www.elsevier.com/locate/euroneuro

The U-shaped relationship between parental age and the risk of bipolar disorder in the offspring: A systematic review and meta-analysis

Giovanna Fico[a], Vincenzo Oliva[a,b], Michele De Prisco[a,c],
Anna Giménez-Palomo[a], Maria Sagué-Vilavella[a],
Susana Gomes-da-Costa[a], Marina Garriga[a], Eva Solé[a],
Marc Valentí[a], Giuseppe Fanelli[b,d], Alessandro Serretti[b],
Michele Fornaro[c], Andre F Carvalho[e], Eduard Vieta[a,*],
Andrea Murru[a]

[a] Bipolar and Depressive Disorders Unit, Institute of Neuroscience, Hospital Clinic, IDIBAPS, CIBERSAM, University of Barcelona, 170 Villarroel st, 12-0, Barcelona, Catalonia 08036, Spain
[b] Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[c] Department of Neuroscience, Section of Psychiatry, Reproductive Science and Odontostomatology, Federico II University of Naples, Naples, Italy
[d] Department of Human Genetics, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands
[e] IMPACT - the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Geelong, Vic., Australia 6 Perinatal Health Unit, Hospital Clinic, IDIBAPS, CIBERSAM, University of Barcelona, Deakin University, Barcelona, Catalonia, Spain

Abstract
Parenthood age may affect the risk for the development of different psychiatric disorders in the offspring, including bipolar disorder (BD). The present systematic review and meta-analysis aimed to appraise the relationship between paternal age and risk for BD and to explore the eventual relationship between paternal age and age at onset of BD. We searched the MEDLINE,

* Corresponding author.
E-mail address: evieta@clinic.cat (E. Vieta).

Scopus, Embase, PsycINFO online databases for original studies from inception, up to December 2021. Random-effects meta-analyses were conducted.

Sixteen studies participated in the qualitative synthesis, of which $k = 14$ fetched quantitative data encompassing a total of 13,424,760 participants and 217,089 individuals with BD. Both fathers [adjusted for the age of other parent and socioeconomic status odd ratio – $OR = 1.29 (95\%C.I. = 1.13\text{-}1.48)$] and mothers aged ≤ 20 years [$(OR = 1.23(95\%C.I. = 1.14\text{-}1.33)$] had consistently increased odds of BD diagnosis in their offspring compared to parents aged 25-29 years. Fathers aged ≥ 45 years [adjusted $OR = 1.29$ (95%C.I. = 1.15-1.46)] and mothers aged 35-39 years [$OR = 1.10(95\%C.I. = 1.01\text{-}1.19)$] and 40 years or older [$OR = 1.2(95\% C.I. = 1.02\text{-}1.40)$] likewise had inflated odds of BD diagnosis in their offspring compared to parents aged 25-29 years.

Early and delayed parenthood are associated with an increased risk of BD in the offspring. Mechanisms underlying this association are largely unknown and may involve a complex interplay between psychosocial, genetic and biological factors, and with different impacts according to sex and age range. Evidence on the association between parental age and illness onset is still tentative but it points towards a possible specific effect of advanced paternal age on early BD-onset.

1. Introduction

A basic tenet of psychiatry is that the disease phenotype results from a combination of genetic and environmental effects. Indeed, bipolar disorder (BD) is a severe psychiatric condition with a prevalence in the general population of 2% (Carvalho et al., 2020) and an estimated family- and twin-based heritability of 60-85% (McGuffin et al., 2003). However, genetics only explains a part of the etiology of BD, thereby a growing body of evidence has related diverse elements of the environment that may influence the risk for BD (Bortolato et al., 2017). The broad range of environmental risk factors vary on time of exposure and may include both pre- or peri-natal factors, adverse childhood experiences, infections, as well as urbanization, migration, major stressful life events, and the misuse of drugs or alcohol (Blanco et al., 2017; Grant et al., 2005; Kessing et al., 2004; Pacchiarotti et al., 2013; Vieta, 2014). Globally, environmental factors contribute up to 32% of the risk of BD (Polderman et al., 2015), proving to be appealing potentially modifiable targets for preventive strategies.

Parental age is a well-known factor involving environmental and genetic contributions that impacts the risk of several disorders in the offspring (Malaspina et al., 2015; Reichenberg et al., 2006). Both extremes of the reproductive age have been associated with worse outcomes, either regarding mother's age, father's age, or both (McGrath et al., 2014). A notable example is the higher risk of Down's syndrome in older mothers (Mai et al., 2013), while a younger childbearing age is associated with educational underachievement, juvenile crimes, substance misuse, and mental health problems (D'Onofrio et al., 2014a; Sujan et al., 2022). Advanced paternal age at birth has been associated with an increased incidence of several neurodevelopmental and psychiatric disorders, including schizophrenia and autism spectrum disorders (Khachadourian et al., 2021; Reichenberg et al., 2006). Mechanisms underlying these relationships are not fully understood, with findings suggesting a role for *de-novo* mutations in the male germline (Fromer et al., 2014;

Malaspina, 2001 a) or even a greater likelihood for pregnancy complications which are more common with delayed parenthood (Chudal et al., 2017; Garcia-Rizo and Bitanihirwe, 2020; Giménez et al., 2019; Talati et al., 2013). Also, advanced paternal age seems to increase the risk for early-onset psychoses due to the possible role of accumulating age-related DNA mutations (Wang et al., 2019).

However, there is still discordant evidence on the association between advanced parental age and risk of BD in the offspring, with some large studies proving the positive association between advanced paternal age and BD risk (D'Onofrio et al., 2014 a; Frans et al., 2008 a; Weiser et al., 2020), whilst others have shown no significant association (Buizer-Voskamp et al., 2011; McGrath et al., 2014).

Considering the increasing trend in average parental age (Bray et al., 1978), the elucidation of such an association might have societal and public health implications. Also, evidence of parental age effects on BD risk may provide insights into the etiology of this complex, multifactorial disorder.

Thus, the first aim of this systematic review and meta-analysis is to determine whether parental age is associated with an increased risk of BD in the offspring. Also, considering that early-onset BD displays homogeneous characteristics and that specific risk factors might operate in this subgroup (Chengappa et al., 2003; Connor et al., 2017), a secondary aim is to assess whether advanced parental age is associated with an earlier onset of BD.

2. Material and methods

The present Systematic Review and Meta-analysis was conducted according to the 2020 version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Stroup, et al., 2000) (Supplementary 1 and 2). The protocol of this systematic review and meta-analysis was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (https://www.crd.york.ac.uk/PROSPERO/; protocol CRD42021293319).

2.1. Eligibility criteria and study outcomes

Original studies were eligible for inclusion if: (i) the study population consisted of people with BD diagnosed according to the Diagnostic and Statistical Manual for Mental Disorders (DSM) any edition (APA, 1994 , 2013) or the International Classification of Diseases (ICD) any edition (WHO 2004) diagnostic criteria with validated diagnosis through structured interviews, and the same criteria had to be applied also to the non-BD group to exclude the presence of psychiatric diagnoses; (ii) they examined maternal and/or paternal age as the variable of interest; (iii) they assessed the association between advanced parental age and risk of BD; (iv) they used a standardized format for presentation of data, allowing for comparisons between studies and calculation of crude ORs. No restrictions about language were applied. Whenever multiple studies considered overlapping study populations, the largest one with the most complete data was included. Reviews, case reports, case series, and studies conducted on animals were excluded.

2.2. Search strategy

The PubMed/MEDLINE, EMBASE, Scopus, and PsycINFO databases were systematically searched from inception until December 1st, 2021. The following string was adopted for the PubMed/MEDLINE search: ((bipolar disorder[MeSH Terms]) OR (bipolar disorder[Title/Abstract])) OR (bipolar*[Title/Abstract])) AND ((parental age[MeSH Terms]) OR (paternal age[Title/Abstract]) OR (maternal age[Title/Abstract])) OR (age of mother[Title/Abstract]) OR (age of father[Title/Abstract]) OR (mother's age[Title/Abstract]) OR (father's age[Title/Abstract]) OR (age of parents[Title/Abstract])). Search strings for the other databases are available in the Supplementary material. The references of each included study, textbooks, and other material were hand searched to identify potential additional studies not captured by the original search-string.

2.3. Study selection and data extraction

Two independent reviewers (GF and MDP) independently screened each study for eligibility. When a consensus could not be achieved, a third author (VO) was consulted.

The following data were extracted (when applicable): author(s), publication year, study design, geographical region, country, diagnostic criteria considered, (semi)structured interview adopted, number of BD cases, number of non-cases, BD type, age of BD onset, birth years, estimates of relative risk of BD (odds ratios from case-control or incidence rate ratios or hazard ratios from cohort studies), maternal and paternal age and how it was modeled (e.g., categorically). In the case of studies fulfilling inclusion criteria without fully available raw data, authors were contacted up to 2 times to ask for data. For studies reporting data in figures only, WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/) was used to extract data from figures manually.

2.4. Methodological quality appraisal

The risk of bias in the included studies was independently assessed by two authors (GF and MDP), and any disagreement was resolved by a third author (VO). The Newcastle-Ottawa Scale (NOS) (Stang, 2010) was adopted to grade studies' quality.

2.5. Statistical analyses

Analyses were performed using RStudio R version 4.1.2 (RStudio Team, 2020) and the metafor R-package (Viechtbauer 2010) using a random-effect model (restricted maximum-likelihood estimator) (Harville, 1977). Effect sizes were calculated as odds ratios (ORs) with their confidence intervals (CIs) when parental age was considered as a categorical measure, and as standardized mean differences (SMDs) with their CI when parental age was considered as a continuous measure. Effect sizes adjusted for the age of the other parent and socioeconomic status - measured as paternal occupation, ethnicity, education, or income (Goldberg et al., 2011) - were used when available.

Heterogeneity between studies was assessed by χ^2 test of fit (Cochrane Q test) and I^2 statistic. A χ^2 statistic having $p < 0.05$ and I^2 statistic $> 50\%$ were considered suggestive of heterogeneity (Higgins et al., 2003).

Sensitivity analyses were conducted by removing one study at time from the analysis; cumulative analyses were performed to evaluate the repercussions of the follow-up length and the year of enrollment on the effect size. Publication bias was explored by visual inspection of funnel plots and using the Egger's test . If the latter was significant, the trim-and-fill procedure was adopted to estimate the impact of the publication bias on the results.

3. Results

3.1. Study selection

A flow diagram showing the results of the literature search and selection of studies is presented in Fig. 1. The literature search involving the electronic databases MEDLINE, PsychInfo, Embase, and Scopus identified a total of 714 records. Of these, 634 articles, including duplicates not fulfilling eligibility criteria, were excluded. Thus, 80 full-text articles were further evaluated for eligibility; of these, 64 were excluded for: (1) not including patients with BD, (2) not reporting data on parental age, (3) not presenting original data, (4) being congress abstracts. A final number of 16 articles were included for their qualitative synthesis, and of these, 14 were included in the quantitative syntheses.

3.2. Study characteristics

Demographic, clinical characteristics and main results of the studies included are presented in Table 1. The included 16 studies (Birmaher et al., 2021; Brown et al., 2013; Buizer-Voskamp et al., 2011; Chudal et al., 2014; D'Onofrio et al., 2014 a; Fountoulakis et al., 2019; Frans et al., 2008 a; Grigoroiu-Serbanescu et al., 2012; Helenius et al., 2013; Laursen et al., 2007; Lehrer et al., 2016; Liang et al., 2021; McGrath et al., 2014; Menezes et al., 2010; Seidman et al., 2013; Weiser et al., 2020) comprised a total 13,424,760 participants and 217,089 individuals with BD.

3.2.1. Design
Of the 14 studies included in the meta-analyses, five reported only paternal age and the offspring's risk of BD (Buizer-Voskamp et al., 2011; D'Onofrio et al., 2014 a; Laursen et al., 2007; Menezes et al., 2010; Weiser et al., 2020), one only maternal age and the offspring's risk of BD

Table 1 Demographic, clinical characteristics, and main results of the included studies.

Author(s), year	Study Design	Study Location	Birth years	Years of follow-up	Controls/ Cohort	BD Cases	Classification of parental age	Adjusted covariates	Main results	Comment
Laursen et al. (2007)	Retrospective cohort study	Denmark	1955-1987	32	2,100,000	4349	Paternal: ≤20, 21-25, 26-30, 31-35, 36-40, 41-45, 46-50, 51-55, ≥56	Adjusted for age, sex, family history of psychiatric admission, and maternal age.	Paternal age reference: 21-25 years (rate 0.11 cases/1000 p-y). Significant higher relative risk at ranges: - 31-35 (RR 1.21, 95% CI 1.09, 1.42). - 36-40 (RR 1.25, 95% CI 1.09, 1.42). - 51-55 (RR 1.71 95% CI 1.21, 2.41). Tendency to higher relative risk with age increase, with no statistical significance in ranges not reported.	Included in quantitative analyses
Frans et al. (2008a)	Case-Control	Sweden	1932-1991	39	13,428 (maternal), 13,428 (paternal)	107,140 (maternal), 67,140 (paternal)	Maternal: < 20, 20-24, 25-29, 30-34, 35-39, 40-44, ≥ 45 Paternal: < 20, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, ≥ 55	Adjusted for age of other parent and family history of psychotic disorder.	Maternal age reference: 20-24 years. Significant higher OR at ranges: - 30-34 (OR 1.07, 95% CI 1, 1.15) - 35-39 (OR 1.15, 95% CI 1.05, 1.25) Paternal age reference: 20-24 years. - 30-34 (OR 1.13, 95% CI 1.03, 1.20). - 35-39 (OR 1.11, 95% CI 1.01, 1.21). - 40-44 (OR 1.17 95% CI 1.06, 1.30). - 45-49 (OR 1.18, 95% CI 1.04, 1.35) - 50-54 (OR 1.24, 95% CI 1.02, 1.50). - ≥ 55 (OR 1.37, 95% CI 1.03, 1.83).	Included in quantitative analyses. Studying the relationship between parental age and age of BD onset.

Table 1 (*continued*)

Author(s), year	Study Design	Study Location	Birth years	Years of follow-up	Controls/Cohort	BD Cases	Classification of parental age	Adjusted covariates	Main results	Comment
Menezes et al. (2010)	Retrospective cohort study	Sweden	1973-1980	28	711,496	493	Paternal: < 21, 21-24, 25-29, 30-34, 35-39, 40-44, 45-49, $\geq$ 50	Adjusted for subject's sex and age, gestational age, family history of psychosis, parents' highest socio-economic status in 1990, parents' highest educational level in 1990 and maternal age.	Paternal age reference: 21-24 years. Significant higher OR at ranges: - 35-39 (OR 1.68, 95% CI 1.09, 2.61) - 40-44 (OR 1.85, 95% CI 1.04, 3.30) OR>1 in all other ranges, with no statistical significance.	Included in quantitative analyses
Buizer-Voskamp et al. (2011)	Case-Control	Netherlands	1999-2008	61	1121	1645	Paternal: < 20, 20-24, 25-29, 30-34, 35-39, $\geq$ 40	Adjusted for average income of the neighborhood, difference in age between the father and the mother and the ethnic background.	Paternal age reference: 25-29 years. No statistical difference in any range, with highest OR (1.68, 95% CI 0.94, 3.01) at < 20.	Included in quantitative analyses
Grigoroiu-Serbanescu et al. (2012)	Retrospective cohort study	Europe		14		564 BDI	Paternal: < 24, 25-34, >35 Maternal: < 24, 25-34, >35		Significant influence of increasing paternal age, and especially age>35years, on age of onset of BD in the total sample (OR= 0.54, CI:0.35-0.80), in the female subsample (OR= 0.44, CI: 0.25-0.78).	Studying the relationship between parental age and age of BD onset
Brown et al. (2013)	Case-Control	USA	1959-1966	16	679 (paternal), 746 (maternal)	83 (paternal), 92 (maternal)	Paternal: 15-24, 25-34, 35-44, $\geq$ 45 Maternal: < 20, 20-29, 30-39, $\geq$ 40	Paternal: adjusted for maternal age. Maternal: adjusted for paternal age and maternal race.	Paternal age reference: 25-34 years. OR 1.45 at $\geq$ 45, non-statistically significant. No statistically significant differences with other ranges. Maternal age reference: 20-29 years. OR 1.46 at $\geq$ 40, non-statistically significant. No statistically significant differences with other ranges.	Included in the quantitative analyses

(*continued on next page*)

Table 1 (*continued*)

Author(s), year	Study Design	Study Location	Birth years	Years of follow-up	Controls/ Cohort	BD Cases	Classification of parental age	Adjusted covariates	Main results	Comment
Seidman et al. (2013)	Case-Control	USA	1996-2007	30	101	35	Mean age cases (maternal): 25.2 years (SD 5.9). Mean age controls (maternal): 26.4 years (SD 6).		Cases with psychoses (schizophrenia or BD disorder) and controls were similar on age at testing, maternal age at birth of subject, socioeconomic status, and offspring sex.	Included in quantitative analyses (means)
Helenius et al. (2013)	Case-Control	Denmark	1950-1997	59	3553	1204	Maternal: 15-35, 35-52. Paternal: 15-35, 35-64.	Adjusted for family history of BD.	Maternal age reference: 15-35 years. Paternal age reference: 15-35 years. Higher OR were observed in the second range of both maternal and paternal groups, which were not statistically significant. Significantly higher family load in the case-probands with pure BD than in the case-probands with BD comorbidities ($p < 0.001$).	
D'Onofrio et al. (2014a)	Retrospective cohort study	Sweden	1973-1997	28	2,615,081	6819	Paternal: < 20, 20-24, 25-29, 30-34, 35-39, 40-44, ≥ 45	Adjusted for maternal age at birth, socioeconomic status and year of birth.	Paternal age reference: 20-24 years. Significant higher OR at ranges: - 25-29 (OR 1.34, 95% CI 1.21, 1.43) - 30-34 (OR 1.71, 95% CI 1.29, 1.95) - 35-39 (OR 2.86, 95% CI 2.41, 3.24) - 40-44 (OR 3.98, 95% CI 3.36, 4.52) - ≥ 45 (OR 6.57, 95% CI 4.81, 8.24) Significant lower OR at < 20 group (OR 0.83, 95% CI 0.7, 0.981).	Included in quantitative analyses

(*continued on next page*)

Table 1 (*continued*)

Author(s), year	Study Design	Study Location	Birth years	Years of follow-up	Controls/ Cohort	BD Cases	Classification of parental age	Adjusted covariates	Main results	Comment
McGrath et al. (2014)	Prospective cohort study	Europe	1955-2011	51	2,894,688	14,618	Maternal: < 20, 20-24, 25-29, 30-34, 35-39, 40-44 Paternal: < 20, 20-24, 25-29, 30-34, 35-39, 40-44, ≥ 45	Adjusted for age of the other parent	No significant association between parental age and BD	Included in quantitative analyses
Chudal et al. (2014)	Case-Control	Finland	1983-1998	25	3643 (maternal), 3601 (paternal)	1861 (maternal), 1821 (paternal)	Maternal: < 20, 20-24, 25-29, 30-34, 35-39, ≥ 40 Paternal: < 20, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, ≥ 50	Adjusted for other parent's age, parental psychiatric history, parental educational level, and place of birth.	Maternal age reference: 30-34 years. No statistically significant differences with any ranges. Paternal age reference: 30-34 years. Significant higher OR at ranges: - 20-24 (OR 1.35, 95% CI 1.06, 1.72) - ≥ 50 (OR 2.84, 95% CI 1.32, 6.12)	Included in quantitative analyses

Table 1 (*continued*)

Author(s), year	Study Design	Study Location	Birth years	Years of follow-up	Controls/ Cohort	BD Cases	Classification of parental age	Adjusted covariates	Main results	Comment
Lehrer et al. (2016)	Case-Control	USA		20	7658	1375	Paternal: - BD with psychosis: < 20, 20-24, 25-29, 30-34, 35-39, 40-44, ≥ 45. - BD without psychosis: < 20, 20-24, 25-29, 30-34, 35-39, 40-44, ≥ 45. BD with psychosis: Mean age (SD) cases/ controls [paternal: 31 (SD 8.2)/ 30.3 (SD 7.5)]; [maternal: 28.1(SD 6.6)/ 27.5 (SD 6.4)]. BD without psychosis: Mean age (SD) cases/ controls [paternal: 30.5 (SD 7.4)/ 30.3 (SD 7.5)]; [maternal: 26 (SD 6.6)/ 27.5 (SD 6.4)]	Adjusted for difference between paternal and maternal ages, sex, race and age.	Paternal age reference: 20-24 years. Among BD with psychosis group, significant higher OR at ≥ 45 subgroup (OR 1.939, 95% CI 1.411, 2.643). Among BD without psychosis group, significant lower OR at < 20 subgroup (OR 0.440, 95% CI 0.22, 0.798). No statistically significant differences observed in other age ranges.	Included in quantitative analyses

Table 1 (*continued*)

Author(s), year	Study Design	Study Location	Birth years	Years of follow-up	Controls/ Cohort	BD Cases	Classification of parental age	Adjusted covariates	Main results	Comment
Fountoulakis et al. (2019)	Retrospective cohort study	Greece			204	42	For BD depression: - Paternal: >25, >30, >40. - Maternal: >20, >22, >26, >35. For BD mania: - Paternal: 25-30, 30-40, >40. - Maternal: 20-22, 22-26, 26-35, >35.		Paternal age reference: none. For BD depression: - Paternal: higher OR observed at >25 (OR 3.71, 95% CI 1.13, 13.02), >40 (6.06, 95% CI 1.84, 19.89). No other statistically significant differences observed. For BD mania: - Paternal: higher OR observed at 25-30 (OR 12.38, 95% CI 1.63, 94.09), 30-40 (OR 5.62, 95% CI 1.97, 15.96), and >40 (OR 4.56, 95% CI 1.29, 16.11). - Maternal: higher OR observed at 22-26 (OR 12.64, 95% CI 1.66, 96.05), and 26-35 (OR 16.68, 95% CI 3.78, 73.66).	Included in quantitative analyses (means)
Weiser et al. (2020)	Prospective cohort study	Israel	1960-1991	31	916,439	883	Paternal: 16-24, 25-29, 30-34, 35-39, 40-44, 45-60	Adjusted for maternal age at birth, socioeconomic status and year of birth.	Paternal age reference: 25-29 years. Significant higher OR at ranges: - 35-39 (OR 1.24, 95% CI 1.00, 1.53) - 45-60 (OR 1.68, 95% CI 1.17, 2.39) OR < 1 only at 16-24 (OR 0.91), with no statistically significant differences.	Included in quantitative analyses

Table 1 (*continued*)

Author(s), year	Study Design	Study Location	Birth years	Years of follow-up	Controls/ Cohort	BD Cases	Classification of parental age	Adjusted covariates	Main results	Comment
Liang et al. (2021)	Prospective cohort study	Taiwan	1991-2004	21	4,138,151	3287 (maternal), 3622 (paternal)	Maternal: < 20, 20-24, 25-29, 30-34, 35-39, ≥ 40 Paternal: < 20, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, ≥ 50	Adjusted for demographic data (parental age at childbirth, sex of children, income, and residence).	Maternal age reference: 25-29 years. Significant higher OR at < 20 group (OR 1.23, 95% CI 1.04, 1.45). No statistically significant differences with other ranges. Paternal age reference: 25-29 years. Significant higher OR at ≥ 50 group (OR 1.87, 95% CI 1.33, 2.64).	Included in quantitative analyses
Birmaher et al. (2021)	Case-Control	USA		9.6	99	17	Mean age cases/controls (maternal): 26.4 years (SD 5.2)/29.4 years (SD 5.5). Mean age cases/controls (paternal): 27.5 (SD 7.1)/31.8 years (SD 6.5).	Adjusted for within family correlations, ethnicity, living with both biological parents, pharmacological treatment.	Significant differences found between parental (both maternal and paternal) age and BD in offspring ($p < 0.05$), with lower mean parental age in BD groups.	Included in quantitative analyses (means)

Abbreviations: BD: bipolar disorder; RR: relative risk; CI: confidence interval; OR: odds ratio; SD: standard deviation.
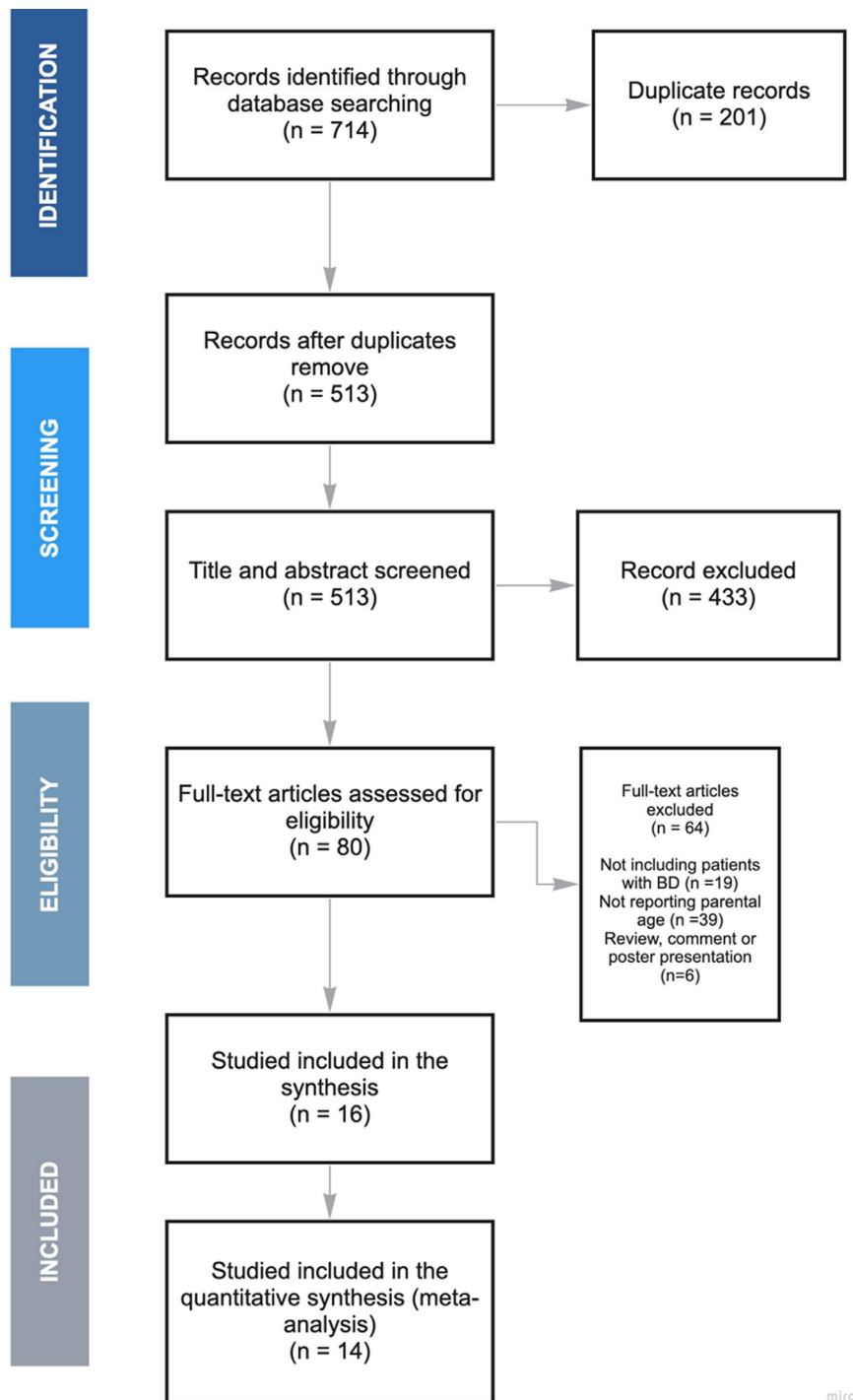
Fig. 1 PRISMA flowchart of systematic review search process.

(Seidman et al., 2013), and eight both paternal and maternal age and the offspring's risk of BD (Birmaher et al., 2021; Brown et al., 2013; Chudal et al., 2014; Fountoulakis et al., 2019; Frans et al., 2008 a; Lehrer et al., 2016; Liang et al., 2021; McGrath et al., 2014). Parental age was reported as means or ranges.

3.2.2. Outcomes
Most of the studies included in the meta-analyses reported effect size as adjusted OR. The minority of included stud-

ies reported adjusted relative risk (RR), incidence rate ratio (IRR), or hazard ratio (HR). As the proportion of outcome was reported as rare (i.e., < 0.07%) in those studies, OR approximated well to other effect sizes, thus we assumed these measures as equal to OR (Schmidt and Kohlmann, 2008; Zhang and Yu, 1998).

Paternal age was categorized into the following age groups: < 20, 20-24, 25-29, 30-34, 35-39, 40-44, and ⩾ 45 years. Maternal age was categorized into the following age groups: < 20, 20-24, 25-29, 30-34, 35-39, ⩾ 40. The high-

est category of parental age was chosen by considering the one appraised by most of the included studies. For studies that had other over-age categories (i.e., 45-49, > 50), the highest category of parental age was chosen by considering the one appraised by most of the included studies (Chudal et al., 2014; Frans et al., 2008 a; Liang et al., 2021; Menezes et al., 2010). The calculated pooled OR between these categories was included in the highest ones ($\geqslant$ 45 or $\geqslant$ 40 years). One study classified age into 10-year intervals (Brown et al., 2013), so it was included in the secondary meta-analysis of unadjusted data by calculating OR using the lowest age group as a reference (15-24). For this specific case, we included only the calculated OR for the highest age category of paternal age ($\geqslant$ 45 years) in the respective quantitative analysis.

3.3. Meta-analyses of studies

As our main aim was to conduct a meta-analysis using data adjusted for the confounding variables, and since the reference category varied among studies, we conducted for each parental sex a first meta-analysis using the 25-29 age group as the reference category and only adjusted effect sizes, and a second one using the 20-24 age group as reference category after calculating ORs from raw data if not already available as adjusted OR in the study.

3.3.1. Adjusted data with reference age 25-29 years
Paternal age. Meta-analysis was possible for 4 studies (Buizer-Voskamp et al., 2011; Liang et al., 2021; McGrath et al., 2014; Weiser et al., 2020). All data were adjusted for socioeconomic status and age of the mother at childbirth. Compared to socioeconomic fathers aged 25-29 years, the random effects pooled estimates of the risk of BD were as follows: 1.29 (95% CI: 1.13-1.48; $I^2 = 0\%$) for offspring of fathers younger than 20 years old; 0.98 (95% CI: 0.86-1.10; $I^2 = 63.9\%$) for offspring of fathers aged 20-24 years old; 1.02 (95% CI: 0.95-1.09; $I^2 = 42.2\%$) for offspring of fathers aged 30-34 years old; 1.03 (95% CI: 0.91-1.16; $I^2 = 69.3\%$) for offspring of fathers aged 35-39 years old; 1.16 (95% CI: 0.97-1.38; $I^2 = 62.3\%$) for offspring of fathers aged 40-44 years old; and 1.29 (95% CI: 1.15-1.46; $I^2 = 0\%$) for offspring of fathers older than 45 years old (Fig. 2) (Supplementary 4).
Maternal age. Meta-analysis was possible for 2 studies (Liang et al., 2021; McGrath et al., 2014). All data were adjusted for socioeconomic status and age of the father at childbirth. Compared with mothers aged 25-29 years, the random effects pooled estimates of the risk of BD were as follows: 1.23 (95% CI: 1.14-1.33; $I^2 = 0\%$) for offspring of mothers younger than 20 years old; 1.05 (95% CI: 1-1.10; $I^2 = 0\%$) for offspring of mothers aged 20-24 years old; 1.04 (95% CI: 0.98-1.1; $I^2 = 0\%$) for offspring of mothers aged 30-34 years old; 1.10 (95% CI: 1.01-1.19; $I^2 = 0\%$) for offspring of mothers aged 35-39 years old; and 1.2 (95% CI: 1.02-1.40; $I^2 = 0\%$) for offspring of mothers older than 40 years old (Fig. 2) (Supplementary 5).

3.3.2. Unadjusted data with reference age 20-24 years
Paternal age. Meta-analysis was possible for 9 studies (Brown et al., 2013; Chudal et al., 2014; D'Onofrio et al.,

2014 a; Frans et al., 2008 a; Laursen et al., 2007; Lehrer et al., 2016; Liang et al., 2021; Menezes et al., 2010; Weiser et al., 2020). Data are unadjusted for all the studies, except for D'Onofrio et al. (2014) b) (adjusted for maternal age at birth and family history of psychiatric disorders) and Frans et al. (2008 b) (adjusted for maternal age at birth, socioeconomic status, and year of birth). Compared with fathers aged 20-24 years, the random effects pooled estimates of the risk of BD were as follows: 1.02 (95% CI: 0.87-1.20; $I^2 = 52.2\%$) for offspring of fathers younger than 20 years old; 1.05 (95% CI: 0.94-1.19; $I^2 = 86.5\%$) for offspring of fathers 25-29 years old; 1.12 (95% CI: 0.93-1.35; $I^2 = 91.1\%$) for offspring of fathers 30-34 years old; 1.23 (95% CI: 0.94-1.60; $I^2 = 95.8\%$) for offspring of fathers 35-39 years old; 1.34 (95% CI: 0.98-1.84; $I^2 = 95.3\%$) for offspring of fathers 40-44 years old; and 1.58 (95% CI: 1.04-2.39; $I^2 = 92.9\%$) for offspring of fathers older than 45 years old (Fig. 3) (Supplementary 4).
Maternal age. Meta-analysis was possible for 3 studies (Chudal et al., 2014; Frans et al., 2008 a; Liang et al., 2021). Data were unadjusted for all the studies, except for Frans et al. (2008 b) (adjusted for maternal age at birth, socioeconomic status, and year of birth). Compared with mothers aged 20-24 years, the random effects pooled estimates of the risk of BD were as follows: 1.20 (95% CI: 0.95-1.53; $I^2 = 82.8\%$) for offspring of mothers younger than 20 years old; 0.96 (95% CI: 0.84-1.11; $I^2 = 85.4\%$) for offspring of mothers aged 25-29 years old; 0.96 (95% CI: 0.8-1.15; $I^2 = 88.4\%$) for offspring of mothers aged 30-34 years old; 1.07 (95% CI: 0.95-1.2; $I^2 = 54.2\%$) for offspring of mothers aged 35-39 years old; 1.1 (95% CI: 0.99-1.23; $I^2 = 0\%$) for offspring of mothers older than 40 years old (Fig. 3) (Supplementary 5).

3.3.3. Means
Paternal age. Meta-analysis was possible for 4 studies (Birmaher et al., 2021; Buizer-Voskamp et al., 2011; Fountoulakis et al., 2019; Lehrer et al., 2016). When age was considered as mean, no evidence for an association between paternal age and risk of BD in offspring emerged (SMD = 0.07, 95% CI: -0.47-0.61).
Maternal age. Meta-analysis was possible for 4 studies (Birmaher et al., 2021; Fountoulakis et al., 2019; Lehrer et al., 2016; Seidman et al., 2013). When age was considered as mean, no evidence for an association between maternal age and risk of BD in offspring emerged (SMD = 0.07, 95% CI: -0.50-0.64).

3.3.4. Sensitivity analyses
In sensitivity analyses of paternal age considered as a categorical variable (adjusted data, reference age 25-29) and risk of BD, the direction of the combined estimates did not significantly vary with the removal of each study in turn, except in the age category ≤ 20 in which, by removing McGrath et al. (2014), the overall effect become non-significant and in the age category 40-44, in which by removing Weiser et al. (2020), the overall effect become significant (OR = 1.27, 95% CI: 1.12-1.44). (Supplementary 6). In sensitivity analyses of maternal age considered as a categorical variable (adjusted data, reference age 25-29) and risk of BD in the age category 35-39, by removing McGrath et al.
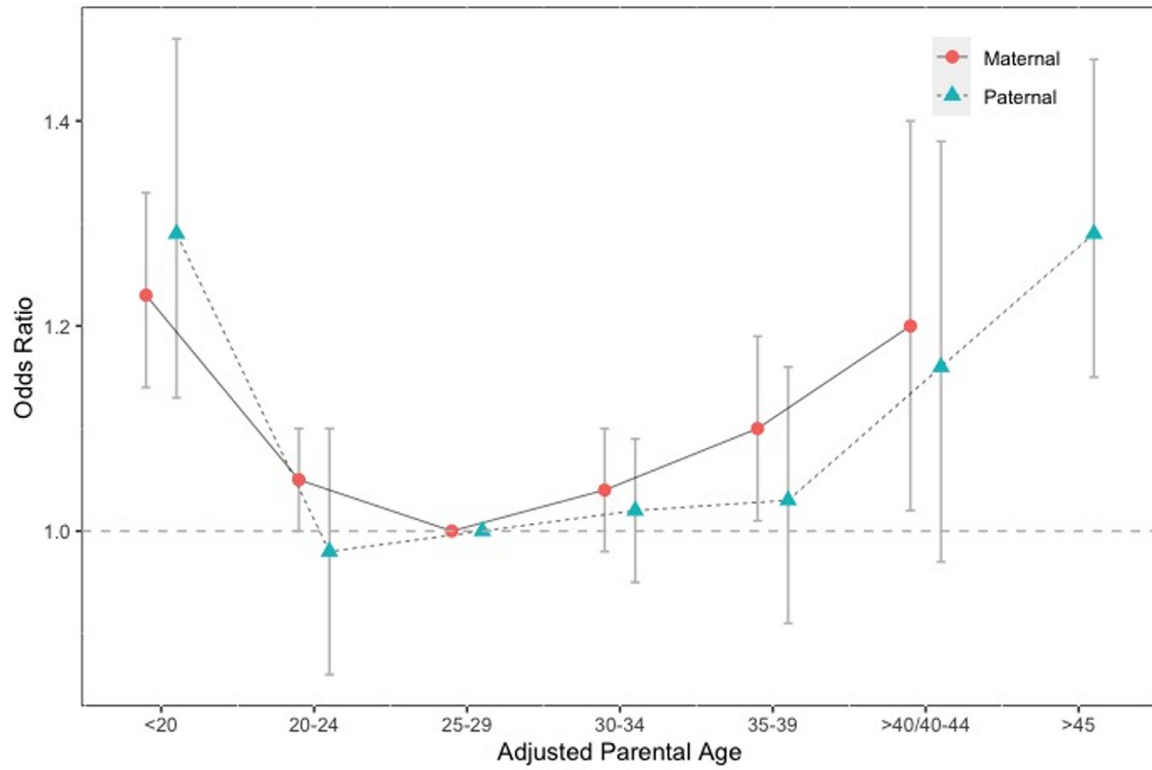
Fig. 2 Pooled odds ratios (OR) with 95% CI for risk of BD by adjusted maternal and paternal age, with age of reference 25–29 years.
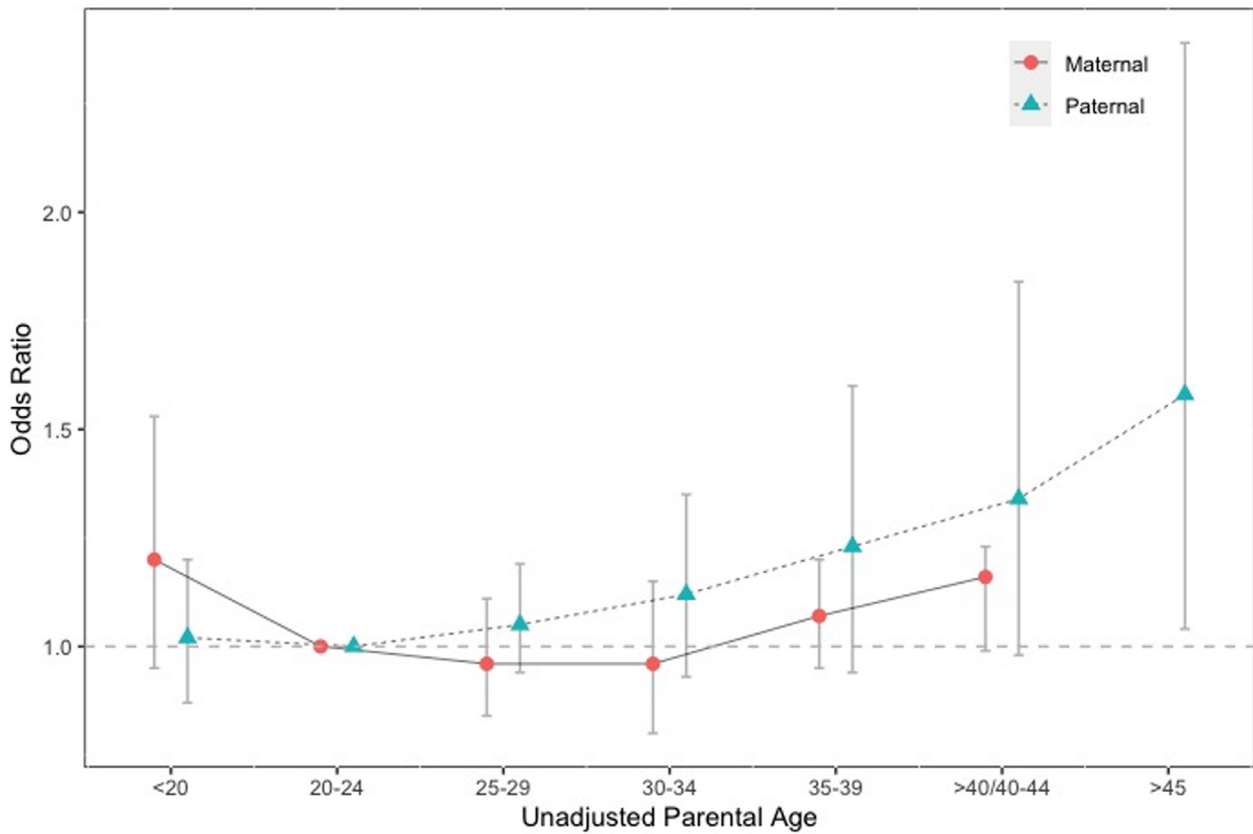

Fig. 3 Pooled odds ratios (OR) with 95% CI for risk of BD by unadjusted paternal age, with age of reference 20–24 years.

(2014), the overall effect become non-significant (Supplementary 6).

3.3.5. Cumulative analyses

Cumulative analyses of the effect of the duration of the observation on paternal or maternal ages (both age of reference 20-24 and 25-29) and the risk of BD in the offspring showed no statistically significant changes in the effect sizes as the duration of the follow-up increased (data available on request). Cumulative analyses based on the year of sample enrollment across different studies showed no statistically significant changes in the effect sizes in almost every age-range considered, with exception to the highest paternal category ($\geq$ 45), which effect size became non-significant (OR = 1.16, 95% CI: 0.97-1.38) as the year of enrollment was more recent (data available on request).

3.3.6. Publication bias

In the analyses of paternal age group 20-24 and the risk of BD (reference age 25-29), the Egger's tests and funnel plots were suggestive of publication bias (Egger's t = -2.76, p = 0.0057), with two possible missing studies estimated with the trim and fill method. In the analyses of paternal age group $\geq$45 and the risk of BD (reference age 20-24), the Egger's tests and funnel plots were suggestive of publication bias (Egger's t = 2.68, p = 0.007), with three possible missing studies estimated with the trim and fill method. In the analyses of maternal age groups 25-29, 30-34 and the risk of BD (reference age 20-24), the Egger's tests and funnel plots were suggestive of publication bias (Egger's t = -2.85, p = 0.004, and t = -3.30, p = 0.0009), with one possible missing study in each test estimated with the trim and fill method. All other analyses on publication bias using Egger's test and inspection of funnel plots were not suggestive of publication bias (data available on request).

3.3.7. Parental age effect on the age of onset of BD in the offspring

Only two studies included in the narrative synthesis reported the effect of parental age on the age of onset of BD (Frans et al., 2008 a; Grigoroiu-Serbanescu et al., 2012). Advanced paternal age was associated with earlier age of BD onset in the first study (Frans et al., 2008 a) (OR = 2.63; 95% CI, 1.19-5.81) and in the second study (Grigoroiu-Serbanescu et al., 2012), showing a negative association between increasing parental ages and decreasing proband age of BD onset (OR = 0.54, 95% CI, 0.35-0.80). Maternal age had no significant effect on BD age of onset in both studies (see Table 1).

3.3.8. Quality of the included studies

Overall, among case-control studies, 5 had "good" quality and 2 were of "poor" quality overall, based on the Newcastle-Ottawa Scale (Supplementary 6). Overall, among cohort studies, 7 had "good" quality and 2 were of "poor" quality overall, based on the Newcastle-Ottawa Scale (Supplementary 7).

4. Discussion

4.1. Main findings

The present study aimed at quantifying, through a meta-analytical approach, whether parental age is associated with an increased risk of BD in the offspring and whether advanced paternal age is associated with an early-onset of BD.

The main results of the quantitative analysis were: (i) younger maternal and paternal ($\leq$ 20 years) or advanced age ($\geq$ 35 or $\geq$ 45 years, respectively) were associated with an increased risk of BD in offspring when the reference age group was 25-29 years and data were adjusted for confounding variables; (ii) when the reference age group was 20-24 years and the data were not adjusted for confounding variables, only advanced paternal age ($\geq$ 45 years) was associated with an increased risk of BD in offspring; (iii) no significant increase in the risk of BD in the offspring was found when parental age was taken as means.

Our results are in line with the ones of another recent meta-analysis on the topic (Polga et al., 2022), in which advanced paternal and maternal age were associated with a higher risk of BD in the offspring. However, this previous quantitative analysis included a total of 7 studies and did not consider two large prospective cohort studies (Liang et al., 2021; McGrath et al., 2014), which recruited over 6 million people and were included in the present meta-analysis. Furthermore, the authors adopted age categories of 10 years, possibly leaving residual confounding within categories (Reijneveld, 2003), and used unadjusted effect sizes. Since the age of mothers and the age of fathers are highly correlated, studies looking only at paternal age may show stronger effects, although the risks are attributable to maternal age (Reijneveld, 2003). Indeed, nonlinear models examining the joint influence of paternal or maternal age and controlling for possible confounders showed a better fit than traditional models (Thompson, 2019). Our results must therefore be considered in this light, with the adjusted results for confounding variables being more reliable than the unadjusted ones.

4.2. Potential mechanisms

The U-shaped association between BD risk in offspring and parental age showed in our results is not surprising, since the previous meta-analysis on schizophrenia or other neuropsychiatric disorders also reported U-shaped risk patterns (Miller et al., 2011; Oldereid et al., 2018; Wu et al., 2017).

There are several plausible underlying mechanisms by which advanced parental age might increase the risk of BD in the offspring, that might derive from a complex interplay between genetic and psychosocial factors. Interestingly, a recent study investigating the association between polygenic risk score for BD in parents and offspring and the risk of lifetime diagnosis of BD in offspring found that the role of genetic risk of the offspring is at least partially independent from clinical parental diagnosis of BD, explaining a big proportion of variance (5%) (Birmaher et al., 2022).

Our study is the first one that draws particular attention to the link between both younger paternal and maternal age

and BD since previous meta-analyses on the matter failed to report this association as significant (Polga et al., 2022). Younger parenthood has been associated with lower educational achievements, adverse social outcomes, violent or criminal behavior both in parents and offspring (Mills et al., 2011). Indeed, adolescent parents may experience more psychosocial stress, stigmatization, anxiety and use fewer coping strategies (Kaye, 2008). Stressful life events might also contribute to the increase of the risk of any mood disorders (Hillegers et al., 2004; Kessing et al., 2003). Increased rates of substance abuse including alcohol, cocaine, marijuana, and methamphetamines, are more common in younger parents (Carroll Chapman and Wu, 2013; Daldegan-Bueno et al., 2021). Also, adolescents might be more prone to engage in non-protected sex, eventually resulting in unplanned pregnancies and increased rates of abortion (Davis and Beasley, 2009). Therefore, evidence highlighted a positive relationship between induced abortion, spontaneous abortion, and an increased risk of psychiatric disorders (Jacob et al., 2019). Younger parents with a tendency toward impulsive behavior, mood fluctuations, risky behaviors (Axelson et al., 2011; Birmaher et al., 2018) or specific affective temperaments (Fico et al., 2019) might also be individuals with a prodrome affective disorder, thus, with a higher genetic load and higher chances to progress to full-threshold BD (Birmaher et al., 2018). However, the recognized role of environmental factors as cues for BD risk should not overshadow the possible biological mechanism involved. Indeed, a stressful environment promotes inflammation (Herbert and Cohen, 1993); therefore, inflammation might be a mediator in the relationship between psychosocial stress and offspring neuropsychiatric outcomes (Csatlosova et al., 2021; Hantsoo et al., 2019; Khalfallah et al., 2022). Furthermore, stress exposure may accelerate telomere shortening as observed in several psychiatric disorders, including BD. Telomere length is heritable and correlates with paternal age (Njajou et al., 2007), but its role in increasing BD risk is unknown (Slagboom et al., 1994). Still, a stressful environment rather than vertical transmission may have a stronger influence on telomere shortening in BD (Powell et al., 2018; Shalev et al., 2013; Valdes et al., 2005). Indeed, sperm telomere length increases with age in humans, and as a result offspring of older fathers inherit longer telomeres (Eisenberg and Kuzawa, 2018).

Substance use is associated with depression in the offspring in pre-clinical studies (Pacheco et al., 2021), and with birth defects and increasing *de novo* mutations in germlines in clinical studies (Laubenthal et al., 2012; Linschooten et al., 2013; Shi et al., 2001), which may ultimately result in an increased risk for BD in the offspring of younger parents. Nonetheless, most de novo mutations occur in paternal germlines, while aneuploidies are mainly of maternal origin and are associated with increased maternal age (Larroya et al., 2021), but doubtfully associated with an increased paternal age (Steiner et al., 2014).

As regards advanced paternal age and the risk of BD, our results replicated previous evidence (Polga et al., 2022). The mechanism underlying the advanced parental age effect has been mainly related to increased rates of *de novo* mutations (Crow, 2000; Kong et al., 2012), epigenetic alternations (Denomme et al., 2020; Malaspina, 2001 a), and

the personality of older fathers (Zammit et al., 2003). More likely, a multitude of interacting factors seems to mediate the impact of advanced paternal age on BD risk, including the role of aging, *de novo* mutations, epigenetic mechanisms, psychosocial environment, and selection into late fatherhood (Vervoort et al., 2022).

For the mechanisms that underlie advanced maternal age effects, evidence differs between BD and other neuropsychiatric disorders. It is well known that advanced maternal age (Cavazos-Rehg et al., 2015)or a mother's history of a severe psychiatric disorder (Solé et al., 2020) are associated with higher rates of obstetric complications that might increase the risk of neurodevelopmental or psychiatric disorders in the offspring (Zhang et al., 2019). However, while for disorders such as schizophrenia and autism spectrum disorder perinatal the association is replicated in several studies (Abel et al., 2013; Buchmayer et al., 2009; Davies et al., 2020), no significant association was found for BD, although evidence is still scarce (Serati et al., 2020). Maternal immune activation at the time of gestation, not limited to infections but considering a spectrum which includes stress or traumatic experiences, epigenetic modification of stress-related pathways or changes in the microbiota, has been linked to increased risk of schizophrenia or BD (Brown and Conway, 2019).

A secondary aim of our study was to assess whether parental age is associated with earlier BD onset, based on the hypothesis that advanced parental age increased the risk of early-onset BD in offspring. BD showed a bimodal (early or late) or trimodal (early, mid- and late) age-of-onset distribution, probably due to a combined effect of environmental and genetic factors (Bolton et al., 2021; Kessing, 2006; Preisig et al., 2016; Vedel Kessing et al., 2021), but to date, the paternal age effect on BD onset is still to be explored. We found only two studies exploring this association, not includable in quantitative analysis. Overall, both studies indicated that advanced paternal, but no maternal, age is associated with earlier age of BD onset. This result is in line with the hypothesis that advanced age is associated with an accumulation of DNA mutations, especially in paternal germ cells (Taylor et al., 2019).

4.3. Clinical and preventative implications

The combination of estimates from all previously published studies allowed a more complete and precise assessment of the parental as a risk factor for BD, supporting the hypothesis that both very young and old parental age is associated with an increased offspring's risk for BD. In older parents, the effect on BD risk might have a stronger genetic or epigenetic influence, while in younger fathers or mothers the effect might result from a complex interaction between psychosocial environment, activation of stress-immune related pathways, and epigenetic and genetic factors.

For both clinical practice and public health programs, our results underline the importance of applying prevention strategies to the patient population diagnosed with BD to minimize the risk of BD in the offspring, and to offspring that would be identified as a BD risk population, along with other known environmental risk factors (Marangoni et al., 2016). However, due to the limitations of our study, such

considerations should be taken into account cautiously before being translated into clinical practice. (Laurenzi et al., 2020)The progressively increased age of parenthood worldwide (Waldenström, 2016; Eurostat, 2020) is a public health concern, and future studies that demonstrate paternal age correlates with specific psychiatric disorders may guide individual and societal interventions. Lastly, although our data were controlled for the presence of parental history of psychiatric disorders, it should be noted that offspring of parents with BD have an increased risk of developing any mood disorder (Mesman et al., 2013), and specific preventive strategies in this at-risk population should be also improved.

4.4. Strengths and limitations

Our study comes with some limitations. To begin, still few studies investigated the association between parental age and BD risk in offspring. Then, only observational studies were included in the analysis. Although there was moderate-to-high heterogeneity in some of the analyses, it was mostly limited to analysis with unadjusted data. Additional information about non-psychotropic drugs, the course of pregnancy, the history of BD in first-degree relatives, the history of other mood disorders in the parents, especially with younger age and possible not-yet diagnosed with BD or other mood disorders, deserves additional primary studies to allow for control of such moderators. Although most studies presented adjusted data for socioeconomic status, they considered it as a single socioeconomic variable rather than a complex and multifactorial one (Braveman et al., 2005). Also, although the majority of the pooled effect sizes in our quantitative analyses have a narrow confidence interval demonstrating a greater degree of precision, these effect sizes are quite small, calling for caution. Finally, in the included studies the authors used a range of parental age as a reference group, being able to assess the risk of BD in the offspring only in lower or higher parental age categories compared to the reference points. However, several strengths should be addressed: we included a larger number of the studies on the topic confirming but, most importantly, significantly extending previous evidence; the majority of the included studies followed a longitudinal design, with long follow-up periods; the pooled effect sizes of risk for BD were largely consistent in several different sensitivity analyses; there was no publication bias in the majority of the analyses, so the probability that our findings are a result of selective publication seems to be minimal.

5. Conclusion

In conclusion, there is evidence that young and advanced parental age is associated with an increased risk of BD in the offspring. Recognition of this risk is of great importance in both clinical psychiatric practice and as a public health issue. It is necessary to inform individuals on the risk of early or delayed reproductive age and to implement interventions to reduce psychosocial stressors in adolescent parents, as well as programs to follow-up offspring at risk of developing BD. Further studies are needed to elucidate the cause-effect relationship and mechanism between parental age and increased risk of BD in the offspring.

Role of the funding source

Contributors

GF designed the study and wrote the protocol, managed the literature searches and analyses and wrote the first draft of the manuscript. Authors GF, MDP and VO undertook the statistical analysis. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

EV has received grants and served as consultant, advisor, or CME speaker unrelated to the present work for the following entities: AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, Sunovion, and Takeda. GF has received CME-related honoraria, or consulting fees from Angelini, Janssen-Cilag and Lundbeck. MSV has received financial support for CME activities or travel funds from Janssen-Cilag and Lundbeck, and has served as a speaker for Casen Recordati. She reports no financial or other relationship relevant to the subject of this article. AM has received funding unrelated to the present work for research projects and/or honoraria as a consultant or speaker from the following entities: Angelini, Janssen, Lundbeck, Otsuka, Sanofi-Aventis and Spanish Ministry of Science and Innovation- Instituto de Salud Carlos III. SGC has received CME-related honoraria, or consulting fees from Janssen-Cilag, Italfarmaco, Angelini and Lundbeck and reports no financial or other relationship relevant to the subject of this article. AS is or has been a consultant/speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boehringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier.

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2022.05.004.

References

Abel, K.M., Dalman, C., Svensson, A.C., Susser, E., Dal, H., Idring, S., Webb, R.T., Rai, D., Magnusson, C., 2013. Deviance in fetal growth and risk of autism spectrum disorder. Am. J. Psychiatry 170, 391–398. doi:10.1176/APPI.AJP.2012.12040543.

APA, 1994. Diagnostic and Statistical Manual of Mental Disorders: DSM-5, 4th ed. APA, Washington DC.

APA, 2013. Diagnostic and Statistical Manual of Mental Disorders : DSM-5. American Psychiatric Association, Arlington, VA.

Axelson, D.A., Birmaher, B., Strober, M.A., Goldstein, B.I., Ha, W., Gill, M.K., Goldstein, T.R., Yen, S., Hower, H., Hunt, J.I., Liao, F., Iyengar, S., Dickstein, D., Kim, E., Ryan, N.D., Frankel, E., Keller, M.B., 2011. Course of subthreshold bipolar disorder in youth: diagnostic progression from bipolar disorder not otherwise specified. J. Am. Acad. Child Adolesc. Psychiatry 50. doi:10.1016/J.JAAC.2011.07.005.

Birmaher, B., Hafeman, D., Merranko, J., Zwicker, A., Goldstein, B., Goldstein, T., Axelson, D., Monk, K., Hickey, M.B., Sakolsky, D., Iyengar, S., Diler, R., Nimgaonkar, V., Uher, R., 2022. Role of polygenic risk score in the familial transmission of bipolar disorder in youth. JAMA Psychiatry 79. doi:10.1001/JAMAPSYCHIATRY.2021.3700.

Birmaher, B., Merranko, J., Hafeman, D., Goldstein, B.I., Diler, R., Levenson, J.C., Monk, K., Iyengar, S., Hickey, M.B., Sakolsky, D., Axelson, D., Goldstein, T., 2021. A longitudinal study of psychiatric disorders in offspring of parents with bipolar disorder from preschool to adolescence. J. Am. Acad. Child Adolesc. Psychiatry 60, 1419–1429. doi:10.1016/J.JAAC.2021.02.023.

Birmaher, B., Merranko, J.A., Goldstein, T.R., Gill, M.K., Goldstein, B.I., Hower, H., Yen, S., Hafeman, D., Strober, M., Diler, R.S., Axelson, D., Ryan, N.D., Keller, M.B., 2018. A risk calculator to predict the individual risk of conversion from subthreshold bipolar symptoms to bipolar disorder I or II in youth. J. Am. Acad. Child Adolesc. Psychiatry 57, 755–763. doi:10.1016/J.JAAC.2018.05.023, e4.

Blanco, C., Compton, W.M., Saha, T.D., Goldstein, B.I., Ruan, W.J., Huang, B., Grant, B.F., 2017. Epidemiology of DSM-5 bipolar I disorder: results from the national epidemiologic survey on alcohol and related conditions – III. J. Psychiatr. Res. 84, 310–317. doi:10.1016/j.jpsychires.2016.10.003.

Bolton, S., Warner, J., Harriss, E., Geddes, J., Saunders, K.E.A., 2021. Bipolar disorder: trimodal age-at-onset distribution. Bipolar Disord. 23, 341. doi:10.1111/BDI.13016.

Bortolato, B., Köhler, C.A., Evangelou, E., León-Caballero, J., Solmi, M., Stubbs, B., Belbasis, L., Pacchiarotti, I., Kessing, L.V., Berk, M., Vieta, E., Carvalho, A.F., 2017. Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses. Bipolar Disord. 19, 84–96. doi:10.1111/BDI.12490.

Braveman, P.A., Cubbin, C., Egerter, S., Chideya, S., Marchi, K.S., Metzler, M., Posner, S., 2005. Socioeconomic status in health re-

search: one size does not fit all. JAMA 294, 2879–2888. doi:10.1001/JAMA.294.22.2879.

Brown, A., Bao, Y., McKeague, I., Shen, L., Schaefer, C., 2013. Parental age and risk of bipolar disorder in offspring. Psychiatry Res. 208, 225–231. doi:10.1016/j.psychres.2013.05.024.

Brown, A.S., Conway, F., 2019. Maternal immune activation and related factors in the risk of offspring psychiatric disorders. Front. Psychiatry 10, 430. doi:10.3389/FPSYT.2019.00430/BIBTEX.

Buchmayer, S., Johansson, S., Johansson, A., Hultman, C.M., Sparén, P., Cnattingius, S., 2009. Can association between preterm birth and autism be explained by maternal or neonatal morbidity? Pediatrics 124, e817–e825. doi:10.1542/PEDS.2008-3582.

Buizer-Voskamp, J.E., Laan, W., Staal, W.G., Hennekam, E.A.M., Aukes, M.F., Termorshuizen, F., Kahn, R.S., Boks, M.P.M., Ophoff, R.A., 2011. Paternal age and psychiatric disorders: findings from a Dutch population registry. Schizophr. Res. 129, 128–132. doi:10.1016/J.SCHRES.2011.03.021.

Carroll Chapman, S.L., Wu, L.T., 2013. Substance use among adolescent mothers: a review. Child. Youth Serv. Rev. 35, 806. doi:10.1016/J.CHILDYOUTH.2013.02.004.

Carvalho, A.F., Firth, J., Vieta, E., 2020. Bipolar disorder. N. Engl. J. Med. 383, 58–66. doi:10.1056/NEJMra1906193.

Cavazos-Rehg, P.A., Krauss, M.J., Spitznagel, E.L., Bommarito, K., Madden, T., Olsen, M.A., Subramaniam, H., Peipert, J.F., Bierut, L.J., 2015. Maternal age and risk of labor and delivery complications. Matern. Child Health J. 19, 1202. doi:10.1007/S10995-014-1624-7.

Chengappa, K.N.R., Kupfer, D.J., Frank, E., Houck, P.R., Grochocinski, V.J., Cluss, P.A., Stapf, D.A., 2003. Relationship of birth cohort and early age at onset of illness in a bipolar disorder case registry. Am. J. Psychiatry 160, 1636–1642. doi:10.1176/appi.ajp.160.9.1636.

Chudal, R., Gissler, M., Sucksdorff, D., Lehti, V., Suominen, A., Hinkka-Yli-Salomäki, S., Brown, A.S., Sourander, A., 2014. Parental age and the risk of bipolar disorders. Bipolar Disord. 16, 624–632. doi:10.1111/BDI.12182.

Chudal, R., Sourander, A., Surcel, H.M., Sucksdorff, D., Hinkka-Yli-Salomäki, S., Brown, A.S., 2017. Gestational maternal C-reactive protein and risk of bipolar disorder among young individuals in a nationwide birth cohort. J. Affect. Disord. 208, 41–46. doi:10.1016/J.JAD.2016.08.056.

Connor, D.F., Ford, J.D., Pearson, G.S., Scranton, V.L., Dusad, A., 2017. Early-onset bipolar disorder: characteristics and outcomes in the clinic. J. Child Adolesc. Psychopharmacol. 27, 875–883. doi:10.1089/cap.2017.0058.

Crow, J.F., 2000. The origins, patterns and implications of human spontaneous mutation. Nat. Rev. Genet. 1, 40–47. doi:10.1038/35049558, 2000 1:1.

Csatlosova, K., Bogi, E., Durisova, B., Grinchii, D., Paliokha, R., Moravcikova, L., Lacinova, L., Jezova, D., Dremencov, E., 2021. Maternal immune activation in rats attenuates the excitability of monoamine-secreting neurons in adult offspring in a sex-specific way. Eur. Neuropsychopharmacol. 43, 82–91. doi:10.1016/J.EURONEURO.2020.12.002.

Daldegan-Bueno, D., Maia, L.O., Glass, M., Jutras-Aswad, D., Fischer, B., 2021. Co-exposure of cocaine and cannabinoids and its association with select biological, behavioural and health outcomes: a systematic scoping review of multi-disciplinary studies. Eur. Neuropsychopharmacol. 51, 106–131. doi:10.1016/J.EURONEURO.2021.06.002.

Davies, C., Segre, G., Estradé, A., Radua, J., De Micheli, A., Provenzani, U., Oliver, D., Salazar de Pablo, G., Ramella-Cravaro, V., Besozzi, M., Dazzan, P., Miele, M., Caputo, G., Spallarossa, C., Crossland, G., Ilyas, A., Spada, G., Politi, P., Murray, R.M., McGuire, P., Fusar-Poli, P., 2020. Prenatal and perinatal risk and protective factors for psychosis: a system-

atic review and meta-analysis. Lancet Psychiatry 7, 399–410. doi:10.1016/S2215-0366(20)30057-2.

Davis, A.R., Beasley, A.D., 2009. Abortion in adolescents: epidemiology, confidentiality, and methods. Curr. Opin. Obstet. Gynecol. 21, 390–395. doi:10.1097/GCO.0B013E3283307B84.

Denomme, M.M., Haywood, M.E., Parks, J.C., Schoolcraft, W.B., Katz-Jaffe, M.G., 2020. The inherited methylome landscape is directly altered with paternal aging and associated with offspring neurodevelopmental disorders. Aging Cell 19, e13178. doi:10.1111/ACEL.13178.

D'Onofrio, B.M., Rickert, M.E., Frans, E., Kuja-Halkola, R., Almqvist, C., Sjölander, A., Larsson, H., Lichtenstein, P., 2014a. Paternal age at childbearing and offspring psychiatric and academic morbidity. JAMA Psychiatry 71, 432–438. doi:10.1001/JAMAPSYCHIATRY.2013.4525.

D'Onofrio, B.M., Rickert, M.E., Frans, E., Kuja-Halkola, R., Almqvist, C., Sjölander, A., Larsson, H., Lichtenstein, P., 2014b. Paternal age at childbearing and offspring psychiatric and academic morbidity. JAMA Psychiatry 71, 432–438. doi:10.1001/jamapsychiatry.2013.4525.

Eisenberg, D.T.A., Kuzawa, C.W., 2018. The paternal age at conception effect on offspring telomere length: mechanistic, comparative and adaptive perspectives. Philos. Trans. R. Soc. B 373. doi:10.1098/RSTB.2016.0442.

Fico, G., Luciano, M., Sampogna, G., Zinno, F., Steardo, L.J., Perugi, G., Pompili, M., Tortorella, A., Volpe, U., Fiorillo, A., Maj, M., 2019. Validation of the brief TEMPS-M temperament questionnaire in a clinical Italian sample of bipolar and cyclothymic patients. J. Affect. Disord. 260, 458–462. doi:10.1016/j.jad.2019.09.034.

Fountoulakis, K.N., Gonda, X., Siamouli, M., Panagiotidis, P., Moutou, K., Nimatoudis, I., Kasper, S., 2019. A case-control study of paternal and maternal age as risk factors in mood disorders. Int. J. Psychiatry Clin. Pract. 23, 90–98. doi:10.1080/13651501.2018.1519079.

Frans, E.M., Sandin, S., Reichenberg, A., Lichtenstein, P., Långström, N., Hultman, C.M., 2008a. Advancing paternal age and bipolar disorder. Arch. Gen. Psychiatry 65, 1034–1040. doi:10.1001/ARCHPSYC.65.9.1034.

Frans, E.M., Sandin, S., Reichenberg, A., Lichtenstein, P., Långström, N., Hultman, C.M., 2008b. Advancing paternal age and bipolar disorder. Arch. Gen. Psychiatry 65, 1034–1040. doi:10.1001/ARCHPSYC.65.9.1034.

Fromer, M., Pocklington, A.J., Kavanagh, D.H., Williams, H.J., Dwyer, S., Gormley, P., Georgieva, L., Rees, E., Palta, P., Ruderfer, D.M., Carrera, N., Humphreys, I., Johnson, J.S., Roussos, P., Barker, D.D., Banks, E., Milanova, V., Grant, S.G., Hannon, E., Rose, S.A., Chambert, K., Mahajan, M., Scolnick, E.M., Moran, J.L., Kirov, G., Palotie, A., McCarroll, S.A., Holmans, P., Sklar, P., Owen, M.J., Purcell, S.M., O'Donovan, M.C., 2014. De novo mutations in schizophrenia implicate synaptic networks. Nature 506, 179–184. doi:10.1038/nature12929.

Garcia-Rizo, C., Bitanihirwe, B.K.Y., 2020. Implications of early life stress on fetal metabolic programming of schizophrenia: a focus on epiphenomena underlying morbidity and early mortality. Prog. Neuropsychopharmacol. Biol. Psychiatry 101. doi:10.1016/J.PNPBP.2020.109910.

Giménez, A., Pacchiarotti, I., Gil, J., Murru, A., Gomes, S.P., Pinzón, J.E., Anmella, G., Gómez-Ramiro, M., Verdolini, N., Valentí, M., Goikolea, J.M., Vieta, E., 2019. Adverse outcomes during pregnancy and major congenital malformations in infants of patients with bipolar and schizoaffective disorders treated with antiepileptic drugs: a systematic review TT – Działania niepożądane w czasie ciąży i poważne wrodzone wady. Psychiatr. Pol. 53, 223–244. doi:10.12740/PP/105906.

Goldberg, S., Fruchter, E., Davidson, M., Reichenberg, A., Yoffe, R., Weiser, M., 2011. The relationship between risk of hospi-

talization for schizophrenia, SES, and cognitive functioning. Schizophr. Bull. 37, 664. doi:10.1093/SCHBUL/SBR047.

Grant, B.F., Stinson, F.S., Hasin, D.S., Dawson, D.A., Chou, S.P., Ruan, W.J., Huang, B., 2005. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the national epidemiologic survey on alcohol and related conditions. J. Clin. Psychiatry 66, 1205–1215.

Grigoroiu-Serbanescu, M., Wickramaratne, P.J., Mihailescu, R., Prelipceanu, D., Sima, D., Codreanu, M., Grimberg, M., Elston, R.C., 2012. Paternal age effect on age of onset in bipolar I disorder is mediated by sex and family history. Am. J. Med. Genet. B Neuropsychiatr. Genet. 159B, 567–579. doi:10.1002/AJMG.B.32063.

Hantsoo, L., Kornfield, S., Anguera, M.C., Epperson, C.N., 2019. Inflammation: a proposed intermediary between maternal stress and offspring neuropsychiatric risk. Biol. Psychiatry 85, 97–106. doi:10.1016/J.BIOPSYCH.2018.08.018.

Harville, D.A., 1977. Maximum likelihood approaches to variance component estimation and to related problems. J. Am. Stat. Assoc. 72, 320–338. doi:10.1080/01621459.1977.10480998.

Helenius, D., Jørgensen, P.M., Steinhausen, H.C., 2013. A three generations nation-wide population study of family load estimates in bipolar disorder with different age at onset. J. Affect. Disord. 150, 146–151. doi:10.1016/J.JAD.2012.12.013.

Herbert, T.B., Cohen, S., 1993. Stress and immunity in humans: a meta-analytic review. Psychosom. Med. 55, 364–379. doi:10.1097/00006842-199307000-00004.

Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. BMJ 327, 557–560. doi:10.1136/BMJ.327.7414.557.

Hillegers, M.H.J., Burger, H., Wals, M., Reichart, C.G., Verhulst, F.C., Nolen, W.A., Ormel, J., 2004. Impact of stressful life events, familial loading and their interaction on the onset of mood disorders: study in a high-risk cohort of adolescent offspring of parents with bipolar disorder. Br. J. Psychiatry 185, 97–101. doi:10.1192/BJP.185.2.97.

Jacob, L., Gerhard, C., Kostev, K., Kalder, M., 2019. Association between induced abortion, spontaneous abortion, and infertility, respectively, and the risk of psychiatric disorders in 57,770 women followed in gynecological practices in Germany. J. Affect. Disord. 251, 107–113. doi:10.1016/J.JAD.2019.03.060.

Kaye, D.K., 2008. Negotiating the transition from adolescence to motherhood: coping with prenatal and parenting stress in teenage mothers in Mulago hospital, Uganda. BMC Public Health 8, 1–6. doi:10.1186/1471-2458-8-83/PEER-REVIEW.

Kessing, L.V., 2006. Diagnostic subtypes of bipolar disorder in older versus younger adults. Bipolar Disord. 8, 56–64. doi:10.1111/J.1399-5618.2006.00278.X.

Kessing, L.V., Agerbo, E., Mortenssen, P.B., 2004. Major stressful life events and other risk factors for first admission with mania. Bipolar Disord. 6, 122–129. doi:10.1111/J.1399-5618.2004.00102.X.

Kessing, L.v., Agerbo, E., Mortensen, P.B., 2003. Does the impact of major stressful life events on the risk of developing depression change throughout life? Psychol. Med. 33, 1177–1184. doi:10.1017/S0033291703007852.

Khachadourian, V., Zaks, N., Lin, E., Reichenberg, A., Janecka, M., 2021. Advanced paternal age and risk of schizophrenia in offspring – review of epidemiological findings and potential mechanisms. Schizophr. Res. 233, 72–79. doi:10.1016/j.schres.2021.06.016.

Khalfallah, O., Barbosa, S., Martinuzzi, E., Davidovic, L., Yolken, R., Glaichenhaus, N., 2022. Monitoring inflammation in psychiatry: caveats and advice. Eur. Neuropsychopharmacol. 54, 126–135. doi:10.1016/J.EURONEURO.2021.09.003.

Kong, A., Frigge, M.L., Masson, G., Besenbacher, S., Sulem, P., Magnusson, G., Gudjonsson, S.A., Sigurdsson, A., Jonasdottir, A., Jonasdottir, A., Wong, W.S.W., Sigurdsson, G., Wal-

ters, G.B., Steinberg, S., Helgason, H., Thorleifsson, G., Gudbjartsson, D.F., Helgason, A., Magnusson, O.T., Thorsteinsdottir, U., Stefansson, K., 2012. Rate of de novo mutations and the importance of father's age to disease risk. Nature 488, 471–475. doi:10.1038/NATURE11396, 20127412 488.

Larroya, M., Tortajada, M., Mensión, E., Pauta, M., Rodriguez-Revenga, L., Borrell, A., 2021. Have maternal or paternal ages any impact on the prenatal incidence of genomic copy number variants associated with fetal structural anomalies? PLoS One 16. doi:10.1371/JOURNAL.PONE.0253866.

Laubenthal, J., Zlobinskaya, O., Poterlowicz, K., Baumgartner, A., Gdula, M.R., Fthenou, E., Keramarou, M., Hepworth, S.J., Kleinjans, J.C.S., van Schooten, F.J., Brunborg, G., Godschalk, R.W., Schmid, T.E., Anderson, D., 2012. Cigarette smoke-induced transgenerational alterations in genome stability in cord blood of human F1 offspring. FASEB J. 26, 3946–3956. doi:10.1096/FJ.11-201194.

Laurenzi, C.A., Gordon, S., Abrahams, N., du Toit, S., Bradshaw, M., Brand, A., Melendez-Torres, G.J., Tomlinson, M., Ross, D.A., Servili, C., Carvajal-Aguirre, L., Lai, J., Dua, T., Fleischmann, A., Skeen, S., 2020. Psychosocial interventions targeting mental health in pregnant adolescents and adolescent parents: a systematic review. Reprod. Health 17, 1–15. doi:10.1186/S12978-020-00913-Y/TABLES/4.

Laursen, T.M., Munk-Olsen, T., Nordentoft, M., Mortensen, P.B., 2007. A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia from a Danish population-based cohort. J. Clin. Psychiatry 68, 1673–1681. doi:10.4088/JCP.V68N1106.

Lehrer, D.S., Pato, M.T., Nahhas, R.W., Miller, B.R., Malaspina, D., Buckley, P.F., Sobell, J.L., Walsh-Messinger, J., Pato, C.N., Abbott, Azevedo, M.H., Bromet, E.J., Escamilla, M.A., Fanous, A.H., Fochtmann, L.J., Kinkead, B., Knowles, J.A., Macciardi, F., Macedo, A., Marder, S.R., McCarroll, S.A., Medeiros, H., Morley, C.P., Nicolini, H., Rakofsky, J.J., Rapaport, M.H., Perkins, D.O., Sklar, P., Smoller, J.W., Vawter, M., Cohort Consortium, G.P., 2016. Paternal age effect: replication in schizophrenia with intriguing dissociation between bipolar with and without psychosis. Am. J. Med. Genet. B Neuropsychiatr. Genet. 171, 495–505. doi:10.1002/AJMG.B.32334.

Liang, C.S., Bai, Y.M., Hsu, J.W., Huang, K.L., Ko, N.Y., Yeh, T.C., Chu, H., te, Tsai, S.J., Chen, T.J., Chen, M.H., 2021. Associations of parental mental disorders and age with childhood mental disorders: a population-based cohort study with four million offspring. Eur. Child Adolesc. Psychiatry doi:10.1007/S00787-021-01914-3.

Linschooten, J.O., Verhofstad, N., Gutzkow, K., Olsen, A.K., Yauk, C., Oligschläger, Y., Brunborg, G., van Schooten, F.J., Godschalk, R.W.L., 2013. Paternal lifestyle as a potential source of germline mutations transmitted to offspring. FASEB J. 27, 2873–2879. doi:10.1096/FJ.13-227694.

Mai, C.T., Kucik, J.E., Isenburg, J., Feldkamp, M.L., Marengo, L.K., Bugenske, E.M., Thorpe, P.G., Jackson, J.M., Correa, A., Rickard, R., Alverson, C.J., Kirby, R.S., 2013. Selected birth defects data from population-based birth defects surveillance programs in the United States, 2006 to 2010: featuring trisomy conditions. Birth Defects Res. A Clin. Mol. Teratol. 97 (709). doi:10.1002/BDRA.23198.

Malaspina, D., 2001a. Paternal factors and schizophrenia risk: de novo mutations and imprinting. Schizophr. Bull. 27, 379–393. doi:10.1093/oxfordjournals.schbul.a006882.

Malaspina, D., Gilman, C., Kranz, T.M., 2015. Paternal age and mental health of offspring. Fertil. Steril. 103, 1392–1396. doi:10.1016/j.fertnstert.2015.04.015.

Marangoni, C., Hernandez, M., Faedda, G.L., 2016. The role of environmental exposures as risk factors for bipolar disorder: a systematic review of longitudinal studies. J. Affect. Disord. 193, 165–174. doi:10.1016/J.JAD.2015.12.055.

McGrath, J.J., Petersen, L., Agerbo, E., Mors, O., Mortensen, P.B., Pedersen, C.B., 2014. A comprehensive assessment of parental age and psychiatric disorders. JAMA Psychiatry 71, 301–309. doi:10.1001/JAMAPSYCHIATRY.2013.4081.

McGuffin, P., Rijsdijk, F., Andrew, M., Sham, P., Katz, R., Cardno, A., 2003. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch. Gen. Psychiatry 60, 497–502. doi:10.1001/ARCHPSYC.60.5.497.

Menezes, P.R., Lewis, G., Rasmussen, F., Zammit, S., Sipos, A., Harrison, G.L., Tynelius, P., Gunnell, D., 2010. Paternal and maternal ages at conception and risk of bipolar affective disorder in their offspring. Psychol. Med. 40, 477–485. doi:10.1017/S003329170999064X.

Mesman, E., Nolen, W.A., Reichart, C.G., Wals, M., Hillegers, M.H.J., 2013. The dutch bipolar offspring study: 12-year follow-up. Am. J. Psychiatry 170, 542–549. doi:10.1176/APPI.AJP.2012.12030401/ASSET/IMAGES/LARGE/542F2.JPEG.

Miller, B., Messias, E., Miettunen, J., Alaräisänen, A., Järvelin, M.R., Koponen, H., Räsänen, P., Isohanni, M., Kirkpatrick, B., 2011. Meta-analysis of paternal age and schizophrenia risk in male versus female offspring. Schizophr. Bull. 37, 1039–1047. doi:10.1093/SCHBUL/SBQ011.

Mills, M., Rindfuss, R.R., McDonald, P., te Velde, E., 2011. Why do people postpone parenthood? Reasons and social policy incentives. Hum. Reprod. Update 17, 848. doi:10.1093/HUMUPD/DMR026.

Njajou, O.T., Cawthon, R.M., Damcott, C.M., Wu, S.H., Ott, S., Garant, M.J., Blackburn, E.H., Mitchell, B.D., Shuldiner, A.R., Hsueh, W.C., 2007. Telomere length is paternally inherited and is associated with parental lifespan. Proc. Natl. Acad. Sci. USA 104, 12135. doi:10.1073/PNAS.0702703104.

Oldereid, N.B., Wennerholm, U.B., Pinborg, A., Loft, A., Laivuori, H., Petzold, M., Romundstad, L.B., Söderström-Anttila, V., Bergh, C., 2018. The effect of paternal factors on perinatal and paediatric outcomes: a systematic review and meta-analysis. Hum. Reprod. Update 24, 320–389. doi:10.1093/HUMUPD/DMY005.

Pacchiarotti, I., Bond, D.J., Baldessarini, R.J., Nolen, W.A., Grunze, H., Licht, R.W., Post, R.M., Berk, M., Goodwin, G.M., Sachs, G.S., Tondo, L., Findling, R.L., Youngstrom, E.A., Tohen, M., Undurraga, J., González-Pinto, A., Goldberg, J.F., Yildiz, A., Altshuler, L.L., Calabrese, J.R., Mitchell, P.B., Thase, M.E., Koukopoulos, A., Colom, F., Frye, M.A., Malhi, G.S., Fountoulakis, K.N., Vázquez, G., Perlis, R.H., Ketter, T.A., Cassidy, F., Akiskal, H., Azorin, J.-M., Valentí, M., Mazzei, D.H., Lafer, B., Kato, T., Mazzarini, L., Martínez-Aran, A., Parker, G., Souery, D., Ozerdem, A., McElroy, S.L., Girardi, P., Bauer, M., Yatham, L.N., Zarate, C.A., Nierenberg, A.A., Birmaher, B., Kanba, S., El-Mallakh, R.S., Serretti, A., Rihmer, Z., Young, A.H., Kotzalidis, G.D., MacQueen, G.M., Bowden, C.L., Ghaemi, S.N., Lopez-Jaramillo, C., Rybakowski, J., Ha, K., Perugi, G., Kasper, S., Amsterdam, J.D., Hirschfeld, R.M., Kapczinski, F., Vieta, E., 2013. The international society for bipolar disorders (ISBD) task force report on antidepressant use in bipolar disorders. Am. J. Psychiatry 170, 1249–1262. doi:10.1176/appi.ajp.2013.13020185.

Pacheco, A.L.D., de Melo, I.S., de Souza, F.M.A., Nicácio, D.C.S.P., Freitas-Santos, J., Oliveira dos Santos, Y.M., Costa, M., de, A., Cavalcante, C., de, M.B., Gomes dos Santos Neto, J., Gitaí, D.L.G., Sabino-Silva, R., Torres de Miranda, C., Borbely, A.U., Duzzioni, M., Shetty, A.K., de Castro, O.W., 2021. Maternal crack cocaine use in rats leads to depressive- and anxiety-like behavior, memory impairment, and increased seizure susceptibility in the offspring. Eur. Neuropsychopharmacol. 44, 34–50. doi:10.1016/J.EURONEURO.2020.12.011.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hrób-

jartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372. doi:10.1136/BMJ.N71.

Polderman, T.J.C., Benyamin, B., de Leeuw, C.A., Sullivan, P.F., van Bochoven, A., Visscher, P.M., Posthuma, D., 2015. Meta-analysis of the heritability of human traits based on fifty years of twin studies. Nat. Genet. 47, 702–709. doi:10.1038/NG.3285.

Polga, N., de Barros, P.M.F., Farhat, L.C., de Almeida, K.M., Bloch, M.H., Lafer, B., 2022. Parental age and the risk of bipolar disorder in the offspring: a systematic review and meta-analysis. Acta Psychiatr. Scand. doi:10.1111/ACPS.13418.

Powell, T.R., Dima, D., Frangou, S., Breen, G., 2018. Telomere length and bipolar disorder. Neuropsychopharmacology 43, 445. doi:10.1038/NPP.2017.125.

Preisig, M., Strippoli, M.P.F., Castelao, E., Merikangas, K.R., Gholam-Rezaee, M., Marquet, P., Aubry, J.M., Vandeleur, C.L., 2016. The specificity of the familial aggregation of early-onset bipolar disorder: a controlled 10-year follow-up study of offspring of parents with mood disorders. J. Affect. Disord. 190, 26–33. doi:10.1016/J.JAD.2015.10.005.

Reichenberg, A., Gross, R., Weiser, M., Bresnahan, M., Silverman, J., Harlap, S., Rabinowitz, J., Shulman, C., Malaspina, D., Lubin, G., Knobler, H.Y., Davidson, M., Susser, E., 2006. Advancing paternal age and autism. Arch. Gen. Psychiatry 63, 1026-1032. doi:10.1001/ARCHPSYC.63.9.1026.

Reijneveld, S.A., 2003. Age in epidemiological analysis. J. Epidemiol. Community Health 57, 397. doi:10.1136/JECH.57.6.397, –397.

RStudio Team, 2020. RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/.

Schmidt, C.O., Kohlmann, T., 2008. When to use the odds ratio or the relative risk? Int. J. Public Health 53, 165–167. doi:10.1007/S00038-008-7068-3, 20083 53.

Seidman, L.J., Cherkerzian, S., Goldstein, J.M., Agnew-Blais, J., Tsuang, M.T., Buka, S.L., 2013. Neuropsychological performance and family history in children at age 7 who develop adult schizophrenia or bipolar psychosis in the New England family studies. Psychol. Med. 43, 119-131. doi:10.1017/S0033291712000773.

Serati, M., Bertino, V., Malerba, M.R., Mucci, F., Barkin, J.L., Grassi, S., Altamura, A.C., Buoli, M., 2020. Obstetric complications and subsequent risk of mood disorders for offspring in adulthood: a comprehensive overview. Nord. J. Psychiatry 74, 470-478. doi:10.1080/08039488.2020.1751878.

Shalev, I., Moffitt, T.E., Sugden, K., Williams, B., Houts, R.M., Danese, A., Mill, J., Arseneault, L., Caspi, A., 2013. Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study. Mol. Psychiatry 18, 576-581. doi:10.1038/MP.2012.32.

Shi, Q., Ko, E., Barclay, L., Hoang, T., Rademaker, A., Martin, R., 2001. Cigarette smoking and aneuploidy in human sperm. Mol. Reprod. Dev 59, 417-421. doi:10.1002/MRD.1048.

Slagboom, P.E., Droog, S., Boomsma, D.I., 1994. Genetic determination of telomere size in humans: a twin study of three age groups. Am. J. Hum. Genet. 55, 876.

Solé, E., Roca, A., Torres, A., Hernández, A.S., Fernández, N., Díaz, C.N., Vieta, E., Garcia-Esteve, L., 2020. Obstetric complications in bipolar disorder: psychiatric factors and the risk of caesarean section. Eur. Neuropsychopharmacol. 32, 47-55. doi:10.1016/J.EURONEURO.2019.12.115.

Stang, A, 2010. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25 (9), 603-605. doi:10.1007/s10654-010-9491-z, Epub 2010 Jul 22. PMID: 20652370.

Steiner, B., Masood, R., Rufibach, K., Niedrist, D., Kundert, O., Riegel, M., Schinzel, A., 2014. An unexpected finding: younger fathers have a higher risk for offspring with chromosomal aneuploidies. Eur. J. Hum. Genet. 23 (4 23), 466–472. doi:10.1038/ejhg.2014.122, 2015.

Stroup, DF, Berlin, JA, Morton, SC, Olkin, I, Williamson, GD, Rennie, D, Moher, D, Becker, BJ, Sipe, TA, Thacker, SB, 2000 Apr 19. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283 (15), 2008-2012. doi:10.1001/jama.283.15.2008, PMID: 10789670.

Sujan, A.C., O'Reilly, L.M., Rickert, M.E., Larsson, H., Lichtenstein, P., Oberg, A.S., D'Onofrio, B.M., 2022. A nation-wide swedish cohort study on early maternal age at first childbirth and risk for offspring deaths, accidents, and suicide attempts. Behav. Genet. 52, 38-47. doi:10.1007/S10519-021-10091-7.

Talati, A., Bao, Y., Kaufman, J., Shen, L., Schaefer, C.A., Brown, A.S., 2013. Maternal smoking during pregnancy and bipolar disorder in offspring. Am. J. Psychiatry 170, 1178-1185. doi:10.1176/APPI.AJP.2013.12121500.

Taylor, J.L., Debost, J.C.P.G., Morton, S.U., Wigdor, E.M., Heyne, H.O., Lal, D., Howrigan, D.P., Bloemendal, A., Larsen, J.T., Kosmicki, J.A., Weiner, D.J., Homsy, J., Seidman, J.G., Seidman, C.E., Agerbo, E., McGrath, J.J., Mortensen, P.B., Petersen, L., Daly, M.J., Robinson, E.B., 2019. Paternal-age-related de novo mutations and risk for five disorders. Nat. Commun. 10. doi:10.1038/S41467-019-11039-6.

Thompson, J.A., 2019. Disentangling the roles of maternal and paternal age on birth prevalence of down syndrome and other chromosomal disorders using a Bayesian modeling approach. BMC Med. Res. Method 19. doi:10.1186/S12874-019-0720-1.

Valdes, A.M., Andrew, T., Gardner, J.P., Kimura, M., Oelsner, E., Cherkas, L.F., Aviv, A., Spector, T.D., 2005. Obesity, cigarette smoking, and telomere length in women. Lancet 366, 662–664. doi:10.1016/S0140-6736(05)66630-5.

Vedel Kessing, L., Ziersen, S.C., Andersen, P.K., Vinberg, M., 2021. A nationwide population-based longitudinal study mapping psychiatric disorders during lifetime in siblings to patients with bipolar disorder. Acta Psychiatr. Scand. 143, 284-293. doi:10.1111/ACPS.13263.

Vieta, E., 2014. Antidepressants in bipolar I disorder: never as monotherapy. Am. J. Psychiatry doi:10.1176/appi.ajp.2014.14070826.

Viechtbauer, W, 2010. Conducting meta-analyses in R with the metafor package. Journal of Statistical Software 36 (3), 1-48. doi:10.18637/jss.v036.i03.

Vervoort, I, Delger, C, Soubry, A, 2022. A multifactorial model for the etiology of neuropsychiatric disorders: the role of advanced paternal age. Pediatr Res. 91 (4), 757-770. doi:10.1038/s41390-021-01435-4, Epub 2021 Mar 5. PMID: 33674740.

Waldenström, U., 2016. Postponing parenthood to advanced age. Ups. J. Med. Sci. 121, 235-243. doi:10.1080/03009734.2016.1201553.

Wang, S.H., Hsiao, P.C., Yeh, L.L., Liu, C.M., Liu, C.C., Hwang, T.J., Hsieh, M.H., Chien, Y.L., Lin, Y.T., Huang, Y.T., Chen, C.Y., Chandler, S.D., Faraone, S.v., Neale, B., Glatt, S.J., Tsuang, M.T., Hwu, H.G., Chen, W.J., 2019. Advanced paternal age and early onset of schizophrenia in sporadic cases: not confounded by parental polygenic risk for schizophrenia. Biol. Psychiatry 86, 56-64. doi:10.1016/J.BIOPSYCH.2019.01.023.

Weiser, M., Fenchel, D., Frenkel, O., Fruchter, E., Burshtein, S., Yehuda, A., Yoffe, R., Bergman-Levi, T., Reichenberg, A., Davidson, M., Sandin, S., 2020a. Understanding the association between advanced paternal age and schizophrenia and bipolar disorder. Psychol. Med. 50, 431-437. doi:10.1017/S0033291719000242.

Wu, S., Wu, F., Ding, Y., Hou, J., Bi, J., Zhang, Z., 2017. Advanced parental age and autism risk in children: a systematic review and meta-analysis. Acta Psychiatr. Scand. 135, 29-41. doi:10.1111/ACPS.12666.

Zammit, S., Allebeck, P., Dalman, C., Lundberg, I., Hemmingson, T., Owen, M.J., Lewis, G., 2003. Paternal age and risk for schizophrenia. Br. J. Psychiatry 183, 405–408. doi:10.1192/BJP.183.5.405.

Zhang, J., Yu, K.F., 1998. What's the relative risk?: A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 280, 1690–1691. doi:10.1001/JAMA.280.19.1690.

Zhang, T., Sidorchuk, A., Sevilla-Cermeño, L., Vilaplana-Pérez, A., Chang, Z., Larsson, H., Mataix-Cols, D., Fernández De La Cruz, L., 2019. Association of cesarean delivery with risk of neurodevelopmental and psychiatric disorders in the offspring: a systematic review and meta-analysis. JAMA Netw. Open 2, e1910236. doi:10.1001/JAMANETWORKOPEN.2019.10236, – e1910236.