Analysis of risk factors for schizophrenia with two different case definitions: a nationwide register-based external validation study.

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Abstract: Different case definitions of schizophrenia have been used in register based research. However, no previous study has externally validated two different case definitions of schizophrenia against a wide range of risk factors for schizophrenia. We investigated hazard ratios (HRs) for a wide range of risk factors for ICD-10 DCR schizophrenia using a nationwide Danish sample of 2,772,144 residents born in 1955-1997. We compared one contact only (OCO) (the case definition of schizophrenia used in Danish register based studies) with two or more contacts (TMC) (a case definition of at least 2 inpatient contacts with schizophrenia). During the follow-up, the OCO definition included 15,074 and the TMC 7562 cases; i.e. half as many. The TMC case definition appeared to select for a worse illness course. A wide range of risk factors were uniformly associated with both case definitions and only slightly higher risk estimates were found for the TMC definition. Choosing at least 2 inpatient contacts with schizophrenia (TMC) instead of the currently used case definition would result in almost similar risk estimates for many well-established risk factors. However, this would also introduce selection and include considerably fewer cases and reduce power of e.g. genetic studies based on register-diagnosed cases only.

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An association study of suicide and candidate genes in the serotonergic system.

https://arctichealth.org/en/permalink/ahliterature117298
Strong evidence demonstrates a genetic susceptibility to suicidal behaviour and a relationship between suicide and mental disorders. The aim of this study was to test for association between suicide and five selected genetic variants, which had shown association with suicide in other populations.

We performed a nationwide case-control study on all suicide cases sent for autopsy in Denmark between the years 2000 and 2007. The study comprised 572 cases and 1049 controls and is one of the largest genetic studies in completed suicide to date. The analysed markers were located within the Serotonin Transporter (SLC6A4), Monoamine Oxidase-A (MAOA) and the Tryptophan Hydroxylase I and II (TPH1 and TPH2) genes.

None of the genetic markers within SLC6A4, MAOA, TPH1 and TPH2 were significantly associated with completed suicide or suicide method in the basic association tests. Exploratory interaction test showed that the minor allele of rs1800532 in TPH1 has a protective effect for males younger than 35 years and females older than 50 years, whereas for the oldest male subjects, it tended to be a risk factor. We also observed a significant interaction between age-group and the 5-HTTLPR genotype (with and without rs25531) in SLC6A4. The long allele or high expression allele tends to have a protective effect in the middle age-group.

We only analysed a limited number of genetic variants.

None of the analysed variants are strong risk factors. To reveal a better understanding of the genes involved in suicide, we suggest future studies should include both genetic and non-genetic factors.
Antipsychotic polypharmacy and risk of death from natural causes in patients with schizophrenia: a population-based nested case-control study.

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OBJECTIVE: Concomitant prescription of more than 1 antipsychotic agent (antipsychotic polypharmacy) in the
treatment of schizophrenia is prevalent, although monotherapy is generally recommended. Mortality from
natural causes is markedly increased in schizophrenia, and the role of polypharmacy remains controversial. The
objective was to investigate if antipsychotic polypharmacy is associated with the excess mortality from natural
causes among patients with schizophrenia. METHOD: A population-based nested case-control study was
conducted using patient data from January 1, 1996, to December 31, 2005, obtained from central Danish
registers. From the study population of 27,633 patients with ICD-8- and ICD-10-diagnosed schizophrenia or other
mainly nonaffective psychoses, aged 18-53 years, we identified 193 cases who died of natural causes within a 2-
year period and 1,937 age- and sex-matched controls. Current drug use was defined as at least 1 prescription
filled within 90 days before the date of death or the index date. The data were analyzed by conditional logistic
regression. RESULTS: Risk of natural death did not increase with the number of concurrently used antipsychotic
agents compared with antipsychotic monotherapy (no antipsychotics: adjusted odds ratio [OR] = 1.48 [95% CI,
0.89-2.46]; 2 antipsychotics: OR = 0.91 [95% CI, 0.61-1.36]; 3 or more antipsychotics: OR = 1.16 [95% CI, 0.68-2.00]).
Current use of benzodiazepine derivatives with long elimination half-lives (more than 24 hours) was associated
with increased risk of natural death in patients with schizophrenia treated with antipsychotics (OR = 1.78 [95% CI,
1.25-2.52]). CONCLUSIONS: Antipsychotic polypharmacy did not contribute to the excess mortality from natural
causes in middle-aged patients with schizophrenia. The detected increased risk of death associated with
benzodiazepines with long elimination half-lives calls for further clarification.

Association between parental hospital-treated infection and the risk of schizophrenia in adolescence
and early adulthood.

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Abstract: It has been suggested that infection during perinatal life may lie at the etiological root of schizophrenia. It has thus been hypothesized that the origin of schizophrenia may lie either in direct fetal infection and/or in a generally increased familial susceptibility to infections, some of which may occur during pregnancy. We explored these 2 hypotheses by assessing maternal infection during pregnancy and maternal as well as paternal infection in general as predictors of schizophrenia in their offspring. We found a slightly increased risk to be associated with prenatal infection exposure. However, the effect of prenatal infection exposure was not statistically significantly different from the effect of infection exposure in general. Parental infection appeared to be associated with development of schizophrenia in adolescence and early adulthood. Our study does not exclude a specific effect of infection during fetal life; yet, it does suggest that schizophrenia is associated with an increased familial liability to develop severe infection.
Association between prepartum maternal iron deficiency and offspring risk of schizophrenia: population-based cohort study with linkage of Danish national registers.

https://arctichealth.org/en/permalink/ahliterature145935
Recent findings suggest that maternal iron deficiency may increase the risk of schizophrenia-spectrum disorder in offspring. We initiated this study to determine whether maternal prepartum anemia influences offspring risk of schizophrenia. We conducted a population-based study with individual record linkage of the Danish Civil Registration System, the Danish Psychiatric Central Register, and the Danish National Hospital Register. In a cohort of 1,115,752 Danish singleton births from 1978 to 1998, cohort members were considered as having a maternal history of anemia if the mother had received a diagnosis of anemia at any time during the pregnancy. Cohort members were followed from their 10th birthday until onset of schizophrenia, death, or December 31, 2008, whichever came first. Adjusted for relevant confounders, cohort members whose mothers had received a diagnosis of anemia during pregnancy had a 1.60-fold (95% confidence interval = 1.16-2.15) increased risk of schizophrenia. Although the underlying mechanisms are unknown and independent replication is needed, our findings suggest that maternal iron deficiency increases offspring risk of schizophrenia.
Association of the polygenic risk score for schizophrenia with mortality and suicidal behavior - A Danish population-based study.

https://arctichealth.org/en/permalink/ahliterature290891
Abstract: It is unknown whether an increased genetic liability to schizophrenia influences the risk of dying early. The aim of the study was to determine whether the genetic predisposition to schizophrenia is associated with the risk of dying early and experience a suicide attempt.

Case control study, Denmark. The main measure was the mortality rate ratios (MRR) for deaths and odds ratios (OR) for multiple suicide attempts, associated with one standard deviations increase of the polygenic risk-score for schizophrenia (PRS).

We replicated the high mortality MRR=9.01 (95% CI: 3.56-22.80), and high risk of multiple suicide attempts OR=33.16 (95% CI: 20.97-52.43) associated with schizophrenia compared to the general population. However, there was no effect of the PRS on mortality MRR=1.00 (95% CI 0.71-1.40) in the case-control setup or in cases only, MRR=1.05 (95% CI 0.73-1.51). Similar, no association between the PRS and multiple suicide attempts was found in the adjusted models, but in contrast, family history of mental disorders was associated with both outcomes.

A genetic predisposition for schizophrenia, measured by PRS, has little influence on the excess mortality or the risk of suicide attempts. In contrast there is a strong significant effect of family history of mental disorders. Our findings could reflect that the common variants detected by recent PRS only explain a small proportion of risk of schizophrenia, and that future, more powerful PRS instruments may be able to predict excess mortality within this disorder.

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Associations between HIV and schizophrenia and their effect on HIV treatment outcomes: a nationwide population-based cohort study in Denmark.

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Abstract:

Associations between HIV and schizophrenia in people with and without substance use disorders and the effect on timeliness of HIV diagnosis, antiretroviral therapy (ART), and treatment outcomes are poorly understood. We aimed to assess the association between HIV and schizophrenia and the effect on HIV treatment outcomes in people with and without substance use disorders.

We did a population-based cohort study with data from nationwide registries in Denmark to investigate the risk of schizophrenia after a diagnosis of HIV and the risk of HIV after a diagnosis of schizophrenia, accounting for substance misuse, timeliness of HIV diagnosis, and treatment success in relation to schizophrenia. We selected the cohort from people born in Denmark between Jan 1, 1955, and Dec 31, 1995, who we followed up from their 16th birthday or Jan 1, 1995 (whichever occurred last) until their death, emigration from Denmark, onset of schizophrenia, or Dec 31, 2011 (whichever came first). We estimated incidence rate ratios (IRRs) with Poisson and Cox regression, with adjustment for calendar period, and age and its interaction with sex.

We identified 2,786,286 individuals, of whom we included 2,646,154 people in analyses of risk of schizophrenia diagnosis and 2,658,662 people in analyses of risk of HIV diagnosis. In 35,353,633 person-years of follow up, HIV was associated with an increased risk of schizophrenia (IRR 4·09, 95% CI 2·73-5·83) and acute psychosis (7·15, 4·45-10·8); the IRR was highest within the first year of HIV diagnosis for both disorders (8·24, 2·95-17·7 and 12·7, 3·15-32·9, respectively). Schizophrenia was not associated with an increased risk of HIV in individuals without substance misuse disorders (IRR 1·42, 95% CI 0·81-2·27). The risk of schizophrenia in individuals with HIV decreased after ART (IRR 0·53, 0·32-0·87). The risk of acute psychosis did not differ between HIV-infected individuals receiving antiretroviral regimens with and without efavirenz (IRR 0·70, 95% CI 0·32-1·54). We recorded no differences in CD4 cell counts, time to ART, or viral suppression between individuals with schizophrenia with HIV and those without schizophrenia when substance use was taken into account. Between 1999 and 2011, the mortality rate ratio comparing HIV-infected individuals with schizophrenia with HIV-negative individuals without schizophrenia was 25·8 (95% CI 18·8-34·3).

Our findings emphasise the need for interventions to prevent HIV in people with schizophrenia, especially for those with substance use disorders, and for accessible mental health services for individuals with HIV.

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Notes:


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Autism spectrum disorder in individuals with anorexia nervosa and in their first- and second-degree relatives: Danish nationwide register-based cohort-study.

Clinical and population-based studies report increased prevalence of autism spectrum disorders (ASD) in individuals with anorexia nervosa and in their relatives. No nationwide study has yet been published on co-occurrence of these disorders.

To investigate comorbidity of ASD in individuals with anorexia nervosa, and aggregation of ASD and anorexia nervosa in their relatives.

In Danish registers we identified all individuals born in 1981-2008, their parents, and full and half siblings, and linked them to data on hospital admissions for psychiatric disorders.

Risk of comorbidity of ASD in probands with anorexia nervosa and aggregation of ASD in families of anorexia nervosa probands were increased. However, the risk of comorbid and familial major depression or any psychiatric disorder in anorexia nervosa probands.

We confirm aggregation of ASD in probands with anorexia nervosa and in their relatives; however, the relationship between anorexia nervosa and ASD appears to be non-specific.

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Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study.

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Young Adult
Mood disorders frequently co-occur with medical diseases that involve inflammatory pathophysiologic mechanisms. Immune responses can affect the brain and might increase the risk of mood disorders, but longitudinal studies of comorbidity are lacking.

To estimate the effect of autoimmune diseases and infections on the risk of developing mood disorders.

Nationwide, population-based, prospective cohort study with 78 million person-years of follow-up. Data were analyzed with survival analysis techniques and adjusted for calendar year, age, and sex.

Individual data drawn from Danish longitudinal registers.

A total of 3.56 million people born between 1945 and 1996 were followed up from January 1, 1977, through December 31, 2010, with 91,7637 people having hospital contacts for mood disorders.

The risk of a first lifetime diagnosis of mood disorder assigned by a psychiatrist in a hospital, outpatient clinic, or emergency department setting. Incidence rate ratios (IRRs) and accompanying 95% CIs are used as measures of relative risk.

A prior hospital contact because of autoimmune disease increased the risk of a subsequent mood disorder diagnosis by 45% (IRR, 1.45; 95% CI, 1.39-1.52). Any history of hospitalization for infection increased the risk of later mood disorders by 62% (IRR, 1.62; 95% CI, 1.60-1.64). The 2 risk factors interacted in synergy and increased the risk of subsequent mood disorders even further (IRR, 2.35; 95% CI, 2.25-2.46). The number of infections and autoimmune diseases increased the risk of mood disorders in a dose-response relationship. Approximately one-third (32%) of the participants diagnosed as having a mood disorder had a previous hospital contact because of an infection, whereas 5% had a previous hospital contact because of an autoimmune disease.

Autoimmune diseases and infections are risk factors for subsequent mood disorder diagnosis. These associations seem compatible with an immunologic hypothesis for the development of mood disorders in subgroups of patients.

Notes:
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Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study.
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Abstract:
Autoimmune diseases have been associated with an increased risk of schizophrenia. It has been suggested that brain-reactive autoantibodies are part of the mechanisms behind this association. Furthermore, an increased permeability of the blood-brain barrier has been observed during periods of infection and inflammation. The authors therefore investigated whether autoimmune diseases combined with exposures to severe infections may increase the risk of schizophrenia.

Nationwide population-based registers in Denmark were linked, and the data were analyzed in a cohort study using survival analysis. All analyses were adjusted for calendar year, age, and sex. Incidence rate ratios and accompanying 95% confidence intervals (CIs) as measures of relative risk were used.

A prior autoimmune disease increased the risk of schizophrenia by 29% (incidence rate ratio=1.29; 95% CI=1.18-1.41). Any history of hospitalization with infection increased the risk of schizophrenia by 60% (incidence rate ratio=1.60; 95% CI=1.56-1.64). When the two risk factors were combined, the risk of schizophrenia was increased even further (incidence rate ratio=2.25; 95% CI=2.04-2.46). The risk of schizophrenia was increased in a dose-response relationship, where three or more infections and an autoimmune disease were associated with an incidence rate ratio of 3.40 (95% CI=2.91-3.94). The results remained significant after adjusting for substance use disorders and family history of psychiatric disorders. Hospital contact with infection occurred in nearly 24% of individuals prior to a schizophrenia diagnosis.

Autoimmune disease and the number of infections requiring hospitalization are risk factors for schizophrenia. The increased risk is compatible with an immunological hypothesis in subgroups of schizophrenia patients.

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