TECHNICAL COMMENTARY

Age at illness onset

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Introduction

Differences are observed in the age of onset of psychotic symptoms, which may be influenced by genetic or environmental risk factors, or sex. For example, although schizophrenia typically has an onset during late adolescence or early adulthood, research has shown that males generally display a younger age of onset than females. Understanding the factors that impact on age at the onset of symptoms could lead to better understanding of the risk factors for the disorder and earlier and improved intervention strategies for patients.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. Reviews with pooled data were given priority for inclusion. When multiple copies of reviews were found, only the most recent version was included.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist that describes a preferred way to present a meta-analysis[1]. Reviews rated as having < 50% of items checked have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCT) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion of staff of NeuRA (Neuroscience Research Australia).

Results

We found seven reviews that met inclusion criteria[3-9].

- Moderate to high quality evidence suggests the incidence (new cases) of schizophrenia is higher in males up until 40 years of age, then higher in females after 50 years of age.
- Moderate to high quality evidence finds a small effect of any lifetime substance use being associated with an earlier age of onset

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

of psychosis. The effect was medium-sized for cannabis use, and there was no effect of tobacco use.

- Moderate to high quality evidence suggests a small effect of an earlier age at onset in people with a family history of psychosis than in people without a family history of psychosis.
- Moderate quality evidence finds small associations between younger age at onset and more hospitalisations, more negative but not positive symptoms, more relapses, poorer overall functioning and poorer overall clinical outcomes (in males only).
- Moderate to low quality evidence suggests there were more males than females in first-episode psychosis samples, and a younger age at first contact with services in males compared to females in Western countries (small effects).

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Cascio, MT, Cella, M, Preti, A, Meneghelli, A, Cocchi, A

Gender and duration of untreated psychosis: A systematic review and meta-analysis

Early Intervention in Psychiatry 2012; 6(2): 115-127

View review abstract online

Comparison	**Sex differences in duration of untreated psychosis (DUP) and age at first contact with treatment.**
Summary of evidence	**Moderate to low quality evidence (unclear sample size, some imprecision, inconsistent, direct) suggests more males in first-episode psychosis samples, and a younger age at first contact with services in Western countries (small effects).**
DUP and age at first episode	
Small effects shows males had a younger age at first contact with a mental health professional, but only in studies using 'any definition' of DUP, and only in samples from Western countries; DUP by any definition: 16 samples, N not reported, g = -0.18, 95%CI -0.37 to 0.001, p = 0.051 DUP defined as the start of psychotic symptoms to first treatment: 7 samples, g = -0.11, 95%CI -0.41 to 0.20, p = 0.49 Samples from Western countries: 15 samples, g = -0.37, 95%CI -0.56 to -0.17, p = 0.0001 Samples from non-Western countries: 7 samples, g = -0.08, 95%CI -0.33 to 0.11, p = 0.54 *A significant, medium-sized effect of more males than females in first-episode psychosis samples;* 23 samples, OR = 2.1, 95%CI 1.6 to 2.9, p = 0.0001	
Consistency in results‡	Authors state that heterogeneity was substantial (>60%).
Precision in results§	Imprecise for the overall analysis, precise for other analyses.
Directness of results‖	Direct

Esterberg ML, Trotman HD, Holtzman C, Compton MT, Walker EF

The impact of a family history of psychosis on age-at-onset and positive and negative symptoms of schizophrenia: A meta-analysis

Schizophrenia Research 2010; 120: 121-130 View review abstract online	
Comparison	**The impact of a family history of psychosis on age of onset of first psychotic symptom or age at first treatment.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a small effect of people with a family history of psychosis having an earlier age of onset than people without a family history of psychosis. Males without a family history of psychosis may have an earlier age of onset than females without a family history of psychosis**.
Age of Onset	
Significant, small effect suggests people with a family history of psychosis have a younger age of onset of psychosis symptoms; 15 studies, N = 6,969, d = -0.17, 95%CI -0.14 to -0.20, $p < 0.05$, Q-test $p < 0.05$ *No differences were reported between males and females with a family history of psychosis, although a medium effect size shows males without a family history of psychosis have a younger age of symptom onset than females without a family history;* d = -0.47, 95%CI= -0.40 to -0.55	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Immonen J, Jaaskelainen E, Korpela H, Miettunen J

Age at onset and the outcomes of schizophrenia: A systematic review and meta-analysis

Early Intervention in Psychiatry 2017; 11: 453-60 View review abstract online	
Comparison	**Associations between age at onset and outcomes.**
Summary of evidence	**Moderate quality evidence (unclear sample sizes, mostly inconsistent, precise, direct) finds small associations between**

	younger age at onset and more hospitalisations, negative but not positive symptoms, relapses, poorer overall functioning and poorer clinical outcomes (in males only).
Age at onset and outcomes	
Significant, small associations between younger age at onset and more; Hospitalisations: 9 studies, r = 0.17, 95%CI 0.09 to 0.25, p < 0.001, I^2 = 95%, p < 0.001 Negative symptoms: 7 studies, r = 0.14; 95%CI 0.01 to 0.27, p = 0.04, I^2 = 63%, p = 0.01 Relapses: 3 studies, r = 0.11, 95%CI 0.02 to 0.20, p = 0.01, I^2 = 11%, p = 0.32 Poorer social/occupational functioning: 12 studies, r = 0.15, 95%1CI 0.05 to 0.25, p = 0.002, I^2 = 81%, p < 0.001 Poorer global outcomes: 13 studies, r = 0.14, 95%CI 0.07 to 0.22, p < 0.001, I^2 = 48%, p = 0.03 The association between younger age at onset and poorer general clinical was significant only in samples with a higher proportion of males. There were no significant associations with remission, positive or total symptoms, or employment, and no moderating effects of length of illness and study design. There was no evidence of publication bias.	
Consistency in results	Consistent for relapse only.
Precision in results	Precise
Directness of results	Direct

Large M, Sharma S, Compton MT, Slade T, Nielssen O

Cannabis use and earlier onset of psychosis

Archives of General Psychiatry 2011; 68(6): 555-561

View review abstract online

Comparison	**Age at onset in people with schizophrenia who have comorbid substance use, compared to people with schizophrenia and no substance use.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, mostly precise, direct) finds a small effect of any lifetime substance use being associated with an earlier age of onset of**

	psychosis.
Age at onset	
Any substance use *A small effect shows patients who had used any substance had a significantly younger age of onset than those who had not used any substances;* 131 samples, N = 22,519, *d* = -0.264, 95% CI -0.453 to -0.075, *p* = 0.006, I^2 = 78.1%, *p* < 0.001 *No significant differences in this effect between males and females;* Females: 13 samples, *d* = -0.365, 95%CI -0.622 to -0.108 Males 24 samples, *d* = -0.325, 95%CI -0.513 to -0.138 *No significant differences in this effect between heavy and light substance use;* Light/discontinued use: 10 samples, *d* = -0.301, 95%CI -0.522 to -0.08 Heavy/continuous use: 10 samples, *d* = -0.428, 95%CI -0.644 to -0.211 Lifetime cannabis use *A medium-sized effect shows patients who had used cannabis had a significantly younger age of onset than those who had not used cannabis;* 41 samples, *d* = -0.414, 95%CI -0.526 to -0.301, *p* < 0.001 Alcohol use *There was no significant differences in age of onset between patients with and without alcohol use;* 22 samples, *d* = -0.038, 95%CI -0.196 to 0.120, *p* = 0.64	
Consistency in results	Inconsistent
Precision in results	Mostly precise
Directness of results	Direct

Myles N, Newall H, Compton MT, Curtis J, Nielssen O, Large M

The age at onset of psychosis and tobacco use: a systematic meta-analysis

Social Psychiatry Psychiatric Epidemiology 2012; 47: 1243-1250

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Comparison	**The impact of tobacco use on age at onset.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests no differences in the age at onset between people who use tobacco and people who do not use tobacco.**
Age of Onset	
No differences between groups; 29 studies, N = 5,062, *d* = -0.03, 95%CI -0.14 to 0.08, *p* = 0.59, I^2 = 60.6% Authors report that no study or sample characteristic contributed significantly to between-study heterogeneity. These characteristics were; male vs. female, first episode vs. chronic patients, age at first treatment vs. onset of positive symptoms, different measurement of tobacco use, different measurement of diagnosis, schizoaffective disorder vs. schizophrenia, differences in study quality, and study recruitment techniques.	
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Myles N, Newall H, Nielssen O, Large M

The association between cannabis use and earlier age at onset of schizophrenia and other psychoses: meta-analysis of possible confounding factors

Current Pharmaceutical Design 2012; 18: 5055-69

View review abstract online

Comparison	**The impact of cannabis or tobacco use on age at onset.**
Summary of evidence	**Moderate to high quality evidence (large sample, inconsistent, precise, direct) suggests a medium-sized effect of cannabis use being associated with an earlier age of onset of psychosis, with no effect of tobacco use.**
Age of Onset	

Clinically significant cannabis use

A medium-sized effect shows patients with cannabis use had a significantly younger age of onset (equivalent to 32 months);

46 samples, N = 8,914, SMD = -0.399, 95% CI -0.493 to -0.306, $p < 0.001$, $I^2 = 73\%$

Daily tobacco smoking

No significant differences between groups;

47 samples, N = 9,664, SMD = 0.002, 95%CI -0.094 to 0.097, $p = 0.974$, $I^2 = 67\%$

The effect sizes increased when the analysis contained only people with a diagnosis of a schizophrenia-spectrum disorder (+25%), people of the same sex (+12%), and studies using initiation of symptoms (not initiation of treatment) as the marker of age of onset (+12%).

The effect sizes decreased when the analysis contained only studies of consecutively recruited patients (-31%), studies using systematic methods to assess substance use (-10%) or psychiatric diagnosis (-9%), higher quality studies (-9%), and results adjusted for publication bias (-19%).

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

van der Werf M, Hanssen M, Kohler S, Verkaaik M, Verhey FR, RISE Investigators, van Winkel R, van Os J, Allardyce J

Systematic review and collaborative recalculation of 133693 incident cases of schizophrenia

Psychological Medicine 2014; 44(1): 9-16

Link to review abstract

Comparison	**Distribution of rates of the incidence of schizophrenia by age and sex.**

TECHNICAL COMMENTARY

Age at illness onset

Summary of evidence	**Moderate to high quality evidence (large samples, direct, unable to assess consistency, precise) suggests higher incidence of schizophrenia in males up until 39 years.** **Moderate quality evidence (large samples, direct, unable to assess consistency, imprecise) suggests no differences in incidence between 40 to 49 years, and higher incidence of schizophrenia in females over 50 years.**
Incidence rates for males versus females by age	
The risk of schizophrenia was significantly greater in men aged 20 to 39 years, and in women aged over 50 years, after adjusting for year of study, sample size, sampling frame (admission or contact), case ascertainment (clinical, systematic or interview) and diagnostic classification system. No differences were found between males and females aged 40 to 49 years; 33 samples, N = 63,550 incident cases of schizophrenia, females vs. males < 20 years: IRR 0.53, 95%CI 0.41 to 0.69, $p < 0.05$ 20–29 years: IRR 0.47, 95%CI 0.41 to 0.54, $p < 0.05$ 30–39 years: IRR 0.80, 95%CI 0.71 to 0.91, $p < 0.05$ 40–49 years: IRR 1.18, 95%CI 0.99 to 1.41, $p > 0.05$ 50–59 years: IRR 1.50, 95%CI 1.25 to 1.80, $p < 0.05$ 60–69 years: IRR 1.50, 95%CI 1.13 to 1.99, $p < 0.05$ ≥ 70 years: IRR 1.38, 95%CI 0.93 to 2.05, $p > 0.05$	
Consistency in results	Unable to assess; no measure of consistency is reported within age groups.
Precision in results	Precise for 20 to 39 year age groupings only.
Directness of results	Direct

Explanation of acronyms

CI = Confidence Interval, *d* = Cohen's *d,* measure of effect, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), IRR = incidence rate ratio, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), Q = Q statistic for the test of heterogeneity, SMD = standardised mean difference, vs. = versus

TECHNICAL COMMENTARY

Age at illness onset

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[10].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) that allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[10].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[11]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[10];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[12].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

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