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Glucocorticoids and the risk of schizophrenia spectrum disorder in childhood and adolescence – A Danish nationwide study

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ABSTRACT

Glucocorticoids can have psychosis as a potential side effect, but have also been suggested to yield protective effects due to anti-inflammatory properties. Nonetheless, knowledge is sparse on the association between glucocorticoid treatment and development of psychosis, which we aimed to study in this first large-scale longitudinal study.

Among all individuals born in Denmark 1995–2003 ($n = 597{,}257$), we compared individuals who had redeemed ≥1 prescription for glucocorticoids to an active comparator group and a non-exposed group concerning subsequent development of schizophrenia spectrum disorders until 2013. Hazard rate ratios (HRR) were estimated using Cox regression adjusted for calendar year, age, gender, urbanization, somatic diseases, parental educational level and psychiatric history.

The risk for a subsequent diagnosis of early-onset schizophrenia spectrum disorder ($N = 1141$) was increased after exposure to both non-systemic (HRR = 1.47; 95%-CI = 1.25–1.73; $N = 371$) and systemic glucocorticoids (HRR = 1.66; 95%-CI = 1.13–2.43; $N = 34$), when compared to non-exposed individuals. Similar elevated risks were observed when comparing to the active comparator group, for schizophrenia and acute psychosis, and within an older cohort. The risk of psychosis was elevated the most within the first year after exposure to glucocorticoids ($P < 0.001$) without any indication for a dose-response association. However, in individuals with asthma, exposure to glucocorticoids did not further increase the risk of psychosis.

Glucocorticoid exposure was associated with an increased risk for psychotic disorders, which may be explained by an effect of the underlying somatic disease, such as asthma. A potential beneficial effect of glucocorticoids on psychotic symptoms should be investigated in clinical trials.

1. Introduction

A potential and well-known side effect of glucocorticoids includes psychotic symptoms and glucocorticoids might, in a dose-dependent manner, increase risk for severe neuropsychiatric symptoms (including panic disorder, suicidality and psychosis) (Fardet et al., 2012). However, due to the potent immune-suppressive properties of glucocorticoids, potential protective effects against the development of psychosis have also been proposed based on the mounting evidence that indicates the immune system as an important contributor to the development of schizophrenia (Benros et al., 2011; Khandaker et al., 2015; Meyer et al., 2011; Müller et al., 2015; Nielsen et al., 2014; Sekar et al., 2016). Therefore, it is important to investigate the efficacy of administering broad-acting, potent immune suppressive agents, such as glucocorticoids, before onset of the schizophrenia disorder. Recent meta-analyses of randomized controlled trials (Nitta et al., 2013; Sommer et al., 2014,

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2012) have indicated small to moderate effect sizes concerning the efficacy of some anti-inflammatory agents as add-on to antipsychotic treatment in subgroups of patients with schizophrenia. It is less studied whether specific anti-inflammatory agents, such as glucocorticoids, may have potential protective effects against the development of psychosis and whether these potential protective effects outweigh the potential to induce psychosis as a direct side-effect. A prior study has displayed a significant protective effect of glucocorticoids in men only (Laan et al., 2009). Yet, the interpretation of these data is complicated by several factors. The study included patients with psychosis independent of prior diagnoses of psychosis or duration of illness; it only had information on glucocorticoid exposure during the last year prior to the diagnosis of psychosis along with missing adjustment for important covariates. Moreover, pharmacoepidemiological studies imply the risk of confounding by indication, with the indication for glucocorticoids treatment in young individuals mainly being asthma. Indeed, asthma in itself constitutes a risk factor for developing psychotic disorders (Pedersen et al., 2012). Hence, additional studies on this aspect applying longitudinal follow-up are needed.

In a nationwide setting, we investigated if glucocorticoid administration during childhood and adolescence affected the risk of developing a psychotic disorder before age 20, the maximum age at which lifetime exposure to prescribed medication was available in the applied Danish registers. The primary objective was to investigate associations between the prescription for glucocorticoid treatment and the incidence of schizophrenia-spectrum disorders as compared to an untreated group and an active comparator group (beta$_2$-agonists or leukotriene receptor antagonists). We performed dose-response, time-since and age-at-first exposure analyses and specifically investigated schizophrenia, schizoaffective, and acute psychotic disorder.

2. Methods

2.1. Data sources

The study used information extracted from Danish medical and socio-demographic registries including: The Danish National Registry of Patients (inpatient data: 1977-; outpatient data: 1995-) (Lynge et al., 2011); the Danish Psychiatric Central Research Registry (inpatient data: 1969-; outpatient data: 1995-) (Mors et al., 2011); the Danish National Prescription Database (1995-) (Kildemoes et al., 2011); the Danish Civil Registration System (1969-) (Pedersen, 2011); the Danish National Registry of Causes of Death (Helweg-Larsen, 2011); and the Danish Education Register (Jensen and Rasmussen, 2011).

2.2. Study population

We conducted a population-based cohort study within the entire Danish population (approximately 5.5 million inhabitants) utilizing the Danish Civil Registration System (Pedersen, 2011). The primary study population consisted of all individuals born in Denmark between January 1, 1995, and December 31, 2003. The start date for inclusion, January 1, 1995, was chosen to coincide with the establishment of the Danish National Prescription Database in order to have complete overview of medication prescribed. We followed all individuals from the age of 1 year until their first outcome diagnosis (see below), death, emigration, or end of the study period on July 1, 2013 (end of follow-up), whatever came first.

2.3. Older study population for sensitivity analyses

Since the abovementioned study population would only include very young individuals, we further identified a cohort born between January 1, 1985, and December 31, 2003 in order to have an older study population concerning the investigated outcomes. We excluded individuals who had experienced hospital contacts with any mental disorder (ICD-8 codes: 290–315) before 1995, and individuals diagnosed with schizophrenia spectrum disorder (ICD-10: F20-F29) prior to their 10th birthday, identified from the Psychiatric Central Research Register (Mors et al., 2011). This additional "control" study population was chosen only for sensitivity analyses since records of prescribed medication were not available for individuals born before 1995, when the Danish National Prescription Database was established.

2.4. Exposure to glucocorticoids

The exposure of interest was any prescription drug use of glucocorticoids except for topical formulations and combinations with other drugs. Specifically, we extracted prescriptions for the glucocorticoids (Anatomical Therapeutic Chemical (ATC) codes (WHO, n.d.) for systemic use (H02AB) and for the respiratory system (R03BA), budesonide (A07EA06), and corticosteroids (R01AD). Based on the route of administration, H02AB drugs were classified as systemic glucocorticoids, while R01AD and R03BA were classified as non-systemic glucocorticoids. A07EA06 was classified as non-systemic due to low bioavailability (Nunes et al., 2013). Amount of glucocorticoid exposure was calculated based on the total number of defined daily doses (DDD) during follow-up.

2.5. Reference group

We identified two reference groups:

- First, non-exposed individuals, i.e. individuals who did not redeem prescriptions for glucocorticoids (as defined above), beta$_2$-agonists (ATC-codes: R03AC, R03CC02, R03CC03, R03CC12) or leukotriene receptor antagonists (ATC-code: R03DC03).
- Second, an active comparator group (i.e. a group with the same indication as glucocorticoids) defined as subjects exposed to beta$_2$-agonists, such as salbutamol, or leukotriene receptor antagonists.

We applied an intention-to-treat approach of the three exposure categories: Subjects added risk time to the unexposed group until their first prescription of glucocorticoids or drugs in the active comparator group. Individuals were grouped as exposed to glucocorticoids from the date of the first glucocorticoid prescription. Individuals were grouped as exposed to the active comparator drugs from the date of the first prescription until the end of follow-up or until the date of the first prescription for glucocorticoids.

2.6. Outcome

Within the established cohort, we identified psychiatric hospital contacts, including inpatient admissions and outpatient contacts. We included the first psychiatric diagnosis after January 1, 1995 for the following outcomes diagnosed after the 10th birthday:

1) The first diagnosis within the schizophrenia spectrum disorder (International Classification of Diseases, 10th edition (ICD-10): F20-F29)
2) The first diagnosis of schizophrenia (ICD-10: F20), acute psychotic disorder (ICD-10: F23), or schizoaffective disorder (ICD-10: F25).

Covariates:

We included the following covariates: calendar year, age, gender, degree of urbanization at birth (defined as capital, capital suburb, provincial city, provincial town, and rural area). For their parents, we identified their psychiatric history (any psychiatric diagnosis within the secondary psychiatric sector since 1969) and their educational status at birth of the included individual. Finally, we identified use of non-steroidal anti-inflammatory drugs (NSAIDs; ATC-codes: M01A), any

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