Lecture

Myths and plain truths about schizophrenia epidemiology – the NAPE lecture 2004


Objective: Science needs to constantly match research models against the data. With respect to the epidemiology of schizophrenia, the widely held belief that the incidence of schizophrenia shows little variation may no longer be supported by the data. The aims of this paper are (i) to explore data-vs.-belief mismatch with respect to the incidence of schizophrenia, and (ii) to speculate on the causes and consequences of such discrepancies.

Method: Based on a recently published systematic review of the incidence of schizophrenia, the distribution of incidence rates around the world was examined. In order to examine if the incidence of schizophrenia differed by sex, male vs. female risk ratios were generated.

Results: The distribution of incidence rates for schizophrenia is asymmetrical with many high rates skewing the distribution. Based on the central 80% of rates, the incidence of schizophrenia varies in a five-fold range (between 7.7 and 43.0 per 100 000). Males have a significantly higher incidence of schizophrenia compared with females (median male to female risk ratio = 1.4), and this difference could not be accounted for by diagnostic criteria or age range.

Conclusion: The beliefs that (i) the incidence of schizophrenia does not vary between sites and (ii) males and females are equally affected, may have persisted because of an unspoken deeper belief that schizophrenia is an egalitarian and exceptional disorder. Our ability to generate productive hypotheses about the aetiology of schizophrenia rests on an accurate appraisal of the data. Beliefs not supported by data should be identified and relabelled as myths.

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Introduction

Bertrand Russell made a memorable comment about belief systems; ‘Every man, wherever he goes, is encompassed by a cloud of comforting convictions, which move with him like flies on a summer day’ (1). Scientists use belief systems to organize data, to build models and to generate hypotheses. Belief systems are handed down from generation to generation and, along with data, form a shared currency within communities of researchers. However, what happens when our beliefs depart from the data? When belief systems become seriously disconnected from the data, why is it that some are readily rejected while others linger on well past their use-by date? Is it possible that some discrepant beliefs persist because they serve a deeper role within the culture of science?

Categories of knowledge: data, research models, beliefs, myths

In this paper the following definitions will be used. The term hypothesis will be used in its narrow sense – a precisely stated prediction of what data will be found in future studies. The term research model
(or model) will be used to describe the category of the overall theory or the explanatory framework. Data are the raw 'stuff' upon which research models are built. These models serve to bring order to the data (e.g. an infectious agent causes 'consumption' or tuberculosis). From these models, hypotheses can be generated (e.g. isolation of consumptives should reduce transmission). Good models should generate hypotheses that make accurate predictions. Sitting over the shifting landscapes of data and models is a neglected category, which, for the purposes of this paper, I will label as beliefs. Beliefs are organizing principles – higher-order expectations that can influence the choice between competing models (e.g. consumption is a disorder that afflicts sensitive and emotional persons vs. consumption is a disorder that affects the poor). Belief systems are part of the socio-cultural landscape of science. The distinction between beliefs and models is not always clear. However, beliefs tap into a deeper and sometime hidden stratum of cultural knowledge.

In order to understand the ontogeny of beliefs, first we need to reflect on the links between data and hypotheses. Goethe noted that data are the natural enemy of hypotheses. However, the links between data and hypotheses are complex and transactional. Hypotheses are built upon data. New data can also destroy hypotheses. The accumulation of data usually advances in a steady crawl. Sometimes this glacier-like process can be punctuated with short bursts (i.e. the avalanche of data as the release of the human genome is one such saltation). From the data, scientists build research models in order to explain as much of the data as possible and in order to generate new hypotheses. In one sense, this is a Darwinian process – the accumulation of data alters the landscape such that 'unfit' models should be less prosperous. In other words, the addition of new data should assist in the culling of less heuristic research models.

Data, hypotheses and models do not exist in sterile isolation from the culture of science (nor from culture in general). One of the defining features of science is that data are published and available for sharing in a wider group. Hypotheses and models are outlined in publications and discussed amongst peers. Individuals within these scientific tribes have a range of beliefs that have been handed down to them by their elders. Like light through a prism, data are refracted through a lens that is shaped by culture and beliefs. There is nothing wrong or unusual about this process (2). Nevertheless, occasionally belief systems can warp the scientific landscape, and failing research models may persist longer than they should (and, conversely, good-enough models may be rejected prematurely).

Science should draw attention to instances where models no longer fit the data. Old beliefs can be rejected outright or shelved for later recycling. Pasteur advised colleagues to reject their research models as soon as they were thought to be wrong, comforting them with a caveat based on his own experience – rejected ideas can ultimately be proven correct ('ideas that seem dead and buried may at one time or another rise up to life again, more vital than ever before') (3). Researchers should go about the task of updating models with 'new improved' versions in a cautious fashion and avoid hubris in this process.

In summary, raw data aids in the generation of research models. Models aid in the generation of hypotheses, which then add data to the scientific landscape. Different models compete in this landscape. The fittest model is the one that generates hypotheses that prove correct. Lakatos described research as 'progressing' as long at its theoretical growth predicts novel facts with some success. In contrast, 'degenerating' models have little theoretical growth, and are required to generate post-hoc explanations of chance discoveries or data generated by a competing model (4).

The challenge for the researcher is to ensure that research models continue to respond to and match the ever-changing landscape of data. However, belief systems will influence the choice between competing research models, and may contribute to the retention of models after they have departed from the data. For example, think of the resistance to models that moved the earth out of the centre of the solar system (i.e. our planet became less exceptional). Dogma wins over data – beliefs can be much more potent than scientific truths.

Are there hidden beliefs that are contributing to the retention of 'degenerating' research models with respect to schizophrenia epidemiology? This paper will explore issues related to the links between data and beliefs. Examples from schizophrenia epidemiology will be presented to show how data (the 'plain truth') can overturn false beliefs (the 'myths'). Put simply, a myth is a story passed down from generation to generation that helps us understand deeper and more mysterious features (e.g. creation, higher powers etc). In modern parlance, it also has connotations of falsehood (see Barthes (5) for other interpretations of modern myths). A belief system that persists despite no longer reflecting the evidence base should be relabelled a myth.

In this paper it is proposed that two inter-related beliefs about schizophrenia are biasing our apprai-
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...al of data as reflected in what we think, what we teach, what we write in textbooks, and what we research. For the purposes of this paper, these will be labelled Belief 1: Schizophrenia is an egalitarian disorder and Belief 2: Schizophrenia is an exceptional disorder.

Variations in the incidence of schizophrenia

The most influential study of the incidence of schizophrenia has been the WHO 10 Nation study (6). This landmark study, which employed uniform methodology across sites, provided incidence data from eight sites (seven nations). When narrow criteria for schizophrenia were used (CATEGO S+), the incidence ranged from seven to 14 per 100,000 (Aarhus, Denmark to Nottingham, UK, respectively), while the range for ICD9 schizophrenia was 16 to 42 per 100,000 (Honolulu, Hawaii to the urban Chandigarh, India, respectively). Both definitions found at least a two-fold difference between the highest and lowest sites, and this difference for the broad (but not narrow) definition was statistically significant.

The highly-cited preliminary report of this study concluded; ‘The results provide strong support for the notion that schizophrenic illnesses occur with comparable frequency in different populations…’. (7). This statement continues to resonate within the schizophrenia research community nearly two decades later. The results of the WHO 10 Nation study have been interpreted as providing strong proof that the incidence of schizophrenia does not vary between sites. For example, Crow (8) has stated; ‘The evidence points to the singular conclusion that, contrary to almost any other common condition, the incidence of schizophrenia is independent of the environment and a characteristic of human populations.’ (p. 119). This finding has been widely reported in textbook, web pages, and official reports and underpins Belief 1 – Schizophrenia is an egalitarian disorder. The notion that schizophrenia respects human rights is vaguely ennobling. Certainly, schizophrenia is a very serious brain disease that causes great suffering. However this belief suggests that at least schizophrenia seems to distribute its burden fairly – it affects all people equally regardless of sex, race, colour, citizenship or creed.

Data that have challenged this belief seem to have been discounted in the minds of the research community. However, the ground is beginning to shift. In a recent narrative review, one of the senior authors of the WHO 10 Nation study, Jablensky (9) draws a more finely nuanced conclusion: ‘The general conclusion is that according to the great majority of studies, the prevalence and incidence rates of schizophrenia are similar across populations. However, a small number of populations have been identified that clearly deviate from this central tendency’ (p. 212).

Other opinion leaders are expressing doubt about the interpretation of the WHO finding. Robin Murray notes in a psychiatry textbook (10). ‘The study is frequently quoted as showing that there was no significant variation between countries in the incidence of nuclear schizophrenia as defined by the PSE/CATEGO system. However, it is more correct to say that the study had insufficient power to detect significant differences. Furthermore, when a “broad” concept of schizophrenia was examined, the incidence varied four-fold’ (p. 291). Similar sentiments can be found in a recently published volume examining the epidemiology of schizophrenia (11); ‘The Ten Country study is often cited, in our view mistakenly, as providing the evidence for worldwide “uniform” incidence and symptom expression of schizophrenia’ (p. 21).

Intertwined in the interpretation of the WHO 10 Nation study is Belief 2: Schizophrenia is an exceptional disorder. For example, in the quote from Tim Crow (8), he has drawn attention to the fact that the featureless landscape of schizophrenia incidence is extremely unusual (‘contrary to almost any other common condition’). Jablensky also draws attention to the unusually narrow range of the incidence of schizophrenia across sites; ‘The magnitude of these deviations is modest compared with the difference observed across populations with regard to other multifactorial diseases such as diabetes, ischaemic heart disease or cancer, where 10- to 30-fold differences in prevalence across populations are not uncommon.’ (p. 212) (9). It seems that key opinion leaders believe that schizophrenia stands out from all other human disorders. There is something special, or exceptional about this disorder. This notion has led to research models which link schizophrenia to features that make our species ‘exceptional’ compared other animals (‘exceptionalism’). While outside the scope of this paper, there has been a series of ‘defining’ features that were originally thought to differentiate humans from other apes, many of which have not been supported by new data (e.g. tool use, cultural transmission of knowledge, ‘language’, theory of mind). Saying that schizophrenia is exceptional also sets up a mind-set that, unlike other common-or-garden disorders, schizophrenia may ‘never be known’. Once again, there is something vaguely ennobling about this notion.
The incidence of schizophrenia in males and females

Much has been written on sex differences in schizophrenia (12, 13). Usually, these papers focus on aspects such as age of onset (14), symptoms profile (15, 16) and treatment response (17). However, until very recently, there was a widely held belief that males and females are equally at risk of developing schizophrenia. The methodological difficulties related to determining sex differences in the incidence of schizophrenia have been the subject of a good deal of scholarly research. For example, diagnostic differences (especially ones that exclude onsets above a certain age) are known to impact on sex ratios (18). Incidence studies that have restrictive age ranges (e.g. cut off at 54 years) can also result in late-onset cases in women being systematically excluded (19, 20).

While the methodology issues are non-trivial, the received wisdom has been that the incidence of schizophrenia in males and females is equal. This belief can be found a range of authoritative sources such as the DSM-IV (21), the World Health Report 2001 (22), and a recent review published in the Lancet (23). This belief is promulgated in the countless websites designed for consumers and caregivers (e.g. World Federation for Schizophrenia and Allied disorders) (24).

However, the ground is now also shifting on this belief. A recent systematic review of sex differences in the incidence of schizophrenia (25) found that the risk ratio for men to develop schizophrenia relative to women were 1.42 (95% confidence interval, 1.30–1.56). This study adjusted the analyses in an attempt to account for known biases (e.g. age range, quality of the study), however, the sex difference persisted. The belief that men and women are equally affected by schizophrenia warrants revisiting. Is it possible that Belief 1 Schizophrenia is an egalitarian disorder, has blinded us to the data? To suggest that men have a higher risk of developing schizophrenia would compete with the belief that schizophrenia affects humankind without bias.

A recent review has systematically compiled the world literature on the incidence of schizophrenia (26). Findings from this study allow us to scrutinize the two beliefs detailed above.

Aims of the study

The aims of this paper are to briefly outline the data on the incidence of schizophrenia and to encourage discussion about how data (the ‘plain truth’) influence false beliefs (‘myths’).

Material and methods

Data on the incidence of schizophrenia were examined in a recent systematic review, full details of which are provided elsewhere (26). In addition, the full data-set upon which this systematic review was based is available at the following web site (http://www.qcmhr.uq.edu.au/epi) In brief, studies with original data related to the incidence of schizophrenia (published 1965–2001) were identified via searching electronic databases, reviewing citations and writing to authors. Traditional incidence studies (based on the enumeration of new cases within a geographically-defined general population) were selected. Between- and within-study filters were applied in order to identify discrete rates (i.e. no individual could appear in more than one rate calculation). The analyses presented in this paper did not examine incidence rates generated from migrant studies, cohort studies or studies based on Other Special Groups. The distribution of the data is shown in rank order for incidence rate (lowest to highest ranks) with the cumulative percent of rates shown on the vertical axis. These distributions were compared when the underlying rates were sorted according to sex and various methodological features. It should be noted that there is no one ‘perfect’ design for measuring the incidence of schizophrenia – different studies have different strengths. Most of the studies provide rates that are in reality the ‘treated incidence’ of schizophrenia. However, we can reasonably infer that the studies included in this systematic review probably underestimate the true (underlying) incidence of schizophrenia.

Results

The systematic review identified 55 studies that provided data on traditional measures of the incidence of schizophrenia. These studies generated 170 rates for persons (and 100 rates each for males and for females). These studies were derived from the following 25 nations; Barbados, Brazil, Canada, China, Croatia, Denmark, Finland, Germany, Iceland, India, Ireland, Italy, Jamaica, Japan, New Zealand, Norway, Pakistan, Russian Federation, Singapore, Spain, Sweden, The Netherlands, Trinidad, USA, and the UK.

The distribution of rates was asymmetric and had a median value of 15.2 per 100 000 (see Fig. 1). The central 80% of rates for the incidence of schizophrenia (i.e. those between the 10th and 90th percentiles) lie within a range of 7.7 to 43.0 per 100 000, which is over a five-fold difference.
The distribution of rates was not significantly different when sorted by possible sources of bias such as diagnostic criteria, method of diagnostic confirmation (e.g. register-based diagnosis, face-to-face interview), the use of age-standardization, age-range or quality of the study [full details are provided elsewhere (26)].

The systematic review identified 31 studies, and 100 rates that allowed the derivation of precise male:female rate ratios. The distribution of rates was significantly higher in males compared with females \( (F_{1,30} = 76.8, \ P < 0.001) \); the male/female rate ratio median was 1.40 (see Fig. 2). The male excess could not be explained by the influence of age range or diagnostic criteria (data not shown).

**Discussion**

There is substantial variation in the incidence of schizophrenia across studies, and robust evidence showing that males have a significantly higher incidence of schizophrenia than females. Our beliefs about the epidemiology of schizophrenia need to be revised in light of the data.

With respect to the variation in the incidence of schizophrenia, some may argue that a five-fold difference in the incidence of schizophrenia shown in the systematic review is still ‘narrow’. However, a WHO-sponsored systematic review of studies of the incidence of Type I diabetes described the range of 10 to 40 per 100,000 as ‘prominent worldwide variation’ (27). It could be argued, therefore, that the range identified for schizophrenia (7.7 to 43.0 per 100,000) is also ‘prominent’. While the studies included in the systematic review of the incidence of schizophrenia did not use a uniform methodology, there are features of the cumulative distribution (Fig. 1) that add weight to its interpretation. Apart from the brute strength of the data (i.e. the distribution is derived from 55 studies conducted in 25 nations), the central, near-linear segment of the distribution is densely underpinned by data.

Two independent meta-analyses (based on overlapping data) have now shown that men are at increased risk of developing schizophrenia compared with women (25, 26). The sex difference could not be explained by known systematic biases. The data contributing to these analyses have been collected over several decades from many different nations, and have been based on many different design features. Meta-analyses based on intervention studies have utilized a statistic called the ‘fail-safe n’, which is defined as the number of studies with a non-significant result that would bring a significant pooled analysis to non-significant levels (28). In order to ‘wash out’ the male excess, several dozen studies that find equivalent incidences in males and females would need to be added to the distribution.

Evidence, even when from data-rich systematic reviews, does not always decide controversies. The evidence is never totally determinate, and while doubts persist about sources of bias, arguments will persist. However, scientists must be ‘slaves to the data’ and be prepared to acknowledge shifting weights of evidence (including evidence that resurrects previously rejected models). The history of science is not a passive process whereby knowledge accumulates over time like sedimentary rocks. It is a tectonic process where data crashes against research
Can plain truth overturn myths?

This paper proposes that myths are distorting the landscape of schizophrenia epidemiology. These myths are subliminal, but serve to infuse schizophrenia with quasi-heroic elements. If schizophrenia is egalitarian, then it becomes the psychiatric equivalent of original sin – the stain of schizophrenia is uniformly distributed. If schizophrenia is unique in the pantheon of human diseases (i.e. is ‘exceptional’), then researchers cannot help linking it to other supposedly exceptional human traits. This myth may have contributed to the theory that schizophrenia is the price we pay for language (8). This model (which rests on the assertion that the WHO 10 study ‘proves’ that the incidence of schizophrenia is invariant) involves the speciation of Homo sapiens, the Diaspora of humankind, language development, cerebral asymmetry, the X chromosome and sexual selection. The myth that schizophrenia is exceptional may also fuel the speculation that schizophrenia and creativity are linked. This notion has attracted a steady stream of advocates over the decades (30–36).

Should schizophrenia researchers be drawn into these metaphors? Schizophrenia is a disabling brain disorder that causes much distress to the affected individuals and their families. Despite public education, serious mental disorders such as schizophrenia are stigmatized by the general public (37). While people with schizophrenia show great inner strength and tenacity dealing with this disorder, what good will come from inaccurate models, however ennobling or romantic they are? As noted by Susan Sontag, feared diseases seem to attract the most florid and potent metaphors (e.g. consumption, cancer, HIV, mental illness) (38). There also seems to be an inverse relationship between the fund of information about a disorder and the tendency to develop myths and metaphors around that disorder. We can only hope that as we learn more about schizophrenia, we will be less inclined to myth-building.

It could be argued that if myths are persisting in the absence of data, they must be serving some other good purpose. Some commentators have acknowledged that theory choice for scientists is influenced by how other scientists will evaluate them – aligning one’s belief system with senior culture bearers is often a good career move (2). Perhaps myths persist because they provide a soothing balm for anxious researchers or help clinicians make meaning out of a perplexity group of disorders. However, there may be deeper issues that keep us clinging to myths that ennable schizophrenia. Recently, startling findings have emerged from research about ‘best buys’ with respect to the cost of averting disability (39, 40). With respect to schizophrenia, with the current mix of interventions we can only reduce 13% of the burden. If we improve efficiencies within the current services, we can do somewhat better (22%). In a utopian world, even if unlimited funding were available, three quarters of the burden of schizophrenia would remain unavoidable. While this sobering statistic is a powerful argument for investing in research, it also reminds us of our clinical limitations. We are a long way from being able to provide treatment packages that provide immediate, complete and sustained recovery for all individuals who develop schizophrenia. Perhaps romantic and ennobling myths about schizophrenia serve to distract us from an awareness of our therapeutic impotence.

There are serious implications for the advancement of knowledge when beliefs depart from the data. In particular, the belief that schizophrenia does not vary has important implications for schizophrenia research. If researchers do not believe that the incidence of schizophrenia has gradients, they will not actively look for gradients in new studies, nor promptly recognize them when they emerge by chance (41). They may discount indirect evidence that suggests that the incidence of schizophrenia has varied over recent centuries (42, 43). However, there is reason for optimism. The schizophrenia research community has shown itself willing to respond to data and reshape beliefs. For example, narrative and systematic reviews have shown convincingly that winter-spring birth is associated with an increased risk of developing schizophrenia (44–46). This fact is now often reflected in textbooks and even in information for the general public. While the general public may not yet be aware of it, there is now robust evidence showing that migrants have an increased risk of developing schizophrenia and this is slowly being reflected in what we write and teach (47–52, 26). Similarly, it is becoming increasingly accepted that urban birth and residence is associated with an increased risk of schizophrenia (53–56, 26). Thus, plain truths can overturn myths.

To conclude, scientists need to generate belief systems by swapping data and models. This is an important component of social grooming within our tribe. Occasionally, beliefs will persist too long, and distort the optics of the scientific lens that we use. They can blind us to the truth. Schizophrenia
researchers, like all good scientists, must remain vigilant that our beliefs are data-based, and work on the annulment of myths. Perhaps all future research models should have a used-by date as well as a publication date. We should ensure that ‘out-of-data models’ become ‘out-of-date models’. Like old fish, perhaps models beyond their used-by date should emit a foul odour so as to warn scientists of the tainted product at hand.

Freed from the blinkers of mythology, schizophrenia turns out to be much more interesting than previously thought. Alas, it is not exceptional and contrary to the egalitarian notions, schizophrenia does affect some segments of our society unfairly. We now appreciate that schizophrenia has variations between sites, between sexes, by urban-rural gradient, by migrant status and by season of birth. In short, schizophrenia is a group of disorder marked by variability on many criteria. While a small band of zealots, for example, still believe that the earth is flat, schizophrenia researchers no longer need think that the epidemiological landscape of schizophrenia is flat. There are gradients across space and across time. The more gradients we find, the more candidate exposures we can generate. At long last, we will be able to ‘gain traction’ on the epidemiological landscape.

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References

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