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Citation for published version (APA):

Provenzani, U., Damiani, S., Bersano, I., Singh, S., Moschillo, A., Accinni, T., Brondino, N., Oliver, D., & Fusar-Poli, P. (2022). Prevalence and incidence of psychotic disorders in 22q11.2 deletion syndrome: a meta-analysis. *International Review of Psychiatry*.

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PREVALENCE AND INCIDENCE OF PSYCHOTIC DISORDERS IN 22q11.2 DELETION SYNDROME: A META-ANALYSIS

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Abstract: 200 words

Text: 4328

Figures: 3

Supplementary tables: 8

Supplementary figures: 4

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SHORT ABSTRACT

22q11.2 deletion syndrome (22q.11.2DS) might be one of the strongest genetic risk factors for psychosis, but robust estimates of prevalence and incidence of psychotic disorders in this condition are not available. To address this gap, we performed a multistep systematic PRISMA/MOOSE-compliant literature search of articles reporting prevalence (primary outcome) or incidence (secondary outcome) of psychotic disorders in 22q11.2DS samples (protocol: <https://osf.io/w6hpg>) using random-effects meta-analysis, subgroup analyses and meta-regressions. The **meta-analytical pooled** prevalence of psychotic disorders was 11.50% (95%CI:9.40-14.00%), largely schizophrenia (9.70%, 95%CI:6.50-14.20). Prevalence was significantly higher in samples with a mean age over 18 years, with both psychiatric and non-psychiatric comorbidities and recruited from healthcare services (compared to the community). Mean age was also significantly positively associated with prevalence in meta-regressions ($p < 0.01$). The **meta-analytical pooled** incidence of psychotic disorders was 10.60% (95%CI:6.60%-16.70%) at a mean follow-up time of 59.27 ± 40.55 months; meta-regressions were not significant. To our knowledge, this is the first comprehensive systematic review and meta-analysis of the prevalence and incidence of psychotic disorders in 22q11.2DS individuals. It demonstrates that around one in ten individuals with 22q11.2DS displays comorbid psychotic disorders, and around one in ten will develop psychosis in the following five years, indicating that preventive approaches should be implemented systematically in 22q11.2DS.

ABSTRACT

~~Previous evidence indicates that 22q11.2 deletion syndrome (22q.11.2DS) might be one of the strongest genetic risk factors for psychosis. In individuals affected with 22q11.2DS, the prevalence and incidence of psychotic disorders are widely variable. The lack of robust estimates is an obstacle to effective preventive approaches. To fill this gap, the current meta-analysis addressed the uncertainty of prevalence and incidence of psychotic disorders in 22q11.2DS.~~

~~A multistep systematic PRISMA/MOOSE-compliant literature search of original articles reporting on the prevalence (primary outcome) or incidence of psychotic disorders in 22q11.2DS samples (protocol: <https://osf.io/w6hpg>) was performed from inception until 1st February 2022 searching Web of Science database, complemented by manual search. Random-effects meta-analysis was employed, in addition to meta-analyses for specific diagnoses (e.g., schizophrenia), quality assessment (Newcastle Ottawa Scale [NOS]), heterogeneity assessment (I^2 index) and sensitivity~~

analyses (leave one out; subgroup analyses dividing samples by mean age (under and over 18), method of ascertainment of 22q11.2DS, presence of comorbidities, continent and setting of recruitment). For the primary outcome, we performed meta-regression analyses for independent moderators (year of publication, mean age, proportion of females, sample size, mean IQ, NOS score). For the secondary outcome, we performed multiple meta-regression analyses using follow-up time as a fixed meta-regressor, combined with 6 moderators (publication year, mean age, proportion of females, sample size, mean IQ of the sample, NOS score).

The meta-analytical prevalence of psychotic disorders (n=74 studies, k=7,041 individuals, mean age 18.08±6.84 years, average proportion of females: 51%) was 11.50% (95%CI 9.40-14.00%); largely schizophrenia (9.70%, 95%CI 6.50-14.20). There were significant subgroup differences: 6.50% (95%CI 4.70-9.00%) in samples with a mean age under 18 years and 19.50% (95%CI 15.10-24.80%) in samples with a mean age over 18 years; prevalence was also higher (14.20%, 95%CI 10.10-19.70%) in individuals with both psychiatric and non-psychiatric comorbidities compared to those with psychiatric comorbidities only (8.20%, 95%CI 6.00-11.20%) and in individuals recruited from healthcare services (14.50%, 95%CI 10.10-19.00), compared to those recruited from the community (7.20%, 95%CI 4.80-10.70%). Mean age of samples was also significantly positively associated with prevalence in meta-regressions ($p < 0.01$), but the other moderators (year of publication, proportion of females, sample size, mean IQ of the sample, NOS score) were non-significant.

The meta-analytical incidence of psychotic disorders (n=8 studies, k=533 individuals, baseline mean age 14.39±3.24, average proportion of females 45%±9%) was 10.60% (95%CI 6.60%-16.70%) at a mean follow-up time of 59.27±40.55 months. Multiple meta-regressions using follow-up time as fixed meta-regressor, combined with 6 moderators (year of publication, mean age, proportion of females, sample size, mean IQ, NOS score) were not significant.

To our knowledge, this is the first comprehensive systematic review and meta-analysis of the prevalence and incidence of psychotic disorders in 22q11.2DS individuals. It demonstrates that around one in ten individuals affected with 22q11.2DS display comorbid psychotic disorders, indicating that systematic screening for psychosis should be conducted in this population. Around one in ten individuals affected with 22q11.2DS will develop psychosis in the following five years, indicating that monitoring and clinical follow-up should be implemented systematically. Overall, these findings corroborate the need to include 22q11.2DS in preventive approaches for psychotic disorders.

Keywords : 22q11.2DS, psychosis, prevalence, incidence, risk

1. BACKGROUND

The 22q11.2 deletion syndrome (22q11.2DS) is one of the most common syndromes caused by a rare Copy Number Variation, with a prevalence estimated at around 1/3000 to 1/6000 live births [1]. In the majority of cases, it is caused by a 3 Mb hemizygous deletion in chromosomal region 22q11.2, de novo in 85-90% of cases [2, 3]. The term is used to refer to a heterogeneous group of disorders that share the same genetic alteration: DiGeorge syndrome or velo-cardio-facial syndrome, Cono-Truncal Anomaly Face Syndrome, Opitz syndrome and CHARGE syndrome (coloboma, heart defects, atresia choanae, growth retardation, genital abnormalities, and ear abnormalities) [4]. It can affect both sexes, and it is present in different ethnic groups thus not being characteristic of Caucasians [5], but it has a higher prevalence in western countries [6]. The gold-standard diagnostic test is fluorescence *in situ* hybridization [7], while other recent techniques include multiplex ligation-dependent probe amplification (which uses probes directed towards the entire 22q11 region) and microarray comparative genome hybridization [8].

22q11.2DS is associated with a high rate of morbidity and mortality, being primarily responsible for a wide range of congenital conditions but also for an increased risk of premature death [1]. The clinical manifestations of 22q11.2DS can be highly variable, depending on age and the investigations performed, but they usually include: palatal abnormalities, immunodeficiency, congenital cardiac abnormalities, hypocalcaemia due to hypoparathyroidism, genitourinary abnormalities and gastrointestinal manifestations [9]. The neuro-cognitive phenotype of 22q11.2DS is also variable, heterogeneous and complex. Seizures, epilepsy and early-onset Parkinson's disease have a greater prevalence in comparison to the general population [10, 11]. During early childhood, alterations in neuromotor control and delay in language development predominate [12-15]. Neurodevelopmental delay often becomes more evident in adolescence, usually with borderline intellectual functioning (IQ 75-85) or mild intellectual disability (IQ (55-75), although moderate or severe disability is possible. These abnormalities persist into adulthood, often leading to the development of full-blown psychiatric comorbidities, which are present in 41% of adult individuals with 22q11.2DS [12, 16, 17]. Children and adolescents are often diagnosed with anxiety disorders and "neurodiversity", such as autism spectrum or attention deficit hyperactivity disorder. The developmental stages that follow are characterized by the onset of mood disorders and, above all, psychosis. [10, 12, 18, 19].

The critically high lifetime prevalence of ~~this condition~~ psychotic disorders among individuals with 22q11.2 DS places ~~22q11.2DS~~ this syndrome as the strongest genetic risk factor for psychosis, with some evidence suggesting that the risk is increased by up to 30 times in the presence of 22q11.2DS [1], compared to the general population. Therefore, 22q11.2DS is considered a neurogenetic model to investigate the processes underlying psychosis [20]; and further research on this association complementing might support indicated prevention in a refined group of people at clinical high-risk for psychosis (CHR-P) ~~the recent achievements in this area mostly related to primary indicated prevention in those at clinical high risk for psychosis (CHR-P)[21-27],~~ which could include a 22q11.2DS subgroup. Preliminary findings in CHR-P individuals with 22q11.2DS indicate that those affected tend to experience negative symptoms earlier and more frequently than non-deleted CHR-P [28].

Preventive approaches for this condition are limited, owing to widely heterogeneous estimates of psychosis prevalence in this population. Few studies report subthreshold psychotic symptoms in 22q11.2DS, with prevalence ranging from 20% to 85% [29, 30], while diagnoses of overt psychotic disorders in adults with 22q11.2DS range from 5% to 40% [17]. This uncertainty may be attributed to several factors, including differences in sample size, clinical criteria or assessment tools [29]; however, no systematic reports are available on this topic yet. Additionally, it is difficult to establish the incidence of new cases of psychosis in these individuals, thus limiting clinical follow up and monitoring purposes [31].

Given the potential preventive capacity of interventions in those affected with 22q11.2DS, it is essential to robustly estimate the global prevalence and incidence of psychotic disorders in this condition. The aim of this study is to fill this gap by meta-analysing data on the prevalence and incidence of psychosis in 22q11.2DS individuals. The additional evidence obtained through this analysis may contribute to the development of tailored preventive strategies in terms of baseline assessment and longitudinal follow up.

2. METHODS

This study was conducted accordingly to the Preferred Reporting Items for Systematic reviews and Meta-Analyses [32] and the Meta-analysis Of Observational Studies in Epidemiology [33](eTable1, eTable2). The study protocol was registered and published online on <https://osf.io/w6hpg>.

2.1 Search and Selection Strategies

Three independent researchers performed a systematic PRISMA-compliant electronic search for articles published from inception until February 1st, 2022. We ~~searched~~used the Web of Science ~~database-platform~~ (employing the “all databases options” which includes multiple databases: Web of Science Core Collection, BIOSIS Citation Index, Current Contents Connect, Data Citation Index, Derwent Innovations Index, KCI - Korean Journal Database, MEDLINE, ~~Russian Science Citation Index and~~ SciELO Citation Index and Zoological Record) using the following search string: “(22q11 OR DiGeorge OR VCFS OR velo-cardio-facial) AND (psychosis OR schizophrenia)”. References of relevant studies, systematic reviews and meta-analyses identified during this phase were manually searched. Articles were first screened as abstracts, then the remaining articles were assessed against the inclusion and exclusion criteria on a full-text basis and decisions were taken regarding their inclusion in the meta-analysis.

The inclusion criteria were: a) original studies conducted on living human individuals, published in peer-reviewed journals, written in English; b) conducted in individuals with 22q11.2DS ascertained with the gold-standard technique (fluorescence in situ hybridization or confirmed genetically with another validated and disclosed approach (e.g multiplex ligation-dependent probe amplification, quantitative fluorescent polymerase chain reaction, microarray) [34]. c) reporting raw numbers or percentage of individuals with non-organic psychotic disorders (see eTable3 for details) ascertained with DSM (American Psychiatric Association) or ICD (World Health Organization (WHO)-any version criteria at baseline (prevalence) or baseline and follow up (incidence).

The exclusion criteria were: a) reviews, conference proceedings, study protocols, case series or reports, studies conducted post-mortem or on non-human individuals, unpublished data; b) studies which did not declare the method of ascertainment of 22q11.2DS based on genetic analysis (defined as above); c) for the primary outcome (prevalence), studies employing selection criteria (inclusion or exclusion) regarding the presence or the absence of psychotic disorders at baseline; d) studies not reporting raw numbers or percentage of individuals with psychotic disorders at baseline (prevalence) or baseline and follow up (incidence; studies not ascertaining psychotic disorders at baseline cannot reliably address the emergence of new cases) e) studies defining psychotic disorders using criteria other than DSM/ICD or including less than 10 patients in the 22q11.2DS group; f) overlapping data sets.

To analyze potential overlapping datasets, we contacted experts in the field to discuss and reach a consensus (T.A, A.M). We excluded studies where overlaps were clearly disclosed in the methods

and studies where patients were recruited from the same healthcare services (specialized in 22q11.2DS) by the same authors in a 5-year span, preferring the studies with the largest sample size and most recent. When the overlap, despite our efforts, was unclear, such as in large consortia ([see eMethods](#)), we conservatively included only the largest/most recent study of the consortium and then performed one study removal sensitivity analyses to test the impact of our selection. Disagreements in selection criteria were resolved through discussion and consensus with a senior researcher.

2.2 Outcome measure and data extraction

The primary outcome was defined as the cross-sectional prevalence of psychotic disorders (defined as the proportion of cases in the sample) among individuals with 22q11.2DS. The secondary outcome was defined as the cumulative risk of developing new psychotic disorders that were not present at baseline among individuals with 22q11.2DS at different timepoints. Two independent researchers (I.B., S.S.) extracted data. Any discrepancies arising in extraction criteria were resolved through discussion with a senior researcher. The variables extracted and recorded in the main database were: author and year of the study, sample size of 22q11.2DS group, mean age and proportion of females in 22q11.2DS group, type of control group (if present, e.g. healthy controls) and relative sample size, study design (e.g. case-control), criteria used for psychosis diagnosis (e.g. DSM), method of ascertainment of 22q11.2DS (e.g. fluorescence in situ hybridization), mean IQ of 22q11.2DS group, comorbidities (non-psychiatric and psychiatric), number of patients with psychotic disorders at baseline, number of patients with psychotic disorders at follow up (if present), follow up time, continent where the study was conducted and setting of recruitment (e.g. community, healthcare services, hospitals). We also recorded the specific psychotic disorder and matched it with the corresponding ICD-10 diagnosis [35] (eTable3).

2.3 Quality assessment

The quality of the studies included in the meta-analysis was evaluated using the Newcastle-Ottawa Scale (NOS) for case-control, cross-sectional (adapted) and cohort studies, which have been repeatedly used [36, 37] to assess study quality [in meta-analyses](#). Studies were awarded a minimum of zero and a maximum of nine points [following the coding manual published by the authors](#)[38], on items related to the selection and definition of 22q11.2DS patients and controls, representativeness, comparability and exposure.

2.4 ~~Strategy for d~~Data synthesis

The effect size for the primary outcome was defined as the percentage of individuals with a diagnosis of psychotic disorders at baseline within those affected with the 22q11.2DS (prevalence). We also performed meta-analyses for specific diagnoses (e.g. schizophrenia) if there were enough studies available. The effect size for the secondary outcome was the ~~meta-analytical~~pooled cumulative risk of transition to psychosis at 1,2,3,4 and more than 4 years' follow up, estimated using the number of individuals with 22q11.2DS developing psychosis at each of these time point. In the case of too few available studies to stratify the cumulative risk at these timepoints, we planned to pool all timepoints reporting the average follow-up time and then use meta-regression to test the effect of follow up time. Meta-analyses were performed when at least 5 studies were available for each outcome. Random-effects models (DerSimonian and Laird method[39]) were selected to account for expected heterogeneity between studies, logit transformation was used to estimate effect sizes and pooled outcomes. Q statistic was used to assess heterogeneity among study point estimates, while the proportion of total variability in prevalence was evaluated with the I^2 index [40] ~~which is not influenced by the number of studies included~~. For the primary outcome ~~We performed the following~~ sensitivity analyses (~~for the primary outcome: leave-one-out~~) to confirm the robustness of the findings, ~~and~~ subgroup analyses dividing samples by mean age (under and over 18), method of ascertainment of 22q11.2DS, presence of comorbidities, continent and setting of recruitment. Differences between subgroups were tested using mixed effect models. For the primary outcome (prevalence), we also performed meta-regression analyses for independent moderators (year of publication, mean age, proportion of females, sample size, mean IQ of the sample, Newcastle Ottawa Scale score). For the secondary outcome (incidence), we performed multiple meta-regression analyses (i.e., using 2 meta-regressor factors at the same time) using follow up time as a fixed meta-regressor factor. The latter was combined with 6 moderators (publication year, mean age, proportion of females, sample size, mean IQ of the sample, Newcastle Ottawa Scale score). ~~We did not evaluate publication bias because studies included in the meta-analyses of proportions are non-comparative; thus, there are no "negative" or "undesirable" results that may have biased publications [41, 42]. Furthermore, the standard methods for the detection of publication bias are not accurate for these types of meta-analyses [43]~~ Publication bias was assessed for the primary outcome by visual inspection of the funnel plot and Egger's test. ~~However, to address potential publication biases~~ Also, we tested the association between the primary outcome and sample size, in line with previous studies [21]. The significance level was set at 0.05 (two-tailed). Meta-analysis was performed using Comprehensive Meta-Analysis Software, Version 3.

3. RESULTS

Database Characteristics of the included studies

The systematic literature search (PRISMA flow-chart, Figure 1) identified 74 independent articles. The total database included 7,041 individuals with 22q11.2DS, with a mean age of 18.08 ± 6.84 years (range from 8.91 to 38.97) and an average proportion of females of 51% (range from 31% to 70%). The mean sample size was 95 ± 208 (range from 14 to 1789). 51 studies (69%) had a control group, the majority including healthy controls (58%) and/or siblings (19%). 40 studies (54%) had a case-control design, 20 studies (27%) were cross-sectional, 14 studies (19%) were longitudinal. Only one study included employed ICD criteria, while the other studies employed DSM criteria for psychiatric diagnosis of psychotic disorders. For the molecular diagnosis of 22q11.2DS, 40 studies (54%) used fluorescence in situ hybridization, 12 studies (16%) used polymerase chain reaction, 4 studies (5%) used array or microarray, 17 studies (23%) used more than one technique. The mean IQ of the samples was 73.80 ± 5.62 (range from 64.00 to 89.93). 34 studies (46%) recruited individuals with psychiatric comorbidities, 25 studies (34%) with psychiatric and non-psychiatric comorbidities and in 15 studies (20%) comorbidities were not clear or not disclosed. 8 studies (11%) were conducted in Asia, 33 studies (45%) in Europe, 26 studies (35%) in North America and 7 studies (9%) were conducted in multiple continents. Regarding the setting of recruitment, 26 studies (35%) recruited patients from the community, 29 studies (39%) from general healthcare services, 12 studies (16%) from both settings, and 7 studies (9%) did not disclose the setting of recruitment (there were no studies recruiting hospitalized patients). The mean NOS score was 6.31 ± 1.45 .

The secondary outcome (incidence) was reported in a subset of 8 studies, including 533 individuals. The mean sample size was 67 ± 63 , the mean age at baseline was 14.39 ± 3.24 years, the average proportion of females was $45\% \pm 9\%$, and the mean number of individuals with psychosis at baseline was 2 ± 5 . The mean follow up time was 59.27 ± 40.55 months.

Overlap check of the studies which were included after the screening is reported in Supplementary (eTable4). 8 studies included data from international consortia [29, 44-50], gathering data from multiple sites and authors. Even through discussion with experts in the field who directly participated and sent data to these consortiums, it was impossible to determine clear overlaps in these studies, given the multiple connections with samples and authors in our databases and lack of clear information about whether data from consortia were already included in previous publications. We thus included the largest and most recent study from these

international consortia [51] and we performed sensitivity analysis without this study to highlight any significant differences (see below: sensitivity analyses).

The characteristics of the studies included in the meta-analyses are illustrated in eTable5.

Prevalence of psychotic disorders in 22q11.2DS

The ~~meta-analytical~~pooled prevalence of psychotic disorders in 22q11.2DS individuals (74 studies) was 11.50% (95%CI 9.40-14.00%) (Figure 2). Meta-analyses for specific diagnoses, matched with the corresponding ICD-10 diagnosis (van Drimmelen-Krabbe et al., 2001) (eTable3), revealed that the ~~meta-analytical~~pooled prevalence of schizophrenia (F20.0-6 and F20.9, 26 studies) was 9.70% (95%CI 6.50-14.20), schizophreniform disorder (F20.81, 6 studies) was 0.90% (95%CI 0.40-2.00%), schizoaffective disorder (F25.0-8, 15 studies) was 2.90% (95%CI 2.10-4.10%), other/unspecified nonorganic psychosis (F28-29, 14 studies) was 2.40% (95%CI 1.30-4.30%) and affective psychoses (F30.2, F31.2, F31.5, F32.3, F33.3, 8 studies) was 1.90% (95%CI 1.40-2.50%). There were not enough studies to report ~~meta-analytical~~pooled prevalences for other psychotic disorders. Heterogeneity (I^2) was 32% high (86%), which we tried to analyze through subgroup analysis and meta-regression. Visual inspection of the funnel plot (eFigure1) revealed possible small-study effect, with larger studies reporting higher proportions of individuals with psychotic disorders. Egger's test for funnel plot asymmetry was also significant ($p<0.01$). The association between the primary outcome and sample size was not significant ($\beta=0.0005$; $F=0.74$; $t=0.86$; $p=0.39$).

Incidence of psychotic disorders in 22q11.2DS

The ~~meta-analytical~~pooled incidence of psychotic disorders in 22q11.2DS individuals was estimated across all timepoints due to the low number of studies. The ~~meta-analytical~~pooled cumulative risk of psychotic disorders was 10.60% (8 studies; 95%CI 6.60%-16.70%) at a mean follow up time of around five years (59.27 ± 40.55 months) (Figure 3). Heterogeneity was considerable (69%)0%.

Heterogeneity

Heterogeneity (I^2) was 32% for the prevalence and 0% for incidence.

Sensitivity and subgroup analyses

Excluding one study at a time, including the above-mentioned study published by an international consortium [51] for the primary and secondary outcome, confirmed the robustness of the findings and did not significantly change our results (eFigure1aeFigure2a).

Results of subgroup analyses for the primary outcome were the following:

- 1) Age: there was a significant between groups difference ($Q=27.47$, $p<0.01$). Prevalence of psychotic disorders in 22q11.2DS individuals was 6.50% (95%CI 4.70-9.00%) in studies (n=45), including individuals with a mean age under 18 years, 19.50% (95%CI 15.10-24.80%) in studies (n=29) with a mean age over 18 years. Heterogeneity (I^2) was respectively 082% and 3788% in the two groups.
- 2) Method of ascertainment of 22q11.2DS: the difference between groups was not significant ($Q=4.62$; $p=0.32$).
- 3) Comorbidities: there was a significant between-group difference ($Q=8.29$, $p=0.02$). Prevalence of psychotic disorders in studies including individuals with psychiatric comorbidities (n=34) was 8.20% (95%CI 6.00-11.20%), with psychiatric and non-psychiatric comorbidities (n=25) was 14.20 (95%CI 10.10-19.70%) and with unclear/undisclosed comorbidities (15) was 16.10% (95%CI 10.40-24.20%). Heterogeneity (I^2) was 678%, 2687% and 5583% in the three groups.
- 4) Continent: the difference between groups was not significant ($Q=5.67$, $p=0.07$).
- 5) Recruitment setting: there was a significant between-group difference ($Q=8.29$, $p=0.04$). Prevalence of psychotic disorders in studies including individuals recruited from the community (n=26) was 7.20% (95%CI 4.80-10.70%), from healthcare services (n=29) was 14.50 (95%CI 10.10-19.00%), from both settings (n=12) was 13.40% (95%CI 8.00-21.60%) and with unclear/undisclosed setting (n=7) was 12.90% (95%CI 5.00%-29.50%). Heterogeneity (I^2) was 073%, 4587%, 2289% and 19-76 % in the four groups.

Sensitivity Subgroup plots and data are illustrated in eFigures 12ab-f.

Meta-regression

For the primary outcome (prevalence), meta-regression analyses (eTable6) positively associated mean age ($\beta=0.09$; $F=36.04$; $t=6.00$; $p<0.01$) with a higher prevalence of psychotic disorders (scatterplot is depicted in eFigure32). Meta-regressions of year of publication, proportion of females, sample size, mean IQ of the sample, Newcastle Ottawa Scale score and prevalence were not significant.

For the secondary outcome (incidence), multiple meta-regression analyses (eTable7) using follow up time as fixed meta-regressor, combined with 7 moderators (year of publication, mean age, proportion of females, sample size, mean IQ of the sample, Newcastle Ottawa Scale score) were not significant.

Publication bias

~~The association between the primary outcome and sample size was not significant ($\beta=0.0005$; $F=0.74$; $t=0.86$; $p=0.39$).~~

4. DISCUSSION

To our knowledge, this is the first comprehensive systematic review and meta-analysis of the prevalence and incidence of psychotic disorders in 22q11.2DS individuals. The ~~meta-analytical~~pooled prevalence of psychotic disorders (across 74 studies and 7,041 individuals with a mean age of 18 years) was 11.50%. The ~~meta-analytical~~pooled cumulative risk of developing new psychotic disorders (across 8 studies and 553 individuals with a mean age of 14) was 10.60% at a mean follow up time of 59 months.

Our results confirm the striking difference in the prevalence of psychotic disorders in 22q11.2DS individuals aged on average 18 years, with values (11.50%) that qualitatively exceed almost four times those of the general population (3.06%, from [52]) and of three times those of individuals with intellectual disabilities (3.80% from [53]). These findings are robust because we tested the association between 22q11.2DS and overt psychotic syndromes as operationalised by DSM/ICD diagnostic criteria. The possibility of small-study effect, as revealed by the asymmetry of the funnel plot and the significance ($p<0.01$) of Egger's test, with larger studies showing higher proportions of individuals with psychotic disorders, supports the hypothesis that our pooled prevalence of psychotic disorders in 22q11.2DS might even be underestimated.

This approach is substantially different compared to studies [54-56] exploring the presence of sub-threshold and non-diagnostic symptoms of psychosis in this population. These attenuated symptoms not reaching diagnostic threshold are expected to be even more prevalent, with estimates ranging from 20% to 85% [29, 30]. We observed, in subgroup analyses a significantly lower prevalence (6.5%) of psychotic disorders in studies including individuals with a mean age 18 years compared to those with individuals 18 years (i.e. 19.50%). We also found with meta-regression that the mean age of individuals positively modulated the prevalence of psychosis in

22q11.2DS and could at least partially explain the higher heterogeneity in the >18 years group ($I^2=3788\%$) compared to the youngest ($I^2=082\%$). Despite this difference, our finding of a prevalence of psychosis of around 7% in underage samples corroborates the hypothesis that early-onset psychosis is particularly common in 22q11.2DS [57]. Prevalence of psychosis was also increased by the presence of medical and psychiatric comorbidities (compared to psychiatric only), which could also reflect a higher impact of the genetic load, leading to psychiatric symptoms that are more pronounced. Medical comorbidities in these individuals might also lead to more intensive clinical assistance and easier recognition of psychiatric symptoms. This hypothesis is also confirmed by the higher prevalence of psychosis in 22q11.2DS individuals recruited from healthcare services (compared to the community). Lower functioning and adaptive skills in this population are most probably associated with help-seeking behaviours in healthcare clinics [58].

From a clinical standpoint, these data indicate that psychotic disorders should be systematically assessed in all individuals affected with 22q11.2DS, preferably with the use of semi-structured interviews that can also detect subthreshold psychotic symptoms. For example, some studies have investigated the 22q11.2DS with the Structured Interview for Prodromal Syndromes [59], finding that subthreshold symptoms were common (85% of individuals had 1 or more), with ideational richness (47%) and trouble with focus and attention (44%) being the most represented [30]. The use of assessment measurements already employed in the CHR-P paradigm could harmonise clinical research efforts and comparative analyses across the two paradigms.

Our results also confirm the enhanced risk of developing new psychotic disorders (incidence) in 22q11.2DS individuals aged 14.39 ± 3.24 years, with values (10.60% at 5 years) that qualitatively exceed 70 times those of the general population (0.14% at 5 years, annualised estimates from [60]) and of 3 times those in intellectual disabilities (3.5% at 5 years, annualised estimates from [53]). Transition to psychosis in CHR-P individuals has been reported with a comparatively higher ~~meta-analytical~~pooled risk of 30% at 5 years (Table 2 in [21]), in individuals with a mean age of 20 years. The apparent lower probability of developing psychosis in 22q11.2DS compared to the CHR-P state could be due to the lower age of these samples at baseline (14 years in 22q11.2DS vs 20 years in the CHR-P state). Indeed, the global meta-analytic age of onset of psychotic disorders is around 20 years [61]: the 22q11.2DS samples may not have had sufficient follow-up time to detect most cases of psychotic disorders.

Another explanation for the seemingly lower probability of developing psychosis may be that in about 26% of 22q11.2DS cases, psychotic disorders appear as transient and are not diagnosed as persistent psychotic disorders [57]. This represents an operational difference compared to the CHR-P paradigm, which includes short-lived psychotic episodes [62-66] and calls again for a synergic integration of the two approaches. This suggestion is also supported by the observation that clinically psychotic disorders are indistinguishable across the two paradigms and that some factors leading to a transition to psychosis (e.g. lower level of functioning at baseline) are broadly comparable [54]. The potential synergism is motivated by the complementary nature of the primary prevention encompassing selective (22q11.2DS) and primary (CHR-P)[66] approaches.

From a clinical standpoint, these findings indicate that 22q11.2DS is likely the most important genetic risk factor for the development of schizophrenic spectrum disorders [67], with a predictive value which is way higher than that of any other genetic biomarkers currently available. Sensitivity analyses revealed, in fact, that schizophrenia was the most commonly diagnosed disorder (9.70%), representing 84% of the 22q11.2 individuals with a psychotic disorder. This result is similar to previous observations in CHR-P samples, where 73% of individuals who transitioned to psychosis were diagnosed with schizophrenia [68]. 22q11.2DS also represents an empirical neuro-biological model to study the brain mechanisms leading to psychosis [69, 70]. Given the enhanced risk of developing psychosis in a young population, these findings call for assertive clinical monitoring and follow up and for the development of effective ways of altering the onset of the disorders. These aims could well be targeted by CHR-P services [71-73] that are already deployed in some national healthcare services to facilitate real world primary prevention of psychosis. While the two paradigms appear currently disjointed in most healthcare services, the next generation of research is required to test the potential of synergically combining selective and indicated prevention in young people.

5. STRENGTHS AND LIMITATIONS

First, we conservatively screened studies for valid prevalence and incidence data of psychotic disorders, including many studies for which the main outcome was not primarily related to the investigation of psychosis in 22q11DS. While this approach ensured comprehensiveness, it might as well introduce sampling (e.g. in neuroimaging studies) or assessment biases. To mitigate this issue, we adopted strict inclusion criteria regarding the 22q11.2DS diagnosis (which had to be explicit with a validated method) and the psychiatric assessment (DSM/ICD). The resulting mean quality of the studies was acceptable (mean NOS score of 6.30). Finally, we also conducted sensitivity analyses by testing the impact of potential sampling biases in different healthcare

settings and by removing one study each time and re-running the analyses. The sum of prevalence rates of single disorders (i.e., schizophrenia) seems higher than the prevalence rate of all combined psychotic disorders. These estimates reflect, in fact, different meta-analyses and therefore different sample sizes of individual studies. It is therefore not possible to directly “sum” these estimates, because the effect size for each study could have a slightly different weight in each meta-analysis (overall prevalence and prevalence for single disorders). Heterogeneity of the sample was high, not explained by subgroup analyses and meta-regressions: this value could therefore reflect the different and multiple modalities of recruitment of individuals with 22q11.2DS, related to the great variability in the study types included in our meta-analysis. A further limitation is due to the relatively low number of clinical centres publishing 22q11.2DS data, some large-scale international consortia and unclear recruitment procedures, checking for potential overlaps was challenging. To mitigate this bias, we involved experts in the field (A.M, T.A) who directly collaborated with many of the authors included in our database and cross-checked the potential overlaps under their supervision.

6. CONCLUSIONS

This is the first meta-analysis to demonstrate that about one in ten individuals affected with 22q11.2DS display comorbid psychotic disorders, indicating that systematic screening for psychosis should be conducted in this population. About one in ten individuals affected with 22q11.2DS will develop psychosis in the following five years, indicating that monitoring and clinical follow up should be implemented systematically. Overall, these findings corroborate the need to include 22q11.2DS in preventive approaches for psychotic disorders.

7. AVAILABILITY OF DATA AND MATERIALS

The authors give no permission to share raw data.

8. FUNDING SOURCES

None.

9. CONFLICTS OF INTEREST

FPF received honoraria or grant fees from Lundbeck, Angelini and Menarini in the past 36 months outside the current work.

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Figure 1. PRISMA flow-diagram

Figure 2a. Forest plot for primary ~~meta-analytical~~pooled outcome (prevalence) (part 1)

Figure 2b. Forest plot for primary pooled outcome (prevalence) (part 2)

Figure 3. Forest plot for secondary ~~meta-analytical~~pooled outcome (~~prevalence~~incidence)