that the pituitary gland volume may decrease again during the stable phases of schizophrenia and during treatment with antipsychotics (Pariante et al., 2004b; Upadhyaya et al., 2007) and large recent study has found no difference in pituitary gland volume between healthy controls and patients with schizophrenia who had been ill for longer than a decade (Klomp et al., 2012). In healthy subjects, the pituitary gland decreases with age, it is

larger in females, and increases in volume with puberty, pregnancy, tumours (hypothalamic), Addison's disease or hypothyroidism (Elster, 1993; MacMaster et al., 2007b; Pariante, 2008). The pituitary gland is therefore a dynamic structure that changes in response to different conditions (Garner et al., 2005; Pariante et al., 2005; Pariante, 2008).

In psychosis, it has been hypothesised that the activity of the HPA axis reflects a stress-related hormonal dysregulation (Walker et al., 2008). The stress-vulnerability model of psychosis (Zubin and Spring, 1977) is still a widely used model for research in psychotic disorders. HPA axis hyperactivity has been shown to influence hippocampal volume, cognitive function and symptomatology in patients with first-episode psychosis (Mondelli et al., 2010a, 2010b, 2011; Aas et al., 2011; Belvederi et al., 2012). In addition neuroendocrine abnormalities and increased stress response have been described in patients with "at risk" mental state (Aiello et al., 2012).

Within this theoretical context, a review of pituitary gland volume in 2008 (Pariante, 2008) concluded that the onset of psychosis is associated with an enlargement of the pituitary gland, and that this is independent of antipsychotics. However, this review was not systematic and several new studies have been published since 2008. There is therefore a need for a critical appraisal of the literature on this topic accompanied by meta-analytical evaluation of the data.

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