Season of Birth and Subclinical Psychosis in the General Population: Systematic Review and Meta-Analysis of New and Existing Data

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Abstract

Season of birth (SOB) has been shown to modify risk for several health outcomes, including a number of neuropsychiatric disorders. Besides, empirical evidence indicates that subclinical forms of psychosis in the general population share some risk factors with categorical diagnoses of psychosis. Hence, by systematically reviewing and meta-analyzing new and existing data, the current work aimed to determine whether there is evidence to support an association between winter SOB and subclinical psychosis in the general population. Meta-analytic results do not indicate an association between winter SOB and schizotypy in adult populations, though additional reports indicate winter SOB may be a risk factor for psychotic experiences or symptoms in children around 12-15 years (children's meta-analysis OR = 1.12, 95% CI: 1.03-1.21). In the whole new dataset of adults (n = 481, mean age = 22.8 years) the association was not detected, neither in an unadjusted model (OR = 0.89, 95% CI: 0.61-1.29, p = 0.526) nor adjusting for gender and age (β=-0.36, t=-0.64, p=0.521). Overall, results indicate the association between winter SOB and increased subclinical psychosis may hold in children, but not in the broad adult general population. Nevertheless, epidemiological and clinicopathological significance of winter SOB as a risk factor for subclinical psychosis will probably be slight due to the small effect sizes indicated by reports available to date.

Keywords: Season of Birth, Schizotypy, Subclinical Psychosis, Winter Birth, General Population, Seasonality

1. Introduction

Season of birth (SOB) has been shown to modify risk for several health outcomes, including a number of neuropsychiatric disorders (Brewerton, Dansky, O'Neil, & Kilpatrick, 2012; Cheng et al., 2013; Davies, Welham, Chant, Torrey, & McGrath, 2003; Disanto et al., 2012; Dome, Kapitany, Ignits, & Rihmer, 2010). In effect, there is evidence indicating that seasonality influences fetal growth and development (Currie & Schwandt, 2013; Flouris, Spiropoulos, Sakellariou, & Koutedakis, 2009; Strand, Barnett, & Tong, 2011; Watson & McDonald, 2007), which bears significance for psychiatric research.

Some mechanisms have been proposed to explain how SOB affects early neurodevelopmental trajectories, including pollution, eating patterns, vitamin D deficits, maternal infections and temperature changes (Currie, Neidell, & Schmieder, 2009; Eyles, Burne, & McGrath, 2013; Schwartz, 2011; Siega-Riz, Savitz, Zeisel, Thorp, & Herring, 2004). In effect, recent epidemiological research has pointed out that seasonality exerts a strong influence on fetal features such as gestation length and birth weight, and that these associations may markedly be compelled by maternal influenza and pregnancy weight gain (Currie et al., 2013). Additionally, research has also suggested that SOB exerts a long-lasting effect on the embryonic brain which may persist until at least adulthood (Giezendanner et al., 2013; Moore et al., 2001; Pantazatos, 2013), likely underlying the enduring effect of the mentioned factors in mental health and disease.

While the above psychiatric studies have focused on clinically-defined psychotic phenotypes, there is empirical evidence indicating that attenuated (i.e., subclinical) forms of psychosis in the general population share many –but not all– risk factors with categorical diagnoses of psychosis (Breetvelt et al., 2010; Kelleher & Cannon, 2011; Linscott & van Os, 2010). Remarkably, despite the psychometric, phenomenological and temporal continuity between psychotic disorders and subclinical psychotic features, population structures ranging from disease to normality are likely discontinuous, and models supporting a *continuum of psychosis* need further evaluation (David, 2010; Lawrie, Hall, McIntosh, Owens, & Johnstone, 2010; Linscott et al., 2010; Linscott & van Os,

2013). Hence, to date, more research is needed to determine the precise extent of the risk overlap and its putative epidemiological consequences.

In this regard, even though there is quite between-study agreement indicating that winter SOB increases the risk for some psychotic conditions, studies evaluating its impact on risk for subclinical psychosis in the general population have provided mixed results. Therefore, by reviewing and meta-analyzing previously published reports the current work aimed to determine whether there is evidence to support an association between winter SOB and subclinical psychosis. New data from a community sample of adults was included to increase the statistical power and to replicate previous findings.

2. Methods

2.1. Meta-analysis

2.1.1. Search strategy and inclusion criteria

A literature search was conducted using PubMed, The ISI Web of Knowledge and PsycInfo to screen for studies evaluating the association between SOB and subclinical psychosis in the general population. The string *[("season of birth" OR "seasonality" OR "birth season") AND ("psychotic experiences" OR "psychotic like" OR "psychosis like" OR "subclinical psychosis" OR schizotyp* OR schizoi*)]*, with proper syntax adjustments depending on search engine, was applied to retrieve potentially relevant articles published until October 22nd, 2013. There was no language restriction. Additionally, reference lists of the identified reports and other relevant publications were scrutinized to find further pertinent publications.

Articles were included if they: i) reported results from primary research, ii) examined the association between SOB and subclinical psychosis, iii) presented data using non-ill general population samples (or both patients and controls, but separately showed information for healthy subjects), iv) performed psychometric evaluations with individuals from the Northern Hemisphere, and v) considered psychotic experiences, schizotypal traits, or non-clinical psychotic symptoms as outcomes, and measures were obtained by self-rating scales. This apparently broad category of outcomes was considered in recognition that questionnaires evaluating schizotypal traits show overlap with assessments of other psychosis-proneness traits and psychosis-spectrum symptoms in the general population (Barrantes-Vidal et al., 2013; Wang, Neumann, Shum, & Chan, 2012).

2.1.2. Data extraction

Search results were independently screened by two reviewers (ACP and RC) to identify relevant studies. A data extraction sheet was used to record important information such as main outcome measure, psychometric scale used and number of items, definition of the seasons of the year,

sample size, gender and ethnicity of participants, summary result and other comments. Also, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement checklist (von Elm et al., 2007) was used to assess accurateness and completeness of the observational studies reviewed. Briefly, this checklist consists of 22 items examining six different sections of a report: 1) title and abstract, 2) introduction, 3) methods, 4) results, 5) discussion and 6) other information.

2.1.3. Data analysis

All statistical analyses were performed in R (R Development Core Team, 2011). Since not all studies provided the same effect size measure –for example, when using continuous psychometric scales authors sometimes report mean differences or *t*-statistics–, odds ratio were estimated when necessary using R's compute.es package (Del Re, 2013). This package allows converting statistics from one study to many other common effect size estimates; it is based on previous literature on meta-analytical methodology (Cooper, Hedges, & Valentine, 2009). Along with the existing findings, results from an ongoing sample were included as another independent study (see below: *2.2. New data*).

Meta-analytic procedures were implemented with R's metafor package (Viechtbauer, 2010), accounting for residual heterogeneity (random effects model) with the DerSimonian-Laird (DL) approach. For comparison, sensitivity analyses included fixed effects models for meta-analytic procedures. As there were no large differences across models, and since random effects models are especially suited for sets of studies with non-identical methods and samples (Viechtbauer, 2010), only results obtained with random effects are shown.

Between-study differences were likewise assessed. The following indicators of heterogeneity and variability are reported: τ^2 (estimated amount of total heterogeneity), I^2 (total heterogeneity/total variability), H^2 (total variability/sample variability) and results from Cochran's Q-test for residual heterogeneity (Cochran, 1954), which evaluates whether variability in effect sizes or outcomes is greater than expected by sampling variability. Statistically significant results from the latter test indicate that effects or outcomes in a meta-analysis are heterogeneous.

2.2. New data

2.2.1. Sample description and measures

Data of a sample consisting of 561 individuals was gathered from both a university campus (Jaume I University; Castelló, Spain) and other university offices and technical schools in Barcelona, Spain, between 2005 and 2006. Recruiting was conducted mainly through advertisement in those institutions. Exclusion criteria applied were presence of neurological conditions, medical illnesses affecting brain function, history of head injury and history of psychiatric treatment. This was screened with an interview based on selected items from other questionnaires (First, 1997; Maxwell, 1992). After applying exclusion criteria and due to lack of data about either birth date or psychopathology for some participants, the final sample (i.e., the subset included in all analyses performed; hereafter "new data") consisted of 481 subjects (46.4% male; mean age: 22.8 years, SD: 5.3 years). 80.7% of these individuals were students.

Schizotypal personality traits were assessed with the Schizotypal Personality Questionnaire Brief (SPQ-B) (Raine & Benishay, 1995), a brief, 32-item self-report screening instrument derived from the Schizotypal Personality Questionnaire (Raine, 1991). Items in the SPQ-B are scored "yes" or "no", which is later translated as either presence or absence of a schizotypal trait. Total schizotypal scores were calculated for each subject by adding all the SPQ-B items where he/she answered "yes". Date of birth data was structured into winter (December 22nd-March 21st) and the rest of the year (spring, summer and autumn) births.

All participants were of Caucasian (Spanish) ancestry. They provided written informed consent after a detailed description of the study aims and design, approved by the local Ethics Committee. All procedures were in accordance with the Helsinki Declaration. Additional descriptive details of the sample can be found elsewhere (Aguilera et al., 2009; Arias et al., 2012).

2.2.2. Statistical analyses of the new data

To include the new data in the meta-analytic procedure, raw mean differences in total SPQ scores between individuals from the winter and the rest of the year births were obtained, and unadjusted odds ratio were estimated as described above (see 2.1.3. Data analysis).

Afterwards, multivariate linear regression analysis was performed to evaluate the relationship between total schizotypal scores and SOB. Since some reports indicate that subclinical psychosis may be influenced by both gender and age (Ito, Okumura, & Sakamoto, 2010; Miettunen & Jaaskelainen, 2010; Wigman et al., 2012), and as this variables may have accounted for between-study heterogeneity in the previous meta-analytic section, additional tests were done to include them as covariates (i.e., schizotypy ~ gender + age + SOB). This analysis was conducted using ordinary least squares in the regression tests. For comparison, permutation-based *p*-values were also obtained for the previous linear tests. These *p*-values are useful for saturated designs, non-normal data or with apparent outliers (Wheeler, 2010), thus lessening the probability of false positives due to some statistical artifacts. Since both ordinary least squares and permutation tests for linear regression gave similar results, only those from the first method are reported next.

3. Results

3.1. Meta-analysis

3.1.1. Eligibility of studies

Figure 1 depicts the search process. After applying the search strategy defined above and excluding duplicates and non-article records, 19 full-text articles were retrieved and assessed for eligibility. Eight studies met all inclusion criteria; descriptive information on these reports and the new data (from the independent sample characterized here) can be found in table 1. From the nine data sources included in table 1, an association between winter birth and subclinical psychosis is supported by three studies (Bolinskey, Iati, Hunter, & Novi, 2013; Hori et al., 2012; Tochigi, Nishida, Shimodera, Okazaki, & Sasaki, 2013); one study found increased risk in subjects born during summer (Kirkpatrick, Messias, & LaPorte, 2008), and both the raw new data obtained here (see *2.2. New data*) and three other publications indicated no statistically significant association (Breetvelt et al., 2010; Cohen & Najolia, 2011; Reid & Zborowski, 2006). From the later set of null studies, Reid et al. (2006) reported statistically significant results for the spring group (compared with all other births). Nevertheless, when combining data in their article to arrange a winter/spring birth group, significance of the effects was lost. It is worth noticing that Kirkpatrick et al. (2008) concluded that summer births have increased risk of schizoid-like features, consistent with their previous findings in favor of June/July excess of "deficit schizophrenia" births (Messias et al., 2004). Nevertheless, this result could not be incorporated in the meta-analytic procedure due to the definition of exposure (June/July birth) and since authors provided results from a subset of 171 high schizotypy scorers (i.e., there was no comparison with the low schizotypy scorers), wherein they evaluate the continuous psychopathological score with respect to birth season and gender.

The only adjusted OR came from the study of Breetvelt et al. (2010), who accounted for demographical risk factors and other psychopathological traits. While adjusted and unadjusted effect sizes could be combined in meta-analyses provided they address the same relationship

(Voils, Crandell, Chang, Leeman, & Sandelowski, 2011), it was not included in most analyses since the psychometric assessment of schyzotypy implemented therein was not comparable to others.

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3.1.2 Features of studies in review and meta-analysis

As shown in table 1, two studies reported empirical data from children (Polanczyk et al., 2010; Tochigi et al., 2013). Hence, they were separately examined. The other five studies reported on adult populations. Whereas the new data and two other studies (Cohen et al., 2011; Hori et al., 2012) analyze relationships between schizotypal personality traits with the SPQ, reports by Bolinskey et al. (2013) and Reid et al. (2006) were based on the Chapmann Psychosis Proneness Scales (CPPS) (Chapman, Chapman, & Raulin, 1978; Eckblad & Chapman, 1983; Eckblad, Chapman, Chapman, & Mishlove, 1982). Hence, these five studies were first divided into two subsets (schizotypal personality or psychosis proneness) and later combined into a larger 5-study block for comparison. Data from all seven studies included in meta-analyses was introduced as unadjusted effect size estimates (raw ORs).

Figure 2 depicts results of the accurateness and completeness assessment of studies using the STROBE checklist. Overall, all studies include informative abstracts and accurate explanations of their scientific background, rationale, objectives and hypotheses. Nonetheless, they exhibited some weakness in their discussion sections, either by not offering a cautions interpretation of results or by not discussing the external validity (generalizability) of the outcomes. Meta-analytic tests performed afterwards aimed to overcome such limitations of the currently available literature.

Notably, a cluster of 4 high-quality comprehensive studies (Bolinskey et al., 2013; Breetvelt et al., 2010; Polanczyk et al., 2010; Tochigi et al., 2013) was observed, whose minor drawbacks were

mainly in the above-mentioned discussion of results. In contrast, manuscripts by Kirkpatrick et al. (2008) and Reid et al. (2006) lacked precision in a number of items evaluating their methods (setting, description of participants, variables, data sources, bias, study size or statistics), results and discussion. It is worth noting that none of these two studies seemed to bias subsequent results of meta-analytic tests. First, using a very particular methodological design, Kirkpatrick et al. (2008) concluded that summer SOB is a risk factor for a (non-clinical) proxy for the schizophrenia deficit syndrome (table 1). This conclusion was derived by a new psychometric measure in which scores from the Beck Depression Inventory are subtracted from those of the Social Anhedonia Scale (i.e., anhedonia in the absence of depression). While this new measure may be a bit problematic given the statistical correlation among psychometric scales (Lewandowski et al., 2006), the finding served as a confirmation of authors' previous results indicative of a summer birth excess in clinically defined schizophrenia deficit syndrome (Kirkpatrick, Tek, Allardyce, Morrison, & McCreadie, 2002). This report was not included in the meta-analysis not only in view of the particular psychometric measure employed but also since its statistical approach compared SOB within a high-schizotypy group. Further research is needed to confirm this finding. Secondly, despite some methodological weaknesses, data from Reid et al. (2006) indicate a very similar effect size to that found by other studies, including the new independent sample (see below), probably suggesting that raw CPPS questionnaire scores behave similarly in relation to winter SOB across studies. In fact, meta-analytic results shown in subsequent sections did not seem biased by the presence or removal of the latter study.

In summary, there was no evident relationship between the STROBE quality assessment and the effect size derived from each report.

---------- Figure 2 here ----------

3.1.2. Association between winter birth and subclinical psychosis: meta-analytic results

Figure 3 shows forest plots of two meta-analyses performed. Data from children suggest there is an association between winter/spring SOB and psychotic symptoms or experiences in the general population, though the effect size is relatively small (OR = 1.12, 95% CI: 1.03-1.21, p_{OR} = 0.009; r^2: 0, I^2: 0%, H^2: 1, Q = 0.53, p_Q = 0.469). Publication bias did not seem an issue in this case since there were both a positive and a null result. It is worth noticing that, despite providing a null result, inclusion of the study by Polanczyk et al. (2010) in the children's meta-analysis did increase the overall effect size and narrow the confidence intervals, and Cochran's Q-test indicated no statistically significant between-study sampling heterogeneity. Furthermore, since the latter report was based in a population with mean age of 12 years, and Tochigi et al. (2013) also reported estimates for the youngest half of their sample (whose mean age should also be around 12 years), an additional meta-analysis was performed comparing these two 12-year-old samples (supplementary figure 1). Remarkably, an increase in effect size was observed, and indexes of heterogeneity were smaller (i.e., samples were more homogeneous) in the former case (OR = 1.15, 95% CI: 1.03-1.29, p_{OR} = 0.014; r^2: 0, I^2: 0%, H^2: 1, Q = 0.33, p_Q = 0.563).

Data in adults did not support statistically significant associations (OR = 1.22, 95% CI: 0.87-1.7, p_{OR} = 0.256; r^2: 0.09, I^2: 66.44%, H^2: 2.98, Q = 11.92, p_Q = 0.018) (figure 3), with no evidence of publication bias (test for funnel plot asymmetry: z = 1.82, p = 0.069). Complementary analyses were performed to explore this data, assorted by psychometric scale. Nevertheless, associations were detected neither when evaluating schizotypal personality traits (OR = 1.17, 95% CI: 0.8-1.71, p_{OR} = 0.408; r^2: 0.08, I^2: 69.63%, H^2: 3.29, Q = 6.59, p_Q = 0.037) nor when assessing psychosis proneness (OR = 1.69, 95% CI: 0.45-6.36, p_{OR} = 0.439; r^2: 0.76, I^2: 81.04%, H^2: 5.28, Q = 5.28, p_Q = 0.022) (supplementary figure 2).

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3.2. Further results using new data

In the previous meta-analysis, mean differences in raw SPQ scores were used to compute OR from the new data. This allowed comparison with other effect size estimates which were mostly unadjusted as well. Hence, additional tests using linear regression models were performed to evaluate whether adjusting for gender and age –two important sources of heterogeneity in the former results, which indeed influence measures of subclinical psychosis– could provide additional insights.

As expected from the literature, higher schizotypy scores were found associated with both male gender and younger age (β_{gender} = 1.91, t_{gender} = -3.95, $p_{gender} < 10^{-4}$; β_{age} = -0.19, t_{age} = -4.15, $p_{age} < 10^{-4}$). Nevertheless, there was no association with winter SOB in the same regression test (β_{SOB} = -0.36, t_{SOB} = -0.64, p_{SOB} = 0.521; adjusted R^2 for the whole test = 0.055). Significance of these results did not change when including individuals with a previous history of psychiatric treatment.

4. Discussion

The present study was aimed at determining whether there is enough evidence to support the association between psychometrically-assessed subclinical psychosis and winter SOB, by evaluating previous results and new data. A total of nine independent results were included in a qualitative and systematic review, and seven of them were statistically assessed by means of meta-analytic procedures. New data was explored to control for potentially confounding demographic variables.

4.1. Interpretation of meta-analytic results and literature review

Meta-analytic results indicate that an association between winter SOB and childhood (~12-15 year-old) psychotic symptoms/experiences is sustained by the current empirical evidence, though the effect size is relatively small (OR = 1.12, 95% CI: 1.03-1.21, p = 0.009). In the broad adult population, there was no association between SOB and subclinical psychosis, neither when using an extensive definition of psychosis nor when carefully separating reports according to their psychometrical approach for the assessment of psychopathology (i.e., independently examining schizotypal personality and psychosis proneness). Of note, reports included in the meta-analysis of children psychotic symptoms/experiences displayed large sampling homogeneity, suggesting reliability of the winter SOB-psychosis relationship in children samples. However, currently available reports in adults may have lacked homogeneity. It is likewise worth noticing that all these outcomes were based on unadjusted effect size estimates.

An important topic raised by these meta-analytic results is the contrast in the relationship between SOB and psychopathological profiles across ages: while winter SOB seems to increase risk for psychotic symptoms in children, this may not be the case in adults. In this regard, it is worth noting that lower schizotypal scores are typically found with increasing age in adults, as shown in the literature (Badcock & Dragović, 2006) and confirmed with the new community sample used here.

One could speculate that, since the effect size of winter SOB on children's subclinical psychosis is small, the continuous –and perhaps stronger– influence of age may render SOB effects nearly undetectable in adults.

As in all meta-analyses, feasibility of results largely depends on quality of the incorporated data. Although publication bias does not seem to be present in the included studies (all null results were derived from reports emphasizing further positive findings), there was large study heterogeneity, ostensibly derived from differences in gender and age distributions, number of ethnic groups included and length of psychometric instruments. It is worth noticing that all previous reports openly supporting a winter SOB-subclinical psychosis association (Bolinskey et al., 2013; Hori et al., 2012; Tochigi et al., 2013) have been derived from populations with large heterogeneity for such study attributes.

Remarkably, from these features, gender and age have widely been shown to modulate schizotypal traits; nevertheless, reports found in the literature irregularly discuss the putative effect these variables could have in the final outcomes. Additionally, some authors have indeed described diverse effects when stratifying a population by gender or age. Their inclusion as covariates is recommended for future studies. It is worth noting that, when stratifying their sample by gender, Tochigi et al. (2013) found a significant effect in girls but not in boys.

4.2. Analysis of new data

Further analyses were performed with data from an independent adult sample, to evaluate the effect of the aforesaid two potentially confounding variables in the relationship between SOB and subclinical psychosis. Inclusion of this sample helped increasing the statistical power in meta-analytic procedures and also allowed replicating prior findings. This new data came from individuals with no previous history of psychiatric drug consumption (another infrequently controlled variable in prior reports), though results did not change when treated individuals were included in the explorations. Winter SOB was not associated with subclinical psychosis, neither in a univariate

model, nor adjusting by gender and age. Results from this independent sample were in agreement with a number of previously published reports in adult populations, and sensitivity analyses suggested its inclusion improved meta-analytic examinations.

4.3. Further issues and future directions

Limitations of the current study and supplementary recommendations for subsequent research warrant mention. Limitations include the definition of seasonal exposure (winter SOB in the Northern Hemisphere), which was conventionally adopted due to its high rate of recurrence in research reports. Nevertheless, since SOB may be a proxy of prenatal insults occurring during developmental windows prior to birth, further contrast between year seasons may lead to distinct outcomes. For instance, Reid et al. (2006) reported an association between winter/spring when compared to summer/fall births. However, such association was driven by spring births, and comparison of winter versus other seasons led to including data from their report as a non-significant odds ratio.

Recent epidemiological evidence by Currie et al. (2013) is relevant in this context. They concluded that May conception (i.e., birth around mid-February) increases the risk of short gestational length and low birth weight, which is probably mediated by influenza exposure. Therefore, assessment of populations conceived during this narrow window may help identify at-risk individuals. Also, these authors indicate that conception during summer may lead to high pregnancy weight gain, which is often reflected as high birth weight. Inclusion of individuals conceived in this season may possibly bias some results in epidemiological research.

Also, the mentioned problem of a small number of reports may also impact meta-analytic results. Two points must be discussed in this regard. First, in the meta-analysis of children, combining studies gave very optimal homogeneity parameters, indicating the association may have held in two independent samples. Secondly, while two adult samples considered in meta-analyses suggested statistically significant winter SOB-psychopathology associations (Bolinskey et al., 2013; Hori et al.,

2012), one of them provided relatively large confidence intervals. Hence, evidence of a compelling association has only seldom been reported. Hence, meta-analytic results with (broad-sense) adult samples (indicating no statistical association) may be somehow realistic.

Overall, further research using appropriate epidemiological designs is needed to determine if the association is valid for specific demographical subgroups for which particular psychopathological profiles have previously been described. Certainly, associations described here require validation through replication. From the two sets of analyses performed (meta-analysis and complementary scrutiny of independent data), it is reasonable inferring that an association cannot be detected when focusing on demographically diverse populations. Although more research is enthusiastically invited to address this topic, only mild effects could be expected on the basis of the current results. Hence, clinicopathological significance of winter SOB on later subclinical psychotic outcomes may not be severe and epidemiological relevance will probably be small.

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Conflict of interest

Authors have no conflict of interest to declare.

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