Universiteit Utrecht

Lifetime positive psychotic symptoms and subsequent risk of psychotic disorders in individuals with the 22q11.2 Deletion Syndrome

Thesis Master Neuropsychology

Utrecht University

Name: Isa Polman

Studentnumber: 5984092

Date: 11-06-2020

Words: 4153

Supervisors:

MSc Ania Fiksinski (UMC Utrecht, external supervisor)

MSc Larissa Meijer (Utrecht University, first supervisor)

MSc Manja Engel (Utrecht University, first supervisor)

MSc Irene Huenges-Wajer (Utrecht University, second supervisor)

Abstract

Background: The 22q11.2 Deletion Syndrome (22q11DS) is a complex neuro-developmental disorder, which leads to a 25% increased risk of developing schizophrenia compared to approximately 1% chance in the general population. Investigating risk factors for developing psychotic disorders in the 22q11DS population could be an appropriate method to find out risk factors for developing psychotic disorders in the general population. In this study we focussed on the association between positive psychotic symptoms at any time point in life and the development of a full-blown psychotic disorder in adulthood, within the 22q11DS population. **Methods**: The data were analysed via a Binary Logistic Regression analysis, within 442 individuals (M_{age} = 17.72, SD_{age} = 4.20): 34 individuals with a psychotic illness and 408 individuals without a psychotic disorder. **Results**: The findings indicate that the presence of positive psychotic symptoms is a significant risk factor for the subsequent development of a full-blown psychotic disorder, even after accounting for the effects of Baseline IQ and Verbal IQ decline. **Discussion**: This study underlines the importance of early screening of risk factors for developing a full-blown psychotic disorder. Further research could focus on investigating these risk factors in groups at risk for the psychotic disorder, early treatment of psychotic disorders and/or the severity of risk indicated by the SIPS, CAARMS or KSADS. Taken together, this research contributes to identifying risk factors of the development of psychotic disorders, most outstanding the presence of positive psychotic symptoms, in individuals with 22q11DS.

KEYWORDS
22q11DS, schizophrenia, psychiatry, positive psychotic symptoms, Baseline IQ, VIQ decline, clinical implications

Introduction

The 22q11.2 Deletion Syndrome (22q11DS) is a complex neuro-developmental disorder, which is caused by a 1.5-3 Mb deletion on chromosome region 22q11.2 (Rozas, Benavides, Leon, & Repetto, 2019). The 22q11DS is one of the most prevalent chromosomal microdeletion disorders. Approximately, 1 in every 4000 children is born with the syndrome (Gur et al., 2017). This deletion leads to a varied phenotype, including but not limited to, anomalies such as congenital heart disease, overt cleft palate, cleft lip or cleft palate and cognitive deficits (Gur et al., 2017; McDonald-McGinn et al., 2015).

Individuals with 22q11DS are at a 25% increased risk of developing schizophrenia, compared to approximately 1% chance in the general population (Fiksinski et al., 2018). Schizophrenia is a psychotic disorder, defined by negative symptoms (for example apathy) and positive symptoms (for example hallucinations, delusions, illusions and suspiciousness) (Broome et al., 2005; Fett, Maat, & Investigators, 2013; Jones et al., 2016; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). In the general population, schizophrenia typically emerges in late adolescence to early adulthood, approximately around the age of 25 years. In the 22q11DS population, the first psychotic episode starts around 18 to 20 years old (Fiksinski et al., 2017). After the age of 25, the probability of developing a psychotic disorder decreases significantly in both the general population as the 22q11DS population (Gur et al., 2017).

The phenotypic expression of psychotic disorders within the 22q11DS population does not significantly differ from the expression in the general population (Fiksinski et al., 2018). Besides, as noted before, there is an early genetic 22q11DS diagnosis and a relatively high prevalence of psychotic disorders in the 22q11DS population (Fiksinski et al., 2018). Therefore, investigating risk factors for developing psychotic disorders in the 22q11DS population could be an appropriate method to find out risk factors for developing psychotic disorders in the general population (Fiksinski et al., 2018).

Investigating psychotic symptoms in individuals with 22q11DS before the onset of the first psychotic episode may allow identification of early behavioural and/or cognitive markers associated with a psychotic disorder (Gur et al., 2017). When a psychotic disorder is recognised in the first stages of the disorder, prevention or early interventions can be implemented (Yung & McGorry, 2007). As a result, early intervention may lead to a better daily outcome of an individual (Gur et al., 2017).

As of yet, several risk factors for developing schizophrenia have been proposed. Firstly, genetic factors, including rare and common single nucleotide variants as well as larger structural variants such as deletions or duplications, are linked to the development of schizophrenia in the general population (Fanous, Gardner, Walsh, & Kendler, 2001; Gagliano et al., 2016; Jones et al., 2016). Also, in the 22q11DS population there seems to be evidence for such genetic risk factors, other than the deletion itself, for developing schizophrenia (Bassett et al., 2017). Secondly, there is a significant relationship between low IQ scores (<75 points) and the development of schizophrenia in the general population (Boydell, 2001) and the 22q11DS population (Vorstman et al., 2015). Also, cognitive decline over time may be a risk factor for increasing dysfunction and the development of schizophrenia in the general population (Mollon, David, Zammit, Lewis, & Reichenberg, 2018). In line with this finding, Vorstman et al (2015) reported that an IQ decline over time, specifically in Verbal IQ (VIQ), is a high-risk factor for developing schizophrenia in the 22q11DS population. The decline starts around the age of 11 years old. Thirdly, Yung and Mcgorry (2007) proposed that high-risk groups, for psychotic disorders in the general population, consist allegedly of people with characteristics such as schizotypal personality features, depression and negative or positive psychotic symptoms. Positive psychotic symptoms have been proposed as a strong risk factor for developing schizophrenia in the 22q11DS population (Zoller et al., 2019). In the study of Poulton et al. (2000) it becomes clear that positive psychotic symptoms (delusions or hallucinations were reported in 25% of the participants at age 26) are more often reported than negative psychotic symptoms (anhedonia was reported in 1,2% of the participants at age 26). So, in summary, three risk factors have been proposed. Genetic factors, IQ variables and positive psychotic symptoms seem to contribute to developing a psychotic disorder, but are not yet generally assumed and therefore cannot be implemented in clinical practice (Bassett et al., 2017; Boydell, 2001; Fanous et al., 2001; Gagliano et al., 2016; Jones et al., 2016; Mollon et al., 2018; Poulton et al., 2000; Vorstman et al., 2015; Yung & McGorry, 2007; Zoller et al., 2019).

Because of the remaining ambiguity of factors that contribute to the development of a psychotic disorder, this study focuses on the association of positive psychotic symptoms on the development of a full-blown psychotic disorder in individuals with 22q11DS. In this study we aim to answer the research question: *Are positive psychotic symptoms at any time point in life associated with the development of a full-blown psychotic disorder in adulthood?* It is hypothesized that positive psychotic symptoms in 22q11DS patients are indeed related to increased

risk for subsequently developing psychotic disorders (Poulton et al., 2000; Yung & McGorry, 2007).

Methods

Participants

Data from the International 22q11DS Brain Behavior Consortium (IBBC) was used (N = 1789) for the current study. Multiple organizations from all over the world (including UMC Utrecht), specialised in 22q11DS, shared their (genetic and phenotypic) data about 22q11DS patients. These patients were selected via their genetic syndrome and clinical care in the organisation. The primary objective of the IBBC was to elucidate developmental trajectories of schizophrenia in 22q11DS, and potentially generalize this to schizophrenia in the general population (Gur et al., 2017).

In total, 1789 individuals (869 males and 920 females) were included in the IBBC dataset *(*M_{age} = 21.32, SD_{age} = 11.41). Before participating in this study, written informed consent was obtained from participants and their parents or guardians and the study was approved by the local ethics committees. Inclusion criteria in this study were the presence of two or more psychiatric assessments over time. Because of this, we could analyse the development of positive psychotic symptoms and a possible psychotic disorder. When this development wasn't measurable, for example when the psychotic disorder was diagnosed before the data was collected, participants were excluded from the study.

For this study, data from 442 individuals with a confirmed 22q11.2 deletion were used: 231 males and 211 females (M_{age} = 17.72, SD_{age} = 4.20). Within this database, there were 34 individuals with a psychotic illness (M_{age} = 18.82, SD_{age} = 4.46) and 408 individuals without a psychotic disorder (M_{age} = 17.63, SD_{age} = 4.17*)*. Psychotic illnesses in this dataset included schizophrenia (N = 13 (38.24%)), schizoaffective or psychotic disorder not otherwise specified (N = 16 (47.06%)) and other psychotic spectrum disorders (N = 5 (14.71%)). Further descriptives information can be found in table 1.

Table 1

Descriptives

	Total[1]	**Psychotic disorder[2]**	**No psychotic disorder[3]**
N (m/f)	442 (231/211)	34 (18/16)	408 (213/195)
%	100%	7.69%	92.31%
Age	17.72 ± 4.20	18.82 ± 4.45	17.63 ± 4.17
Mean ± SD	(8.00 – 36.00)	(11.00 – 29.00)	(8.00 – 36.00)
(range)			
Interval	5.78 ± 3.32	5.09 ± 3.76	5.84 ± 3.28
Mean ± SD	(1.00 – 14.00)	(1.00 – 14.00)	(1.00 – 14.00)
(range)			
Baseline IQ	73.32 ± 13.64	68.53 ± 11.54	73.72 ± 13.74
Mean ± SD	(40.00 – 114.00)	(50.00 – 94.00)	(40.00 – 114.00)
(range)			
VIQ decline	0.09 ± 0.69	-0.20 ± 0.63	0.12 ± 0.69
Mean ± SD	(-2.11 - 2.51)	(-1.25 - 1.20)	(-2.11 - 2.51)
(range)			

1: For this group, age (in years) was defined by the mean of age at diagnosis and age at last assessment

2: For this group, age (in years) was defined by the age at diagnosis

3: For this group, age (in years) was defined by the age at last assessment

Procedure

Participants participated in a longitudinal study of the IBBC and visited the IBBC organizations several times over time, once in approximately three years. Psychiatric and cognitive parameters were collected by experienced clinicians. During psychological interviews several test were conducted, as discussed with the materials described below.

Furthermore, all data was verified through extensive and standardized quality control procedures. This extensive quality control was conducted to ensure consistency and accuracy of the phenotypic data across all sites (Gur et al., 2017).

Materials

Psychotic Symptoms scales Various psychotic symptom scales were used, which all assess the presence of psychotic symptoms. Per IBBC organization, it differed which one was taken: The Kiddie-Schedule for Affective Disorders and Schizophrenia for School Aged Children (KSADS, Cronbach's alpha = 0.94) (Axelson et al., 2003; Jarbin, Andersson, Rastam, & Ivarsson, 2017); the Structured Interview for Prodromal Syndromes (SIPS, kappa = 0.81) (Miller, 2004); or the Comprehensive Assessment of At-Risk Mental States (CAARMS, kappa = 0.82) (Miyakoshi, Matsumoto, Ito, Ohmuro, & Matsuoka, 2009). Positive psychotic symptoms were deemed present when the individual had a test score of 2 or higher on one or more items of the subscale 'positive psychotic symptoms' (KSADS and CAARMS), or when the individual had a test score of 3-5 on one or more items of the subscale 'positive psychotic symptoms' (SIPS).

IQ scales Furthermore, the latest versions of the entire Wechsler IQ scales (Wechsler, 1991) (WISC-III/WAIS-III/WISC-R, Cronbach's alpha = 0.98) were taken, to determine the overall IQ of the individual (Crawford, 2004). Conform the guidelines, when the participant was 16 years old or younger, the WISC was taken, otherwise the WAIS was taken (Crawford, 2004).

Analyses

After collecting all the required data, R Desktop version 3.4.1 was used for analysing the data. First, to test if the groups with or without positive psychotic symptoms and with or without a psychotic disorder were different, we conducted a Chi-Square analysis.

This is a robust test; a non-parametric statistic. Most of the assumptions, including independent groups and exclusive levels of the variables, were met (McHugh, 2013). Ideally, Chi-Square tests are ideally conducted on randomly collected samples (McHugh, 2013), which was not the case in the current study (see "participants"). However, the Chi-Square test is an excellent test to use if the random collecting assumption is violated (McHugh, 2013). For the Chi Square Analysis, we used *Cohen's W* as an index of effect size. Here, a *Cohen's W* of 0.1 was accepted as a small effect, a *Cohen's W* of 0.3 was a medium effect and a *Cohen's W* of 0.5 was accepted as a large effect (Cohen, 1988).

After the Chi-Square we used a Binary Logistic Regression analysis, to test for possible confounders. Here, we examined the association between the presence of psychotic symptoms and the subsequent presence of a psychotic disorder. The predictor variables were: the presence of

positive psychotic symptoms, age, sex and the clinical interval. The clinical interval variable comprises of the amount of years that a participant was seen in the clinic: the time between the first and last available assessment. The dichotomous outcome variable was the presence of a psychotic disorder at follow-up (yes/no). Then, we also included the independent variables Baseline IQ and VIQ decline in relation to the development of a psychotic disorder, as these have been previously identified as risk factors (Boydell, 2001; Mollon et al., 2018; Vorstman et al., 2015). For the dichotomous variable of baseline IQ we used a cut-off score of 75 and for the dichotomous variable of VIQ decline we used a cut-off score of minus 0.5 standard deviation. For the distribution of the IQ variables between the two groups, see table 1.

The Binary Logistic regression can be used, even if the groupsize distribution is disproportional (participants with a psychotic disorder N = 34, versus participants without a psychotic disorder N = 408). Important assumptions for the regression, including linearity and additivity of the covariates, were met (Bender & Grouven, 1998). For the Binary Logistic Regression, we used the *Odds Ratio* as an indicator for the strength of the association. As determined by Chen (2010), an *Odds Ratio* of 1.68 was a small effect, an *Odds Ratio* of 3.47 was a medium effect and an *Odds Ratio* of 6.71 was a large effect.

This current study had a within-subject design. The individuals with 22q11DS and a psychotic disorder were compared to individuals without a psychotic disorder. Furthermore, all participants with relevant data available (see “participants”) were included and there were no outliers. All statistical tests were one-sided, because there was a directed hypothesis.

Results

Chi-Square test for goodness of fit

The Chi-Square for goodness of fit (with $a = 0.05$) was statistically significant, $X2$ (1, $N = 442$) = 23.46; $p < .001$. As an index of effect size, *Cohen's W* was 0.23, which can be considered small to medium. Taken together, this indicates that having positive psychotic symptoms is significantly associated with a full-blown psychotic disorder later in life. The overview of the analysis and the group differences can be found in figure 1.

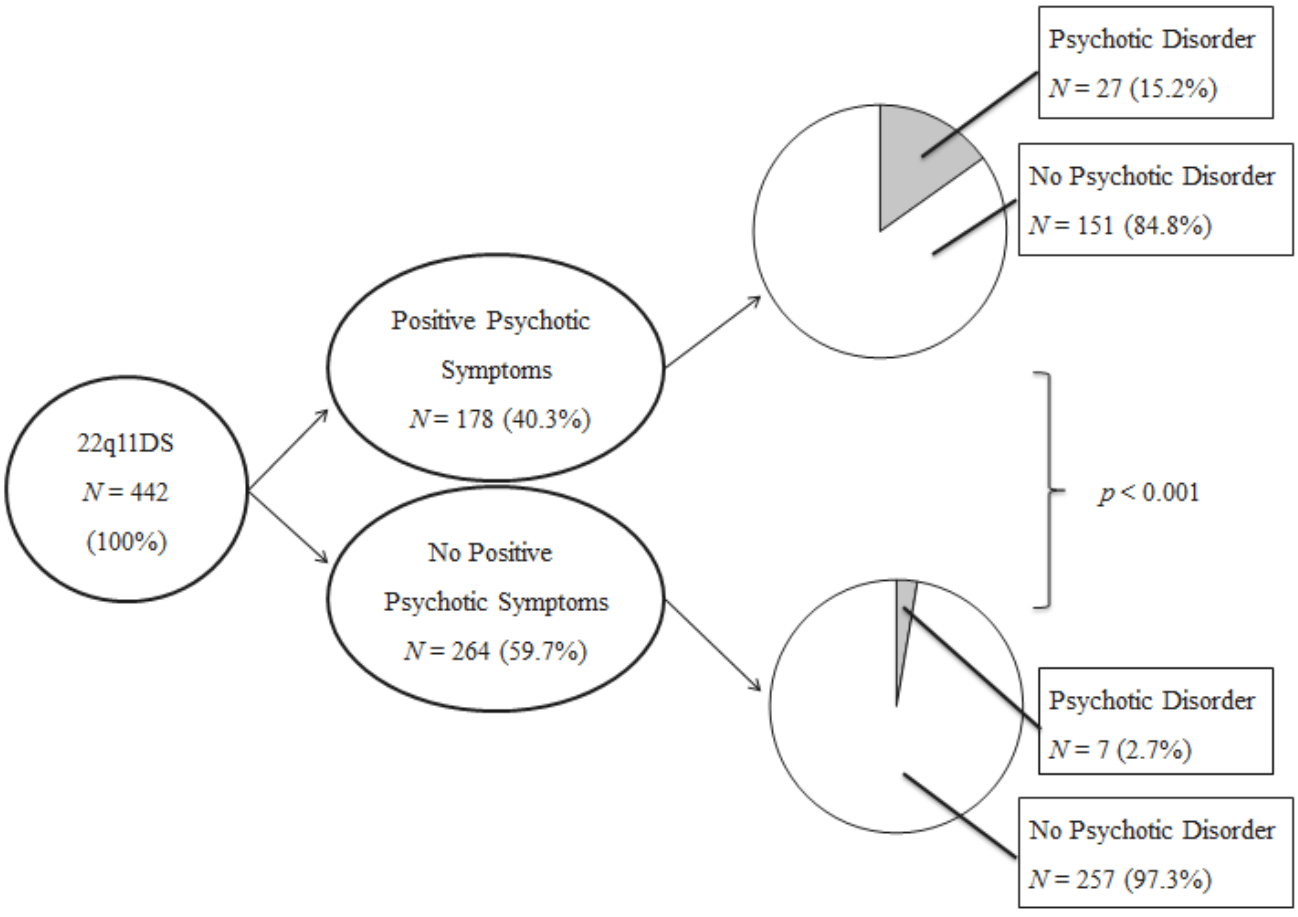

Figure 1. Overview and group differences, based on the results of the Chi-Square analysis

Binary Logistic Regression: Analysis 1

In order to estimate the association between positive psychotic symptoms and the development of a full-blow psychotic disorder, a Binary Logistic Regression was conducted. As demonstrated in Table 2, positive psychotic symptoms, age and interval were predictors which significantly improved the model's predictive capability. Here, positive psychotic symptoms had a stronger effect (*Standardized B* = 3.43) on the development of the psychotic disorder than age (*Standardized B* = 1.80) and interval (*Standardized B* = - 1.55). The *Odds Ratio* of the model was 6.45, the regression model could be interpreted as a strong predictive model. To make sure that the results were valid, we also checked the same Binary Logistic Regression with artificial age-limits of 18, 20 and 25 years. No essential differences in the results were found (Supplemental Table 1).

Table 2

Binary Logistic Regression: Analysis 1

(N = 442 (100%))

	B *[95% CI]*	*SE (b)*	*Odds Ratio*	*Standardized b*	*p*
Positive Psychotic Symptoms	1.86 [1.05, 2.81]	0.44		3.43	**2.47e-05 *****
Age	0.11 [0.02, 0.21]	0.05	6.45	1.80	**0.015 ***
Sex	-0.19 [-0.93, 0.54]	0.37		-0.36	0.606
Interval	-0.12 [-0.25, 0.004]	0.06		-1.55	**0.047 ***

Binary Logistic Regression: Analysis 2

Furthermore, we added two variables to check the association between positive psychotic symptoms and a psychotic disorder later in life. We corrected for Baseline IQ and VIQ decline in the regression model of the positive psychotic symptoms, as these have been previously identified as risk factors. As demonstrated in Table 3, positive psychotic symptoms, Baseline IQ and VIQ

decline are predictors which significantly improved the model's predictive capability. The *Odds Ratio* of the model was 6.89, the model could be interpreted as a large predictive model. Here, positive psychotic symptoms had a stronger effect (*Standardized B* = 3.55) on the development of the psychotic disorder than the Baseline IQ (*Standardized B* = - 2.15) and VIQ decline (*Standardized B* = - 2.33). To make sure that the results were valid, we also checked the same Binary Logistic Regression with continuous IQ variables. No essential differences in the results were found (Supplemental Table 2).

Table 3

Binary Logistic Regression: Analysis 2

(N = 357 (100%))

	B *[95% CI]*	*SE (b)*	*Odds Ratio*	*Standardized b*	*p*
Positive Psychotic Symptoms	1.93 [0.98, 3.06]	0.52		3.55	**0.000214 *****
Age	0.11 [-0.01, 0.24]	0.06		1.67	0.073
Sex	-0.19 [-1.06, 0.67]	0.44		-0.37	0.657
Interval	-0.12 [-0.28, - 0.03]	0.08	6.89	-1.50	0.110
Baseline IQ	-0.04 [-0.08, -0.01]	0.02		-2.15	**0.018 ***
VIQ decline	-0.90 [-1.64, -0.21]	0.36		-2.33	**0.013 ***

Discussion

This study aimed to investigate the association between positive psychotic symptoms at any time point in life and the development of a full-blown psychotic disorder in adulthood, within the 22q11DS population. Multiple studies showed that there are several possible risk factors for developing a psychotic disorder (Bassett et al., 2017; Boydell, 2001; Fanous et al., 2001; Gagliano et al., 2016; Poulton et al., 2000; Vorstman et al., 2015; Yung & McGorry, 2007; Zoller et al., 2019). This study contributes to the understanding of risk factors for developing a psychotic disorder, in the 22q11DS population.

In short, this study showed that, within the 22q11DS population, having positive psychotic symptoms is a significant risk factor for the development of a full-blown psychotic disorder later in life. Furthermore, this study highlighted that a low Baseline IQ and a VIQ decline are indeed strong risk factors for developing a psychotic disorder later in life, within the 22q11DS population.

Our findings are in line with previous studies, demonstrating that positive psychotic symptoms are indeed a strong risk factor for developing a psychotic disorder, within the 22q11DS population (Zoller et al., 2019). Besides, it becomes clear that the significant association between positive psychotic symptoms and the development of a full-blow psychotic disorder stays intact when age-limits were added to the model (Supplemental Table 1). We corrected for several age-limits, in order to investigate if the significant association remained when the chance on false-negatives (saying someone has no psychotic disorder, but could still develop one in the future) was decreased artificially. Despite the increasing – significant - effect of age on the development of a full-blow psychotic disorder, the relation of the symptoms remains. Hence, the significant association between positive psychotic symptoms and the development of a psychotic disorder is a strong self-contained relation, and isn't declared by age.

In this study the regression model was also corrected by adding IQ variables, as these have been previously identified as risk factors (Boydell, 2001; Mollon et al., 2018; Vorstman et al., 2015). Importantly, in this study we found that even when low Baseline IQ and VIQ decline were added to the regression model, the association between positive psychotic symptoms and the development of a psychotic disorder later in life remains.

The findings of this study stresses out the importance of longitudinal, repeated, clinical evaluation in the 22q11DS population. It needs to be empathized that the significant association between positive psychotic symptoms and the development of a full-blown psychotic disorder later

in life remains when other variables in the regression model are adapted, as noted before. From these results, we can carefully conclude that having positive psychotic symptoms is a strong risk factor for developing a psychotic disorder in the 22q11DS population, even when other variables are added to the model. This may mean that when a 22q11DS patient suffers from positive psychotic symptoms, this patient is at large risk for developing a psychotic disorder later in life. When this is indeed the case, these patients could be evaluated more often and critical, so that prevention and/or early treatment can be realized. Early detection of positive psychotic symptoms, may then lead to a better quality of life and daily outcome for these patients (Gur et al., 2017; Yung & McGorry, 2007).

Previous research describes that the risk for the psychotic disorder can be observed via the severity of positive psychotic symptoms, measured by the SIPS (Schneider et al., 2014). In the current study, relevant scores on the SIPS, CAARMS and KSADS were categorized in one variable for the presence of positive psychotic symptoms. Future research may extent previous findings about the indication of risk via these three tests. This can, for example, be analyzed via continue or interval scores within the test scores of the SIPS, CAARMS or KSADS, instead of a dichotomous variable used in this current study.

Moreover, we recommend that future research should try to replicate this study in the general population, instead of the 22q11DS population. One way to replicate this study in the general population can be by following children of psychotic parents. Because of the high heritability of schizophrenia (80%) in the general population, children of people with a psychotic disorder have a relatively high change on developing a psychotic disorder (Jones et al., 2016). Via this study about the development of psychotic disorders in the general population, we can find out if our statement was true. That study could try to confirm if it is indeed true that the development of a psychotic disorder within the 22q11DS population can be used as a model to find out risk factors for developing psychotic disorders in the general population, first stated by Fiksinski et al. (2018).

Furthermore, research has shown that, because of the delay in diagnosis and treatment of schizophrenia, early detection treatment of schizophrenia seems promising. When putative patients will be treated in an early stage of the disease, the quality of life will improve (Riecher-Rossler et al., 2006). More research is needed to investigate the exact positive effect of early treatment of psychotic disorders, both in the 22q11DS population as in the general population.

In contrast to previous research, this research is the first to investigate multiple risk factors on the development of a full-blown psychotic disorder. Next to positive psychotic symptoms, also the risk of low Baseline IQ and VIQ decline on a full-blown psychotic disorder is inspected.

It should be noted that, opposing this strength, there are some limitations to this study. Unfortunately, the data from the large IBBC dataset (N = 1789) were not all useable for this research (Gur et al., 2017). Trying to complete this data, would be an important suggestion for future research. Furthermore, the average age at the time of the last measurement ($M_{maxassessmentage}$ = 17.96, $SD_{maxassessmentage}$ = 4.76, *Range* = 8.00:36.00) is relatively young. Conclusions about this dataset should therefore be interpreted carefully, as individuals in the non-psychotic group may still develop schizophrenia or related psychotic disorders. Nevertheless, the average age of the onset of a psychotic disorder in the 22q11DS population is 18 years (Fiksinski et al., 2017). Therefore, we expect this effect, if at all present, to be small.

There were also limitations in the design of the study. Most importantly, the data of the CAARMS, SIPS and KSADS were conducted by several clinicians. In term of interrater-reliability, we could argue that these tests need to be interpreted carefully. However, the IBBC made sure the data in the IBBC study was checked very strictly via extensive quality controls. Therefore, we can assume that the data are of high quality (Gur et al., 2017).

Further, there was a considerable difference in size between the compared groups (participants with a psychotic disorder N = 34, versus participants without a psychotic disorder N = 408)., which has been posited to potentially lead to less reliable results (McHugh, 2013). However, this considerable difference in size between compared groups is inherent to case-control studies (Gur et al., 2017). Therefore the groups could still be compared, only the results need to be interpreted carefully.

To conclude, the current study has shown that the development of a full-blown psychotic disorder, within the 22q11DS population, could be pronounced by several analysed risk factors. The most prominent would be the presence of positive psychotic symptoms. It should be therefore stressed out, that repeated clinical care is relevant for those who are in high risk of schizophrenia (Jones et al., 2016). Further research could focus on children from parents with a psychotic disorder, risk indication from the SIPS, CAARMS and/or KSADS and early treatment of schizophrenia in groups at risk for the psychotic disorder. Taken together, this research contributes to the clarification of risk factors of the development of psychotic disorders, within the 22q11DS

population. Most importantly, this study shows that having positive psychotic symptoms is a strong risk factor for developing a psychotic disorder later in life, even when other variables are added to the model.

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Appendices

Supplementary table 1
Post-hoc analyses: age-limits

	B ***[95% CI]***	***SE (b)***	***Odds Ratio***	***Standardized b***	***p***
Age-limit: 18 years (*N* = 240 (100%))					
Positive Psychotic	1.66	0.46	5.26	2.36	0.000327 ***
Symptoms	[0.80, 2.63]				
Age$_1$	-0.17	0.08		-1.54	0.034 *
	[-0.34, -0.02]				
Sex	-0.33	0.41		-0.48	0.412
	[-1.14, 0.47]				
Interval	-0.12	0.07		-1.18	0.073
	[-0.25, 0.008]				
Age-limit: 20 years (*N* = 161 (100%))					
Positive Psychotic	1.24	0.51	3.45	1.52	0.015 *
Symptoms	[0.27, 2,30]				
Age$_1$	-0.35	0.10		-2.91	0.000559 ***
	[-0.57, -0.17]				
Sex	-0.53	0.47		-0.65	0.259
	[-1.47, 0.39]				
Interval	-0.07	0.07		-0.65	0.341
	[-0.22, 0.08]				
Age-limit: 25 years (*N* = 47 (100%))					
Positive Psychotic	1.17	1.43	3.22	1.24	0.415
Symptoms	[-1.53, 4.45]				
Age$_1$	-0.81	0.33		-10.64	0.0135 *
	[-1.81, - 0.37]				
Sex	-2.16	1.32		-2.41	0.102
	[-5.26, 0.20]				
Interval	0.30	0.19		2.71	0.114
	[-0.03, 0.75]				

Supplementary table 2
Post-hoc analyses: IQ variables

	B ***[95% CI]***	***SE (b)***	***Odds Ratio***	***Standardized b***	***p***
IQ: Baseline IQ (*N* = 410 (100%))					
Positive Psychotic	1.76	0.45	5.81	3.20	8.64e-05 ***
Symptoms	[0.93, 2.71]				
Age$_1$	0.14	0.05		2.17	0.009 **
	[0.04, 0.25]				
Sex	-0.12	0.39		-0.22	0.765
	[-0.89, 0.66]				
Interval	-0.15	0.07		-1.91	0.025 *
	[-0.29, - 0.02]				
Baseline IQ	-0.02	0.01		-0.98	0.193
	[-0.05, - 0.01]				
IQ: VIQ decline (N = 357 (100%))					
Positive Psychotic	1.98	0.52	7.24	3.65	0.000125 ***
Symptoms	[1.04, 3.11]				
Age$_1$	0.13	0.06		1.92	0.033 *
	[0.01, 0.25]				
Sex	-0.18	0.43		-0.34	0.674
	[-1.03, 0.67]				
Interval	-0.14	0.07		-1.76	0.052
	[-0.30, - 0.002]				
VIQ decline	-0.66	0.33		-1.72	0.049 *
	[-1.34, - 0.02]				

IQ: Baseline IQ (binary) (N = 410 (100%))					
Positive Psychotic Symptoms	1.78 [0.96, 2.74]	0.45	5.96	3.25	6.69e-05 ***
Age$_1$	0.14 [0.03, 0.25]	0.05		2.14	0.010 **
Sex	-0.13 [-0.90, 0.64]	0.39		-0.24	0.740
Interval	-0.15 [-0.29, - 0.02]	0.07		-1.90	0.025 *
Baseline IQ (binary)	0.55 [-0.24, 1.33]	0.40		0.95	0.168
IQ: VIQ decline (binary) (N = 357 (100%))					
Positive Psychotic Symptoms	1.99 [1.05, 3.11]	0.52	7.29	3.66	0.000117 ***
Age$_1$	0.14 [0.02, 0.26]	0.06		1.99	0.0265 *
Sex	-0.12 [-0.96, 0.72]	0.43		-0.22	0.781
Interval	-0.15 [-0.30, - 0.007]	0.07		-1.81	0.045*
VIQ decline (binary)	0.85 [-0.09, 1.74]	0.46		1.24	0.067

IQ: Baseline IQ + VIQ decline (N = 357 (100%))

Positive Psychotic Symptoms	1.96 [1.01, 3.09]	0.52	7.11	3.61	0.000161 ***
Age[1]	0.12 [-0.005, 0.24]	0.06		1.77	0.057
Seks	-0.14 [-0.99, 0.71]	0.43		-0.26	0.747
Interval	-0.13 [-0.29, 0.01]	0.08		-1.62	0.079
Baseline IQ	0.88 [0.001, 1.78]	0.49		1.55	0.049 *
VIQ decline	1.04 [0.07, 1.98]	0.48		1.52	0.031 *

IQ: Baseline IQ + VIQ decline (binary) (N = 357 (100%))

Positive Psychotic Symptoms	1.93 [0.98, 3.06]	0.52	6.89	3.55	0.000214 ***
Age[1]	0.11 [-0.01, 0.24]	0.06		1.67	0.073
Sex	-0.19 [-1.06, 0.67]	0.44		-0.37	0.657
Interval	-0.12 [-0.28, - 0.03]	0.08		-1.50	0.110
Baseline IQ (binary)	-0.04 [-0.08, -0.01]	0.02		-2.15	0.018 *
VIQ decline (binary)	-0.90 [-1.64, -0.21]	0.36		-2.33	0.013 *

1: For this group, age (in years) was defined by the mean of age at diagnosis and age at last assessment