Season of Birth Bias and Eating Disorders - Fact or Fiction?

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Spring 2007

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Title: Season of birth bias in eating disorders - fact or fiction?

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ABSTRACT

A season of birth bias is said to be present if the season of birth pattern for a particular group varies from the pattern within the local normal population. Such a phenomenon may contribute to the aetiological understanding of psychological disorders, perhaps by identifying subgroups within heterogeneous diagnostic categories. This can have implications for treatment. For example, season of birth biases have been identified for subgroups within the eating disorder category, especially for patients with anorexia nervosa (AN).

This dissertation will review the findings from season of birth research in eating disorders and summarize some methodological issues. Two proposed hypothesis that aim to explain this bias, will be explored. As an additional contribution to the field, one of those will be developed further. Directions for future research to expand this field of knowledge will be offered throughout.

Despite methodological issues that need to be addressed, the reviewed papers consistently show a season of birth bias for AN. Here is a brief presentation of the two hypotheses that will be explored:

The first hypothesis claims that the fertility of some thin, food restricting women will vary as a consequence of temperature fluctuation through the year. This is due to a higher need to use energy to maintain bodily temperature in colder months. Conception is more likely in the warmer months, leading to spring births. Encouragement and modelling of restrictive eating will increase the child's vulnerability for AN. The second hypothesis proposes that it is variations in sunlight exposure that lead to the observed bias. This could happen because; i) Intense ultraviolet radiation might cause maternal oxidative stress or mutations, both which may alter the neurodevelopment in some foetuses. This leaves them vulnerable for AN. ii) Higher levels of sunlight exposure might alter the mothers' mood by lifting symptoms of depression. This may improve her sexual life, increasing likelihood of conception in the summer. iii) The interaction between the mother-child might be altered as a consequence of a higher birth weight in the spring due to increased sunlight exposure during the first trimester of gestation. The interaction increases the child's vulnerability to AN.

Based on this discussion of the methodological issues, discussion and development of these hypotheses, future research can settle if the SoBB in ED is a fact or fiction.

CONTENT

SEASON OF BIRTH- FACT OR FICTION

"Whoever would study medicine alright must learn of the following subjects. First he must consider the effect of each of the seasons of the year and the differences between them". Hippocrates (Radice, 1983, p.148)

Even though Hippocrates offered this advice over 2400 years ago, little attention has been paid to the association between season of birth and psychological disorders. During the last century, the interest in season of birth bias across different psychological disorders was renewed. Several disorders have been investigated and some disorders, like schizophrenia and affective disorders, show robust season of birth bias (SoBB). Despite several attempts to explain these findings, few of the hypotheses have met scientific requirements, including being necessary, sufficient, specific, empirical and refutable. Neither has received strong empirical support. The central intention in this dissertation is to scrutinize some of the hypotheses proposed for SoBB in eating disorders. This process will contribute to determine if the season of birth bias in eating disorders is a fact or a fiction.

Aims for this Dissertation

This dissertation has two aims. The first is to present a review of the literature on season of birth bias in eating disorders. This will be done by providing an overview of the main findings and discussing the methodological issues. As an introduction to this, research on season of birth patterns in the general population and season of birth biases in different psychological disorders, traits and phenomenon are provided and briefly discussed.

The second aim is to explore and critically analyse two proposed hypotheses. As a special contribution to this field, one hypothesis will be developed further, by proposing three subsidiary hypotheses. Throughout the discussion, suggestions to further research will be included.

Definitions

This section will provide definitions of important terms in this dissertation. First, a list of important terms and abbreviations are presented in Table 1. The terms are explained, starting with the terms used to describe the distribution of births, followed by terms related to reproduction, and a brief description of anorexia nervosa (AN) and bulimia nervosa (BN).

Abbreviations

To improve readability, the abbreviations and some terms used in this dissertation are included in Table 1.

Table 1

Abbreviations and Terms

Abbreviation/Term	Concept/definition:
SoBB	Season of birth bias
SoBP	Season of birth pattern
SoB	Season of birth
ED	Eating disorder
AN	Anorexia Nervosa
BN	Bulimia Nervosa
SAD	Seasonal Affective Disorder
LH	Luteinizing Hormone
BMI	Body mass index
Fecundability	The probability of conceiving during a cycle in a healthy woman, who regularly engages in unprotected intercourse.
Fecundity	The probability of conceiving and deliver a live child
Fertility	The outcome of reproductive process, the number of children
Trough	Drop/lowest point in a curve, - low/lowest frequency
Excess	A high/the highest frequency
Peak	The top in a curve (the highest frequency)

Describing the Distribution of Births

The terminology found in the literature on season of birth pattern is quite confusing. A number of different terms are used. While they often are used interchangeably, they sometimes are used to convey different meanings. The context may provide some information, but as the reader might have different references, definitions are essential to ensure correct interpretation.

i) “Season of birth” (SoB) simply means the season when a person is born. The term is a non-specific indicator of a factor related to the season of conception, the season of gestation, or the season of the immediate postnatal life for people born in that season.

ii) “Season of birth pattern” (SoBP) refers to the distribution of births across the seasons. It allows for peaks and troughs during different months, quarters, halves or seasons of the year. This would be the term to use to describe the distribution of births in the general population. When used as such, the term “SoBP” has normative qualities. When the SoBP is used on subgroups within populations, there have not yet been established if there are

deviations between the two SoBPs. If there are deviations, these can be described as biases. It is not correct to describe the peaks or troughs in the normal population as biases, as this would imply that the SoBP is compared to something else, for example our expectation of an even distribution of births through the year (which is not the reality for most countries).

iii) "Season of birth bias" (SoBB) refers to situations when the SoBP in an index group differs from the SoBP in a normative comparison group. This means that there is a higher frequency of births in one season in the index group, compared to the expected rate from the SoBP in the comparison group. Other terms that have been used to express this bias, include SoB "effect", "tendency", "phenomenon", "excess", "trough", and "atypical pattern". As there may be subtle differences and implications of causality, clarity is required.

iv) "Seasonality" implies that the distribution of birth show a cyclic tendency, where a peak is followed by a trough six months later. The strict definition requires a perfect fit to a sine-wave.

What are Eating Disorders?

The diagnostic group called *Eating disorders* describes a heterogeneous group of patients who have excessive concerns about weight and shape (Garfinkel, 2002). The patients can be categorised according to eight diagnostic criteria in the International classification of Diseases, 10th edition (ICD-10) (World Health Organization, 1992), three criteria in the Diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994), and six criteria in the Great Ormond street Criteria (GOS**) (**Nicolls, Chater, & Lask, 2000) In this dissertation the reviewed papers include both AN and bulimia nervosa BN.

Anorexia Nervosa

The core psychopathology of AN is a preoccupation with body shape, weight, and food (Garfinkel, 2002) This leads to behaviours that make the patient lose marked amounts of weight, or a failure to gain the appropriate amount of weight when still growing. AN has the highest mortality rate of all psychiatric disorders (Emborg, 1999). It is also associated with considerable physical and psychological comorbidity such as osteoporosis, delayed growth and sexual development, menstrual irregularities, affective disorders, and suicidal behaviour (Comerci, 1990; Steinhausen, 2002). Young people with AN occupy more child and adolescent mental health beds than young people with any other diagnosis (Bryant-Waugh,

2006). This means that in addition to the great cost in human suffering both for the patients and their families, there are also considerable socioeconomic costs.

Bulimia Nervosa

Bulimia means ox-like hunger of nervous origin (Russell, 1979). BN is also associated with a morbid fear of fat. Whereas patients with AN typically restrict their intake, people with BN eat vast quantities of food in a short period of time. Distress and feelings of lack of control often accompany these episodes (Thompson & Kinder, 2003). The binges are often followed by compensatory behaviour such as self-induced vomiting, fasting, abuse of laxatives, diuretics or other medications, and excessive exercise (Beumont, 2002)

Aetiology and Prognoses

The aetiology of the EDs is complex and far from fully understood. Undoubtedly it includes predisposing, triggering and maintaining factors, which can be of a biological, social or psychological nature (Nicolls, 2007). However, the scientific society still struggles to fit all the pieces into a coherent picture.

The prognosis for these disorders is not very good. In Norway, the short-term prognosis of patients with severe BN seems to be good for 44 percent (Rø, Martinsen, Hoffart, & Rosenvinge, 2003). Many patients have long standing AN, when treated as inpatients, the prognosis after one year for these patients is good for only 8 percent (Rø, Martinsen, Hoffart, & Rosenvinge, 2004). The insufficient understanding of the aetiology might be reflected in the poor prognosis. Further information on the SoBB in AN may enhance our understanding of AN and its aetiology.

Reproduction

This dissertation is about the distribution of births throughout the year. This means that topics related to conceptions and births are central to the discussion. Three terms are commonly used; *fecundability*, *fecundity* and *fertility*. Fecundability refers to the probability that a normal, healthy woman will conceive during any one menstrual cycle. Fecundity means the probability for her to both conceive and to deliver a live child, while her fertility is the number of children she delivers (Johnson & Everitt, 2002).

Methods for Reviewing the Literature

This review is based on papers that address the timing of births for patients with clinical eating disorders. Relevant literature on SoBB in ED was identified by searching the

electronic databases PsychINFO, Embrase, and Medline for the years 1920-2006, using combinations of these terms; "season of birth", " pattern of birth", "seasonality", "excess of birth", "eating disorders", "anorexia nervosa" and " bulimia nervosa".

The literature search identified ten papers reporting research on SoBB in EDs. In addition, after personal communication with experts in the field, one paper in press was added to the base of papers included in this review. As this field is relatively narrow, there is reason to believe that the search found all the papers published on this subject.

The information on season of birth pattern in general and for other disorders was originated by a search of Medline and PsychINFO with combinations of the terms “season of birth”, “birth pattern”, “cycle and birth”, “seasonality of birth”, “seasonality and conception” and “excess of birth”, in the years 1998-2006.

Appendix

There is one appendix; Table 7 p.57. This table provides an overview of the samples, comparison groups, findings and methodological strengths and weaknesses for each of the 11 reviewed papers.

SEASON OF BIRTH PATTERNS

Pronounced and persistent SoBP are observed in almost every human population (Lam & Miron, 1994). The patterns differ according to latitude and longitude and for different subgroups of the population. Changes over time have been observed, but the degree of change varies for different continents and between subgroups. Both the patterns and the changes in the patterns are still very much of a puzzle. Here the patterns and the changes in the patterns are presented for Europe, North America and Australia and New Zealand.

Europe

One of most pronounced SoBP though the year is found in Scandinavia. Here the number of births rises substantially during the first six months, and falls during the last six months. Peaks are found in March and April, and a smaller one in September (Lærum, 1984). There is a peak-trough difference of 30 percent in Sweden, while England and The Nederlands have a peak-trough difference below 15 percent. Despite this difference, roughly the same pattern is evident. Luxembourg, France, and Italy also show this rise in the birth frequency in the first six months and a decline in the last six months of the year, but to an even lesser degree than England (Lam & Miron, 1994).

In some regions of Europe the SoBP has changed over time. For example, the variation between the highest and lowest number of births in any month in Sweden was 17% in 1921-1938, and rose to over 30 percent in the years 1969-1987. A similar pattern of birth has been observed in a 300-year analysis in England, but over time the numbers have levelled (Lam & Miron, 1994). In Germany, the SoBP has almost been reversed during the last 50 years. Around 1950 the peak was in February/March, but it is now shifted to September (Lerchl, Simoni, & Nieschlag, 1993). This pattern is more like the one found in America.

It is evident that the SoBP changes with latitude and over time in Europe.

America

On the American continent the SoBP differs from most SoBP in Europe, in various respects. There is a substantial fall in the birth rate in the first six months and a rise the last six months, with a peak in September. This is more pronounced in the Southern states than in the Northern ones, and it is more evident in non-white births (Lam & Miron, 1994). In contrast, the observed SoBP in Mexico resembles that of Scandinavian. In Canada, the SoBP used to be like the European pattern, but has now shifted more towards the US pattern (James, 1990).

Australia and New Zealand

In the Southern hemisphere, the expected pattern would be a six month displacement of the pattern found in the Northern hemisphere. This was not supported by findings. In Australia there is a March and September peak, and a November –December trough, and in New Zealand there is a stronger September peak and a April-May trough (Lam & Miron, 1994). The first is more similar to the Northern Europe one, and the latter more resembles the U.S. pattern.

Summary of Season of Birth Pattern

Almost every human population show SoBPs. For reasons we don't understand, these SoBPs differ between subgroups situated in one area and between populations in different geographical locations. For unknown reasons, some of the SoBPs have become more pronounced, while others have levelled out. How can these patterns be explained? What causes the troughs and peaks? Why are there regional differences and why have some patterns changed in opposite directions?

Several possible explanations have been proposed, often involving fluctuations in temperature or sunlight exposure, social habits, holidays and vacations (James, 1990; Lærum, 1985). It is likely that both environmental and social factors some how influence human fecundity differently, in different parts of the world. It is also likely that some of these factors may have detrimental effects on the child born in specific seasons. This may lead to vulnerability for disorders, as the observed SoBB for specific disorders suggest. Castrogiovanni, Iapichino, Pacchierotti, and Pieraccini (1998) stated this possibility clearly: "The significant association between season of birth and the occurrence of some diseases suggest a periodicity of an environmental etiologic agent, perhaps acting in concert with endogenous rhythmicities in susceptibility to that agent". (p. 175)

In the following section, observed SoBB for some psychological disorders, traits and phenomenon will be presented.

SEASON OF BIRTH BIAS

SoBB research helps to generate aetiological hypotheses and may identify subgroups within different patient populations. This could potentially lead to refinement of the diagnosis criteria and ultimately more focused treatment for subgroups. Earlier reviews, for example Fossey and Shapiro (1992) and Castrogiovanni et al., (1998), have provided good descriptions of the history of SoBB and findings. This section will therefore include the conclusions from Castrogiovanni et al., (1998), followed by an updated review of the papers published after 1998.

Schizophrenia is by far the most researched disorder in this regard, and the findings are the most robust. Other disorders that will be considered are affective disorders, anxiety, various personality traits, hemispheric domination and fertility. The SoBB for eating disorders will be reviewed in the next section, p. 18.

This presentation will reflect how the different papers differ in how detailed and exact the proposed explanations or hypotheses. Most of the papers mention factors that might be related to the SoBB with one sentence. In addition, a frequent problem is the lack of definition of the different seasons, making comparison difficult. This will be discussed thoroughly in the section on Definitions page 21.

Schizophrenia

Castrogiovanni et al., (1998) stated that the literature on SoBB in Schizophrenia shows a peak between December –May in the northern hemisphere and June-October in the Southern hemisphere. Further they report that troughs have been found in summer or autumn months, without specifying which months. Since 1998, several papers support their finding, including a systematic review and meta-analysis of the SoBB literature in schizophrenia (Suvasaari, Haukka, & Lønnquist 2001).

The SoBB is found to increase with latitude (Bembenek, 2005), and the SoBB seams to be increasing for men with schizophrenia (Saha, Chant, Welham, & MaGrath, 2006). It is also likely that there may be different SoBB for men and women, and for different symptom profiles. For example female patients born in January to April have more negative symptoms than those born in April- December. Male patients have the opposite pattern (Troisi, Pasini, & Spalletta, 2001).

There is now emerging evidence that there might be a different subgroup of patients with schizophrenia with a SoBB for June and July (Kirkpatrick et al., 1998; Bralet, Loas &

Marechal, 2002). This subgroup can be described as a Kraepelinian or deficit-syndrome subtype, characterised of enduring, primary amotivational and anhedonic symptoms. These findings may imply that there is a "double dissociation" in the SoBB, where two subgroups show different SoBBs. Such difference, in addition to differences in the course of illness, biological correlates and treatment response could support the hypotheses of separate aetiologies for these subgroups (Messias et al., 2004). Most of the papers to date have proposed explanations for the SoBB with a winter peak. Interestingly and confusingly, some of the same hypotheses have been proposed to explain the SoBB with both summer and winter bias.

The proposed explanations centre on factors in the parents or insults in the pre-peri or postnatal period.

The first proposed hypothesis is that parents of patients with schizophrenia have different procreational habits, indicating familial aggregation of psychological illness (Huntington, 1938). This illness is postulated to lead to a pattern of conception that differs from that of the general population. Future research needs to investigate the possibility of previously unknown biological factors that may regulate fertility in the parents of patients with schizophrenia, that varies through the year, and that somehow is associated with genetic liability to schizophrenia.

Instead of parental variables, the SoB may be conceptualised as a proxy marker for exposure to some factor that operates during the pre- peri- or postnatal period (McGrath, Selten, & Chant, 2002). However, the nature of this seasonally fluctuating risk factor remains unknown. Much of the research done on SoBB in schizophrenia has consisted of investigating the relationship between the SoBB and different variables that may influence the developing foetus. The variables investigated include amongst other sunshine duration (McGrath et al., 2002), rainfall (De Messias, Cordeiro, Sampaio, Bartko, & Kirkpatrick, 2001), foetal growth patterns (Fouskakis et al., 2004), perinatal variables (Kendell, Boyd, Grossmith & Bain, 2002), seasonal differences in expression of candidate genes (Chotai, Serretti, Lattauda, Lorenzi & Lilli, 2003), or maternal exposure to a variety of infections during pregnancy (Izumoto, Inoue, & Yasuda, 1999; Suvisaari, Haukka, Tanskanen, Hovi & Lönnqvist, 1999). The risk of catching measles, influenza-, rubella-, or polioviruses is increased for people in cities, probably because of higher population density (Tochigi, Okazaki, Kato, & Sasaki, 2004). The increased risk of catching viruses in densely populated areas could potentially explain the higher prevalence of schizophrenia in cities than in rural areas. Research aiming to investigate the association between SoBB and infections need to address both the timing of

the peak of risk for infections and when the developing brain of the foetus is at its most sensitive.

Finally, it is very unlikely that the observed SoBBs is caused by environmental risk factors that would work independently of genetic risk factors (Suvisaari, Haukka, & Lönnquist, 2003). This means that in order to explain the SoBB, several variables needs to be incorporated, and that the analysis should be carefully designed to specify the correlated factors. This holds true for investigating the SoBB in schizophrenia, as well as for other disorders.

Affective Disorders

Castrogiovanni at al., (1998) summarised the research on SoBB in AD as consistently showing "a winter/spring excess of births and a deficit in the months of September to November" (p. 177). That probably means that the excess was in the months December to May.

Very few studies on SoBB in AD have been published after 1998. The SoBB for patients diagnosed with bipolar disorder supported the earlier findings of winter excess, where winter is defined as January to March (Moore et al, 2001). Without explaining it further, the authors suggest that the finding could be a consequence of developmental abnormalities from insults, possibly infective, in the uterus or early-life.

A slightly different SoBB was found for patients with seasonal affective disorder (SAD). The SoBB showed a trough in the first quarter of the year, and a slight excess in the second and the third quarter (Pjrek et al., 2004). Pjrek et al., (2004) also showed that patients with melancholic depression had a peak in autumn/winter, and a trough in spring/summer compared with patients with atypical depression.

Anxiety

Castrogiovanni et al., (1998) did not include a section about anxiety in their review. But the following year, Castrogiovanni, Iapichino, Pacchierotti, and Pieraccini (1999) published a paper showing that patients with panic disorder had a SoBB with peaks in September to December. The authors discussed the potential impact of light exposure during the first few weeks after birth. They suggested that this could result in making the pineal gland hypersensitive to light. They also proposed that the yearly variations of 5 HT-metabolism or an abnormal dopamine function could be involved in making the child

vulnerable for developing panic disorder. This makes them one of the few authors that propose a SoBB hypothesis that is specific and empirically based.

Personality Features

Castrogiovanni et al., (1998) reported that the observed SoBB in personality disorders was somewhat conflicting, but tended towards a trough in June-September. A major methodological concern is that the personality disorders included were not specified. This is important, as the development of personality and character traits parallel the development of the turnover of neurotransmitters, and their interactions, in the brain (Chotai, & Adolfsson, 2002). Through research on different traits, different SoBB are indicated for the neurotransmitters. For example, high scores for novelty-seeing show a negative correlation to reactivity in the serotonergic and norepinephrine system, and a positive association to dopamine (Zuckerman, 2003). Women born in February to April are more likely to have high scores on novelty-seeking, then for women born during October to January (Chotai, Forsgren, Nilsson, & Adolfsen, 2001). Lower agreeableness is found for in subjects born during December to February (Tochigi et al, 2004b).

Variations in traits, independently of psychiatric diagnoses, have been postulated to explain observed differences in suicide methods. Hanging, rather than poisoning or suffocation by petrol gas, is more likely used by suicide victims born in February to April, compared to victims born from October to January (Chotai & Renberg, 2002). In addition to neurotransmitters, hormones may influence personal traits and behaviour. One example is melatonin and sleep-wake cycle.

“Morningness”, that is those who are early risers, is found to a greater extent in people born during October to March. Those who are more active during the second half of the day, showing “eveningness” pattern, are those born during April to September (Natale, Adan, & Chotai, 2002). The reason might be that the foetus is affected by seasonal phases of maternal melatonin. This explanation is party based on the findings that infants born in when the length of the day is shorter, have a lower excretion of a melatonin metabolite, than infants born in the time of year with longer hours of sunlight (Natale et al., 2002). This means that the difference in adult morningness or eveningness might partly be due to long-term effects of environmental influences during gestation or the perinatal period. This is also an example of a specific and empirically based hypothesis.

Hemispheric Domination

Research on SoB indicate that there is a SoBB for hemispheric domination. Both the SoBB for handedness, and artistic versus scientific modes of thought, support the claim of a SoBB for hemispheric domination. People who are more inclined to scientific modes of thought or extreme right-handed baseball players are more often conceived in November-December. In contrast, for artists and left handed baseball players a peak in the conception rate is found in May-June (Marzullo & Fraser, 2005). The authors propose that maternal oxidant stress, because of intense solar radiation might interfere with closure of the neural tube. This will be discussed further on p. 43

Fertility

There is little evidence that there are seasonal changes in reproductive maturation or a season of birth for menarche (Johnson & Everitt, 2000), but there seem to be a SoBB for fertility. Women born in or around August have the highest rates of conceptive failure, whilst those born in or around February have more successful conceptions (Smits, Zielhuis, Jongbloet, & Bouchard, 1999).

Winter is the period where most women reach menopause (Cagnacci et al., 2005a). Women born during September through December reach menopause at an older age, than women born between March and June (Cagnacci et al., 2005b). This finding holds true even after controlling for other factors like age, BMI, smoking habits, education level, and type of job. One explanation is that foetal growth can be influenced by environmental temperature and sunlight exposure. They also propose that seasonal variation in maternal diet and prenatal exposure to infections are potential factors that may influence fertility in women (Cagnacci et al., 2005b).

Male fertility is also related to SoB. Men born in October to December have fewer offspring and a higher probability of remaining childless than men born during March to June (Huber, Fieder, Wallner, Iber, & Moser, 2004). The sunlight exposure at a male's birth seems to be positively correlated with his subsequent offspring count, but the mechanisms are still unknown.

Summary of Season of Birth Bias

The brief review of the literature on SoBB after 1998, show that many papers report SoBBs for various psychological disorders, traits and phenomena. For some disorders, the findings consistently show a similar SoBB, while at the same time there are papers showing

different SoBBs, between and within, some disorders. This could reflect actual differences in aetiology between the disorders, and between subgroups within a heterogeneous diagnostic group. The contradictory findings may also reflect differences in definitions and methodological procedures. The congruent findings may imply shared vulnerability for a specific environmental factor, or it could just be a coincidence.

The vagueness and lack of specificity characterising the majority of the hypotheses proposed to explain these findings, reveals the shortcomings of this area. For example, even though over a 100 papers are published on the SoBB in schizophrenia, none of the proposed explanations have proved conclusive (Castrogiovanni et al., 1998). Because of this, many authors end their paper in much the same way as Brenner et al., (2004) “The list of candidate exposures includes infections, many of which vary seasonally, but also maternal diet, environmental toxins, photoperiod, temperature, weather, and hormonal milieu” (p. 280).

The next section will present a detailed review of the 11 papers published on SoBB in ED.

SEASON OF BIRTH BIAS IN EATING DISORDERS

The literature search identified ten papers that had explored the SoBB in clinical samples of EDs. In addition, one paper is being submitted soon. The main findings from these eleven papers are presented here. Complete details about the methods used, findings, strengths and weaknesses in each study are provided in the appendix p.57.

Nielsen (1992) conducted the first study that investigated SoBB in EDs. He studied two groups of patients with AN in Denmark. One sample comprised 140 females from Copenhagen, treated in the period 1960 to 1976. The second sample included 593 patients from The Institute of Psychiatric Demography in Århus from 1973 to 1987. In the first sample a SoBB was found for subjects with an onset before 15 years ($p < 0.01$). This was not found in the second sample. There, a "weak seasonal variation in time of birth" (p. 29) for the years 1959-1964, and a significant SoBB were found for the patients with an onset after 15 years, born during 1963-1968. The peak was late in April. This was significantly different from the birth distribution of Danish females. Nielsen (1992) concludes his paper stating that the relative rarity of AN poses a problem in SoBB research, and welcomes replications from larger countries in different latitudes and hemispheres.

The second study met Nielsen's appeal for replication of his study in a larger sample. Rezaul, Persaud, Takei and Treasure (1996) studied all British referrals, since 1979, of eating disorders to the Maudsley Hospital Eating Disorders Unit. A significant SoBB was found for 1939 subjects, with a peak in May ($p<0.05$). Compared to older patients and the general population, the 882 younger patients (born after 1963) had peak in March ($p<0.01$). Even though the sample was thought to represent mainly AN, the insufficient information about the patients´ diagnostic status is an important drawback.

This weakness was overcome by the third study, also conducted in the UK. Morgan and Lacey (2000) studied 935 patients with a clear diagnosis of BN referred to the St. Georges Hospital Eating Disorder Unit. The authors state that the overall findings did not indicate a significant SoBB for BN, despite of an excess of births in July for patients born in or before 1963 ($n=389$) ($p<0.01$). The authors conclude that this finding "is harder to interpret and appears anomalous" (p. 454). For BN arising from AN, they found an excess of births in March. The authors ended the paper by stating a need for further investigation of factors that might to be related to SoBB and AN.

This suggestion was perused in the northeast by Scotland, Eagles, Andrew, Johnston, Easton and Millar (2001). They included 446 patients with AN in their study, and found an

excess of births in the first six months of the year compared to controls (p= 0,01). The most prominent number was in the second quarter of the year, April to June, with the largest excess in the month of June.

Watkins, Willoughby, Waller, Serpell and Lask (2002) focused on early-onset AN by studying 295 British by children and adolescents with AN. They found an excess of spring births, April-June, in comparison to patients with other eating disorders (n= 149), and the general population norms. Moving the centre of attention from the time of birth to the time of conception, the results showed that a significant greater proportion of early-onset AN, compared to other ED´s, were conceived during the warmer months. This led to the development of the first model (the Environmental temperature at conception hypothesis) constructed specifically to explain the SoBB in AN (described on p. 33)

Waller et al (2002) continued the investigation on subgroups of AN in the UK. They compared 117 patients with restrictive AN with 78 patients with AN binge-purge subtype. A high-risk period was postulated, April through June, and the number born in this period was compared to the number of births in the rest of the year. This showed that a significantly greater proportion of the restrictive AN compared to binge-purge AN were born during the high risk period ($p<0.05$).

All the research done on sob on ED at this point was conducted in Europe. To test the implications of the model described in Watkins et al., (2002), Willoughby et al., (2002) investigated the SoBB in the Southern hemisphere. They studied 199 Australian children/adolescents with early-onset AN, but did not find a significant SOBB. However, a lower number of patients with restrictive AN were conceived in the cooler months, relative to the number of patients with binge-purge AN conceived in cooler months ($p<0.04$).

To further test the Environmental temperature of conception (Watkins et al., 2002) Willoughby, Bowen, Lee, Pathy and Lask (2005) studied 102 patients with early-onset AN in Singapore, where the temperature is stable throughout the year. As predicted by the hypothesis, they found no excess of births at any time of the year.

In Spain, where the temperature is higher than in Northern Europe, Penas-Lledo, Santos, Vaz Leal, and Waller (2003) studied 105 Spanish patients with ED and found an excess of births in June-August among the patients with restrictive AN in comparison to BN (including binge-purge AN & BN) (p= 0.03).

Recently, Crisp (2006) published an analysis of the SoBB for 980 patients with AN in London, compared to population norms. Although, no significant findings, he did show a trend towards a trough in the SoBB in February, and peaks in March, April and October for

patients born before 1964. A similar trend towards peaks in Mars and April was found for patients born later than 1964.

The somewhat "abandoned" part of the EDs, BN, regained some attention when Brewerton, Dansky, O´Neil and Kilpatrick (in press) turned their attention to this group. A national screening identified 85 women with BN (out of about 3000) and found a cyclic trend with a peak in the autumn (September 22- December 20) ($p=0.03$) and a trough in the spring (Mars 22-june 20) ($p=0.03$).

Summary of Season of Birth Bias in Eating Disorders

The 11 papers consistently show a SoBB of spring births for young patients with AN, predominantly restrictive subtype and those with an early onset, compared with binge-purge AN, BN and the general population. There is minimal evidence for a SoBB in BN.

The authors have proposed several possible explanations, but few in any detail. There are several methodological issues that must be addressed. This will be done in the next section.

METHODOLOGICAL ISSUES

In the previous three sections, findings from SoB research have been presented. They suggest that there are differences in the SoBP for the normal population that vary over time, between subgroups in the general population, and between the general population and patient groups suffering from different psychological disorders, including AN and possibly BN. However there are some major methodological issues, regarding definitions, statistical methods and sample, which require detailed consideration.

Definitions

As stated in the beginning of this dissertation, the definitions used in SoB research are quite confusing. In an attempt to avoid further confusion, the terms used to describe the distribution of births in a year were defined on page 6. The failure of the research community to use consistent terms and definitions makes comparison between studies very difficult. This is intensified by the fact that even the seasons are being defined differently.

Divisions of the Year

When first encountered, the task of defining the seasons may seem simple. However there are actually many different ways of defining them, for example through periodic change in the weather, transitions in the animal or vegetable kingdom, the Astronomical way, the Traditional way, or the Meteorological way.

The division of the year through seasons is generally based on *yearly periodic changes* in the weather or through transitions in the vegetable- or animal kingdom. In temperate zones it is common to talk about four seasons, with the seasons reversed in the Northern and Southern hemisphere. As illustrated in Table 2, there are either two or four seasons in the tropical areas; wet or dry, in combination with warmer or colder weather (Wikipedia, 2007a). But there are exceptions, as some Australian Aboriginal tribes have eight seasons a year.

For the purpose of this dissertation, the four seasons in the temporal zones in the northern hemisphere will be described, focusing on Norway.

Table 2
Division of Seasons

Seasons	Temperate regions	Tropical regions
1	Spring	Dry Cool
2	Summer	season Hot
3	Autumn	Wet season
4	Winter	

Note: Table adapted from Wikipedia, 2007a, http://wikipedia.org/wiki/Winter

The Astronomical way, defines the four seasons by letting the solstices and equinoxes mark the beginning of each season. Because of the elliptical orbit of the earth and its different speeds along that orbit, the seasons are not of equal length (Wikipedia, 2007b). *The Traditional way* of defining the seasons, uses the equinoxes and solstices as midpoints, and the cross-quarter days as starting dates for the seasons. This is reflected in the "midsummer" celebrations in some parts of Scandinavia, East Asia and Irish cultures (Wikipedia, 2007b). Table 3 provides an overview of the Astronomical and Traditional way.

Table 3

The Astronomical and Traditional Definition of Season

Season	Solstices and Equinoxes: Starts dates in the Astronomical season	Cross-quarter days: Start dates in the Traditional season
Winter	20-23rd December	5-10th November
Spring	19-22nd March	2-7th February
Summer	19-23rd June	4-10th May
Autumn	21-24th September	3-10th August

Note: Adapted from Wikipedia, 2007b, http://en.wikipedia.org/wiki/Season

In the Meteorological tradition, the four seasons are defined by temperature. The summer consists of the warmest quarter, and the winter includes the coldest quarter of the year. In this tradition, the spring is the first season.

The confusion the different definitions may create is illustrated in Table 4 (p.23). April is a relevant month to look at, as it has been identified as one of the peak months for SoBB in AN. It is easy to see that this month could either be the first, second, or last month of spring. An illustration of how confusing this is, March, April and May, could include winter, spring and summer.

Table 4

Comparison of different definitions of seasons

Astronomical	Meteorological	Traditional	Months
Winter	Winter	Winter	January
Winter	Winter	Spring	February
Winter	Spring	*Spring*	*March*
Spring	***Spring***	***Spring***	***April***
Spring	*Spring*	Summer	*May*
Spring	Summer	Summer	June
Summer	Summer	Summer	July
Summer	Summer	Autumn	August
Summer	Autumn	Autumn	September
Autumn	Autumn	Autumn	October
Autumn	Autumn	Winter	November
Autumn	Winter	Winter	December
Winter			

Note: Adapted from Wikipedia, 2007b, http://en.wikipedia.org/wiki/Season

Some of the papers report peak months (Nilsen, 1992; Morgan & Lacey , 2000; Eagles et al., 2003, Crisp, 2006), others also focus on quarters (Rezaul et al., 1996; Watkins et al., 2002; Waller et al., 2002; Willoughby et al, 2002 & 2005). If the latter group go on to talk about seasons, they might be using the Astronomical way of defining the seasons. This is however imprecise, as the Astronomical seasons does not start in the first of any month (se Table 3).

Pena-Lledo et al., (2003) also use quarters of the year, but they use December-February, March-May, and so on, which resemble the Meteorological definition. It is only Brewerton et al., (in press) who define the seasons used in their paper. However, at the same time they also illustrate the challenges of using definitions, as they define the seasons the same way as is done in the Astronomical way, but call it Traditional definitions.

Whatever system is used to define the seasons, there is a need to adjust for differences in latitudes and longitudes, to allow for differences in weather. Consequently, there will also probably be differences in the exposure to environmental agents that may be involved in the SoBB for AN. This could be dealt with by using, strict meteorological definitions, that uses mean night and day temperature.

According to this, summer is defined by the months when the mean temperature is more than 10 Degrees Celsius. Spring and autumn consists of the months with temperatures between 0 and 10, with temperatures increasing or falling respectively. Winter is comprised of the months with mean temperature under 0 Degrees Celcius. Following these definitions

the lengths of the seasons vary greatly over different longitudes. As the temperature also is dependent upon the proximity to coastal areas, the timing of the seasons will also wary. In Norway, this will result in different length of the seasons depending on where you are. For example, as evident from Table 5, the summer is 60 days longer in Oslo than in Tromsø.

Table 5
Seasons according to temperature in Norway

Season	Oslo; Days	Tromsø; Days
Spring	57	70
Summer	129	69
Autumn	60	66
Winter	119	160

Note: Information adapted from Meterologisk institutt (2007) http://met.no/met/met_lex/index.html

In Stavanger, the mean temperature in the coldest months are 1.1 Degrees Celsius, meaning that a autumn glides into the spring before summer, without what is defined as winter. In Vardø, the spring glides into the autumn, without a summer in between, as the warmest temperature is 9.2 Degrees Celsius.

Despite the pronounced changes in amount of sunlight during the year in the temperate and polar zones, there is no definition of seasons based on sunlight (phonecall, Meterologisk institutt; Ole Nilsen, 19th of April, 2007).

In summary, for knowledge to be advanced in this area, there needs to be more consistency in the definitions of seasons. Further, it would be helpful if the definitions of season used when testing a specific hypothesis matched the variable being considered. For example, using a definition based on temperature cut-off when testing the Environmental temperature of conception.

Diagnoses

There are a number of issues to consider with regards to diagnoses. First, there is a possibility that different understandings and use of the diagnostic systems have evolved in different countries, hospitals and between professions, resulting in variations in how strict or liberal the criteria are used. Secondly, the diagnostic systems are problematic in themselves as the criteria for the ED diagnoses differ between DSM, ICD, and GOS, and between the various editions. The DSM-IV and ICD-10 are found to have very low reliability in younger populations (Nicholls, Charter, & Lask, 2000).

The validity of the DSM diagnostic system might also be questioned as the most common diagnose is the atypical eating disorder ED-NOS. In addition, it is not uncommon that patients drift in and out of the different diagnoses during their illness. For example about 50 percent of patients with AN go on to develop BN, and about one third of patients with BN have had a previous episode of AN (Fairburn & Bohn, 2005).

In prospective research on SoB, the date of birth of a patient could influence the diagnosis given. Therefore clinicians and/or researchers might need to be blinded to the research question or to the date of birth during assessment. In retrospective studies, this would not be a problem, as diagnosis would have been assigned prior to initiation of the study.

Comorbidity as a Confounding Variable

In SoB research, consideration needs to be given to the potential for comorbidity being a confounding variable, given that these conditions do themselves show a SoB. Patients with AN often present symptoms of depression, anxiety and obsessive compulsiveness, and BN is frequently accompanied by depression (Bulik, 2002).

Only one of the 11 papers reviewed in this dissertation addressed this issue, and excluded patients with comorbide disorders (Eagles et al., 2001)

Statistical Methods

To detect a cyclic variation in a distribution of births, the distribution needs to be described and tested to ensure that it is not a consequence of chance probability. In this section, a brief overview of the statistical analysis used in the SoB research in the 11 papers on SoBB in ED, will be presented.

Four of the 11 reviewed papers used Edwards´ test (1961) for seasonality (Rezaul et al., 1996; Morgan & Lacey, 2000; Eagles et al., 2001; Crisp, 2006). Seasonality tests aim to detect a significant seasonal pattern in the data, through identifying a peak and trough six months later. Edwards´ test (1961) identifies seasonality by fitting sine waves to data consisting of independent events, like the births in a sample. This is done by using weights to represent the number of observed events, fitted into a circle where twelve equally spaced points represent the months. In the absence of a cyclic trend, the expected centre of gravity will be at the centre of the circle. When a cyclic trend exists, this will be evident from the pattern created when the force of gravity pulls the weights (Edwards, 1961).

The Edwards´ test does allow for different sample sizes, but does not address the question of minimum sample size. Nor does it not allow for variations in the lengths of

month, assuming they are equal. Furthermore, it does not take into account the size or pattern of the general population. This can lead to Type I errors (incorrectly identifying a SoBB), as seasonality might be spuriously caused by variation in the general population. In other words, where there is an excess of births in the spring in the general population, there is a high probability that a SoBB would be detected for the sample in question because of this excess.

Alternatively, it can cause Type II error (failing to detect a SoBB) when comparing two samples that have different cyclic trends. In these cases, the two cyclic trends may cancel each other out, leading the researchers to conclude that there are no SoBB (Walter & Elwood, 1975).

Although authors have criticised the Edwards´ test (1961) is has been extensively used. One reason to this might be that no favourable alternative has been available (Roger, 1977).

One of the 11 papers (Eagles et al., 2001) used a nonparametric method (Hewitt, Milner, Csima, & Pakula, 1971). This method was developed as a response to the high degree of Type 1 errors, especially in small samples using the Edwards´ test (1961). Through a randomised-number -generated distribution, Hewitt et al., (1971) demonstrated that Edwards´ test (1961) was applicable down to samples of 96 subjects, and the method was called "serviceable" for samples as small as 50 subjects (Hewitt et al., 1971, p. 174). They advised to discount results from Edwards' test when the sample size is under 50. For this non-parametric alternative, there is no lower limit on sample size. However, there is a requirement that there must be at least one birth in each of six months or more.

Two of the 11 papers (Watkins et al., 2002; Willoughby et al., 2002) used a method developed by Roger (1977). In order to reduce the likelihood of Type I errors and to handle small samples of for examples 20 cases, Roger (1977) developed a different method for significant testing of cyclic trends, a form of seasonal chi-square. Seasonal chi-square analysis may not be appropriate to identify SoBB in psychiatric illnesses. The main reason is that the method does not identify peaks in birth rate (single peak in one period, like a month or a quarter), but rather it identifies a seasonal trend (a peak followed by a trough six months later). Significant SoBB that are not seasonal may therefore be lost.

The first paper that reported a SoBB in AN, Nielsen (1992), used a method described by Jones, Ford, and Hamman (1988). Through this method, seasonality between groups can be estimated, thereby meeting the criticism against Edwards' test for not taking into account the size or pattern in the general population. This method allows for testing of seasonal pattern both within a group, and between two or more groups, by determining the best-fitting

seasonal model. It allows for unequal time intervals, different time trends, and different populations. A drawback is that Jones et al., (1988) do not address power in relation to sample size, and that SoBB that is not cyclic is missed.

Five of the 11 papers used (Watkins et al., 2002; Willoughby et al., 2002; Pena- Lledo et al., 2003; Willoughby et al., 2005; and Brewerton at al., in press) used non-seasonal chi-square, or standard chi-square analysis. This allows for the identification of non-cyclic SoBB. The most important disadvantage with the standard chi-square testing is that it requires large samples. Hare (1975) suggested that at least 1500 subjects were needed to identify seasonality (with 96% probability, and an 8% deviation) when considered by quarters, and 4500 when considered by month. Three of the 11 papers (Watkins et al., 2002), Waller et al., 2002; Willoughby et al., 2002) included Yates´ correction for continuity, which tackles the problem of small samples. They also used other nonparametric tests like the Mann-Whitney test.

The conclusion of this is that the different statistical methods used by the eleven papers all have advantages and disadvantages. Various researchers and statisticians will have different preferences and give different rationales for their choice of statistical method. The main concern when using methods that test goodness- of- fit between observed events and sine waves for small samples, is the increased risk of Type I error. This is a serious threat to the SoBB research, because this might lead to a conclusion that there are SoBB, when they in fact are fiction.

In future research, the following issues should be considered when choosing statistical methods. First, the method needs to allow for the fact that different months have different lengths, also including leap years. Second, it has to take into account the size and SoBP of the general population, in the same area where the sample is collected. Third, the method has to be able to detect patterns that differ from cyclic variation, for example by identifying one or more excesses and/or troughs. Fourth, the method needs to overcome the problem of high likelihood of Type I error. Newer methods should be considered, for example the trigonometric regression method by Fellman and Erikson (2000).

Sample

As with the definitions, there are issues attached to the index sample and the comparison sample. In this section, the size, representativeness, and the challenge of not counting one patient more than once will be addressed.

Sample Size

Research is basically about “disproving” hypotheses by testing null hypotheses (Liebert & Langenbach-Liebert, 1995). Incorrectly rejecting the null hypotheses (Type I error) or failing to detect true differences (Type II) error are threats to every scientist. The sample size plays an important part when evaluating the study’s sensitivity for detecting real differences. Since small samples decrease the study’s power, by increasing the standard error, they raise the probability of Type II error. Thus by increasing the sample size, the chance of failing to identify associations that are in fact present, decreases. Although this clearly is relevant for SoB research in ED, practical realities like the rarity of ED, often limits the sample size. This has consequences for choice of statistical methods.

The eleven papers illustrate that in research concerning ED, availability to large numbers of patients either requires a secondary or tertiary service that receives referrals from a large population, or services that have been active for several decades. The largest sample by included 1937 subjects (Rezaul et al., 1996), which were divided in two age groups and analysed by Edwards’s test (1961). The smallest sample used in analysis was 17 subjects when comparing binge-purge AN to restrictive AN in a conventional one tailed chi-squared test (Penas-Lledo et al., 2003). According the Hare (1975), this is a too small a sample to base conclusions on. The other subgroups consist of about 100-300 subjects.

One aim for future research, is to increase the size of the subgroups binge-purge AN and restrictive AN.

Representative Sample

In order to conclude that there is a SoBB in any subcategory of ED, the samples need to be valid representations of the relevant populations. This means that the patients´ diagnoses should be set according to the same criteria (other diagnostic issues will be discussed at p 24). This presupposes that the inter-rater reliability is sufficient, so that cases are categorised correctly.

Representativeness can also be skewed by the level of specialist service the sample is collected from. All samples in the reviewed papers, except Brewerton et al., (in press), represent EDs either on secondary or tertiary level, which may not be representative of ED as a whole. One reason might be that these patients share other characteristics that may be associated to the observed SoBB. Systemic or organisational factors might also contribute to the predominance of secondary or tertiary level patients, for example founding politics or the "easy" access to subjects. Using National records, especially in areas with small population

bypasses this problem, and increases the representativeness. The problem is that not all countries have these. Only one of the 11 reviewed papers used such a register (Nielsen, 1992) Preferably, the research can be done in areas with greater population density. This is also an advantage as diversity in experienced seasonal variations may be restricted. Ensuring that the sample is representative is also important for the control group.

Control and Comparison Group

Finding a SoBP in the general population is interesting in it self; it becomes even more interesting when differences between geographical areas, subgroups, and changes through time are observed. Explaining this is a major challenge. When SoBB is associated to various psychological illnesses, the question of aetiology emerges. Before one sets out to explain the observed SoBB, the validity of the findings needs to must be ensured. Executing the right statistical analysis, being precaution about Type I and Type II errors, making sure that the sample representative and the size is satisfactory all contributes to this. But, if the pattern the SoBP is compared to is not the correct one, then the findings become misleading.

In order to determine the extent to which the SoBP is unique, it must be compared to something that is relevant. The most obvious control group is the general population from the same place as the patient sample. Psychiatric comparison groups are interesting, but potentially contaminating, as they may have SoBBs of their own. However, SoBB differences between subgroups of a disorder could provide important information.

Further more, it is relevant to SoBB research to know whether the control group consists of all births or only live births, as infant mortality may contribute to a SoBP (Hare, 1975).

All the eleven papers, except one (Penas-Lledo et al., 2003), have compared their ED sample to the SoBP in the general population. Eagles et al., (2001) was the only study that used just the *local* general population. Comparison groups have been composed of patients with different time of birth; older or younger than 15 years at first admission (Nielsen, 1992), or grouped according to birthdays in or before 1963 versus those born in or after 1964 (Rezaul et al, 1996; Morgan & Lacey, 2000). Some (Nielsen, 1992; Eagles et al., 2001; Crisp, 2006) focused on AN and did not subdivide that group further or compare it to BN. Rezaul et al., (1996) did not use subgroups of ED, but compared the SoBP to that of the general population. Morgan and Lacey (2000) was the only study that used BN and BN arising from AN, whereas Brewerton et al., (in press) just looked at BN, compared to the general population. Watkins et al., (2002) looked at early-onset AN versus other early-onset ED in children, four of the 11

reviewed papers compared restrictive AN to binge-purge AN (Waller et al., 2002; Willoughby et al., 2002; and Willoughby et al., 2005; Penas-Lledo et al., 2003).

Further research should always include population norms for females (if the index group consist only of females) preferably for the local population, and be explicit as to whether this includes just live births or all deliveries.

As the findings from these 11 papers suggest, there might be a difference between restrictive AN and binge-purge AN, or early-onset AN and other early-onset ED. These relationships should be explored further.

Duplication of Subjects

It is not uncommon for patients with eating disorders to have more than one admission or referral, or to be treated in several centres. Researchers need to be vigilant to cross-centre "duplication-of-subject count", as the accuracy of the findings might be seriously flawed if one patient's date of birth is counted twice.

Performing the appropriate checks such as searching the database for duplicates of subjects by name and cross-referencing key data, for example date of birth, can control for these issues.

However, none of the eleven studies reviewed commented on performing checks to counteract the risk of duplication of subjects within their samples. This needs to be done in future research.

Summary of Methodological Issues

Methodological issues regarding definitions of the seasons, the distribution of births throughout the year, diagnosis, comorbidity and the qualities of the statistical method used must be addressed. It is evident that almost none of the papers commented upon the definition of season. However, as most of them used the quarters, starting with January, or somewhere in the paper stated in which months the peak appeared, this was not a big a problem. However, the lack of attention that was given to the issues concerning diagnosis and the problem of comorbidity is problematic.

It seams that there was a development from the first paper to the last, with a growing focus on the subgroups in AN. Still, there is a large group of BN and ED-NOS that needs to be investigated further. It is critical that the patients are not counted twice.

A variety of statistical methods have been used, which supports the validity of the findings. A claim of "the best" statistical method, will probably be very controversial. This is

good, as it fuels the continuous debate and development of better analysis. Mean time, the areas identified as problematic must be taken into account when choosing analysis in studies to be conducted.

In relation to choice of statistical method, the required sample size must be identified, in order to minimize the risk of missing real differences. However, as all the studies supported the SoBB, either by significant results or trends, this does not seam to be an issue. Of greater concern is the probability that the statistical analysis used may be prone to give false alarms. In order to settle this, it is important that correctional steps are taken.

TWO HYPOTHESES

Environmental temperature or sunlight exposure?

The task of explaining SoBB in ED is important as it might increase the aetiological understanding of ED, thereby improving prevention and specialised treatment. However, in order to be an explanation of SoBB in ED, it has to fulfil five criteria. The first criterion states that the explanation has to be necessary in order to explain the phenomenon. That means that the hypothesised mechanism must be present for the SoBB to occur, without it, it would not arise. The second criterion is that the hypothesised mechanism is sufficient for the SoBB to occur. The third criterion is that the explanation is specific, meaning that it does not predict other psychopathology then the one it is intended to explain. The fourth criterion is that it is empirically derived; based on relevant existing knowledge. The fifth requirement is that the explanation is refutable. This means that if we do not find the predicted abnormalities then the hypothesis is disproved. The overall question is weather the hypotheses have good explanatory power, meaning that it explains why the SoBB is the way it is, and why it is not different.

The eleven papers reviewed earlier all propose explanations for the SoBB, but few if any, meet all criteria listed above. The majority of the explanations might rather be meant to function as inspiration for future research.

In the following section two hypotheses for the SoBB in AN, *Environmental temperature at conception* and *Sunlight exposure,* will be considered, before implications and suggestions for further research are outlined.

The first hypotheses was chosen because it is the only model that specifically aims to explain SoBB in AN (Watkins et al., 2002), and two papers have tested the implications of that model (Willoughby et al., 2002, Willoughby et al., 2005). The second hypothesis was chosen because it is a strong contestant to the first one, as sunlight correlate positively with environmental temperature. It is also a hypothesis that several authors have mentioned (like Morgan & Lacey, 2000; Crisp, 2006), but none have adapted it as an explanation for SoBB in AN. As a special contribution to this field, the sunlight exposure hypothesis will be developed further here. This is done by proposing three subsidiary hypotheses. Each will be explored in turn.

Environmental Temperature at Conception

Description of Hypothesis

Watkins et al., (2002) proposed this model, aiming to explain their findings of a high frequency of early-onset AN conceived in warmer months and a preponderance of births in April to June. The model proposes that the observed SoBB is a result of seasonal variations in fecundability for some thin, food restricting women. Their fecundability varies because colder months increase the need to divert energy to maintain normal body temperature. In consequence, conception is less likely during the colder months and more likely in the warmer months. In addition, specific genes and environmental factors, such as modelling and encouragement of restrictive eating, contributes to making the child vulnerable to develop AN. The premises upon which this hypothesis rests are:

A) Restrictive eating leads to weight loss and low weight

B) Low weight and restrictive eating leads to lowered fecundability

C) Low environmental temperature modifies fecundability through increased need to divert energy to maintain bodily temperature

D) Unhealthy eating patterns can be intergenerationally transmitted

Discussion of the Premises

In this section, arguments for and against the four premises will be presented.

A) Restrictive Eating Leads to Weight Loss and Low Weight

Most people would accept that body weight is a simple function of caloric intake and energy expenditure. This is true, although it is not the whole story. To begin with, this premise begs two questions - First, what is restrictive eating? Second, what is low weight? The latter question will be discussed in regard to the second premise.

Like many other areas, it is problematic when there is inconsistency in the use and definition of terms; like restrictiveness, dietary restrictiveness, dieting, and restrained eating. They can be viewed as synonymous, or used interchangeably for the same or different concepts, while others advocate that they are neither semantically nor functionally equivalent (Lowe, 2002). Both can be understood as either a wish to lose weight, a self-initiated attempt to reduce food intake in order to lose weight, or an attempt to maintain current weight and prevent gaining weight (**Hill**, 2002). Restrained eaters and dieters differ in sweetness preference and salivatory output (Lowe, 2002).

The validity of self-reports of restrictiveness may suffer from memory bias, social desirability, and the extent to which the restriction actually is reflected in reduced energy intake below the energy needs (Hill, 2002). For humans, cognitive factors can in many circumstances override the innate physiological control of food intake. These cognitive factors are influenced by environmental factors, social and emotional reactivity, and classical and operant conditioning (Jebb, 2002)

The essence in the premise under discussion is whether actual food restriction, leading to a negative energy balance, will lead to lowered weight. If a person consistently eats less then 500 kcal/day under the amount of energy needed, the person will loose weight (Dwyer & Melanson, 2002). The amount and speed of loss is dependent upon individual differences related to exercise, body fat composition, normal distribution of levels of the thyroid and androgen hormones, level of activation of the sympatric nervous system, the constituent parts of the diet, and genetics (Bjørneboe, 1999). These factors also predispose to the amount of energy requirements.

There are also different diseases that influence a person's weight, despite a "normal" diet and exercise. Some diseases lead to weight loss, like hyperthyroidism, infections, Parkinson, some types of cancer, leukaemia, Diabetes Mellitus (insulin-dependent type) either through cessation of insulin injections or just after onset (Bjørneboe, 1999). Other illnesses can have the opposite effect, by preventing the body from losing weight despite a negative energy balance. Examples are hypothyroidism, Prader-Willi syndrome, and certain mutations in genes coding for leptin or the hypothalamic leptin receptor gene (Bjørneboe, 1999)

In summary, the premise that restrictive eating leads to weigh loss appears valid. Women, who are other wise healthy, will loose weight if they severely restrict their eating, and maintain a low weight if they restrict it over a period of time.

B) Low Weight and Restrictive Eating Leads to Lowered Fecundability

Mammals partition dietary energy among five major metabolic activities: cellular maintenance, thermoregulation, locomotion, growth and reproduction. When energy is used for one of them, it becomes unavailable for others (European Society of Human Reproduction and Embryology [ESHRE], 2006). If there are insufficient recourses, functions vital for immediate survival will be prioritised, like keeping warm. Because of the great caloric demands involved in gestation, fecundability is lowered when food is scarce (Davis & Levitan). A negative energy balance is also associated to delayed initiation of puberty, or a cessation/pause in normal growth (Johnson & Everitt, 2000). In addition, severe restriction or

undisclosed eating disorders have been linked to unexplained fecundability problems (Stewart; 1992). However, whether it is the low weight or a negative energy balance that is most important have been controversial. This discussion is relevant as this premise postulates that both low weight and restriction of energy intake must be present for the hypothesis to be valid.

Some have argumented that before the hypothalamic-pituitary-gonadal axis is activated and menarche start, a consistent critical body weight at about 47 kg is required (Johnson & Everitt, 2000). Similar, the Frisch hypothesis states that menarche is dependent on achieving a critical percentage of body fat equivalent to an 87 percent weight for height ratio (Frisch & McArthur, 1974). The rationale for a critical body weight for fecundability includes the fact that oestrogen is stored in adipose tissue. In addition have leptin, a hormone secreted proportional to adipose tissue, seems to be involved in the control of the hypothalamic-pituitary- gonadal axis (Johnson & Everitt, 2000). However, recently it is found that leptin secretion is closer related to nutritional status and energy availability than fat storage (ESHRE, 2006). Following this, several papers have criticised the notion about a critical weight needed for menarche, and especially the Frisch- hypothesis (like Key, Mason, Allan, & Lask, 2001).

As was evident in the first premise discussed, a negative energy balance will normally lead to lowered weight. The issue now is whether it is possible for the fecundability to be lowered before a substantial weight loss has occurred, or while maintaining a low weight.

There is now increasing consensus that energy balance is the critical factor for a healthy menstrual cycle and adequate fecundability. Evidence supporting this can be drawn from observations of injuried athletes and ballet dancers with amenorrhoea who start to menstruate, before gaining weight. (Bronson, 1995). The injury prevented them from exercising, thereby retaining energy. It was not the training in it self that caused the amenorrhea, but more probably low energy availability that might have disrupted pulsation of luteinizing hormone (LH). This monthly pulsation is offset by gondothrophin releasing factors produced by the hypothalamus. It stimulates the pituitary gland to produce follicle stimulating hormone (FSH) and LH. FSH leads stimulate the ovaries to generate follicles, which is clusters of cells that allow fertile eggs to develop, while the LH contributes to the last part of the maturing and offsets the ovulation (ESHRE, 2006). An other example is that overweight women who had their stomach volume reduced, experienced amenorrhea while they were still greatly overweight (Loucks, 2003).

Linking reproductive functions to the nutritional status can be seen as a protective mechanism against malnutrition (ESHRE, 2006), as the process of gestation demands about 300 extra Kcal/day (Rösser, 2002). If the food availability is scarce, the body is not further jeopardised by the caloric demands of pregnancy. Stewart (1992) refers to several studies that support the importance of energy balance for optimal fecundability. For example, endocrinological changes have been observed in young women with normal body weight, who dieted for 6 weeks (800-100 kcal/day). In approximately 20 percent of these women, the menstrual cycles were disrupted for 3-6 months after the dieting ceased. Stewart (1992) also refers to studies showing that 50 percent of women with BN, and normal weight, have abnormal menstrual cycles. Further support can be drawn from findings of high levels of otherwise unexplained fecundability problems or menstrual dysfunction in women who restrict their caloric intake for weight control purposes. Almost three quarters conceived spontaneously after ending the restriction. Almost every one of these had previously been assessed by a variety of diagnostic gynaecological studies without any cause being discovered (Stewart, 1992).

The conclusion is that negative energy balance and low weight are associated with lowered fecundability. Still an important question remains, what constitutes low weight? And when is the energy balance is negative? These questions are important for research purposes, for example when conducting outcome studies for EDs. It is also important for clinical work either with reproduction or with EDs, in order to make decisions about start, type and cessation of treatment. It is also highly relevant for understanding and evaluating the premise under discussion, in regard to proposed hypothesis for SoBB in AN.

What constitutes low weight? And when is energy balance negative? The resumption of menses is a very inaccurate measure of reproductive functioning, especially when based on self-reports (Swenne, Belfrage, Thurfjell, & Engstrom, 2005). In regard to clinical work with AN, it is not unlikely that some individuals may report menstruation to avoid further weight gain. Small bleeds, that do not represent ovulatory cycles, may be incorrectly identified as menstruation (Key et al, 2001).

An alternative approach to assess of when the body is healthy, in terms of determining if a woman has an appropriate weight and receives enough energy, is through understanding how the endocrine system govern the reproductive system and how the uterus and ovaries react to a decrease in energy availability. Regarding the endocrine system, Loucks (2003) presents evidence that the LH pulse is disrupted when the energy availability falls beneath a certain level. This interrupts the menstrual cycle, as a brief surge of high levels of LH is

needed for the follicle to grow and ovulation to take place. Short luteal phases seam to indicate that more energy needs to be available. Loucks (2003) argues that there seems to be an energy threshold to preserve normal reproductive function. She argues further that energy intake below this, may increase the risk of chronic effects on ovarian function, perhaps because of low/interrupted LH levels. This might be connected to findings of morphological changes in the pelvic organs.

Pelvic ultrasound shows that the uterus and ovaries regress to prepubertal size and appearance if the weight is to low and the energy balance is negative. Mature pelvic organs indicate adequate body weight. Table 6 illustrates the wide range of individual differences, and how hard it is to identify a normative weight and energy intake. This illustrates that for some a BMI of 16 is adequate for fecundability, whilst for others a BMI of 21 is inadequate.

Table 6

Maturity of pelvic organs according to weight

BMI	15	16	17	18	19	20	21
Mature pelvic organs	0%	3%	6%	12%	29%	86%	96%

Adapted from Key et al 2002

In relation to the premise discussed in this section, the conclusion must be that low weight does lead to lowered fecundity, but that there are individual differences in what can be defined as "low weight". In addition, the endocrine system is affected by energy availability regardless of weight gain or weight loss. The challenge now is to ascertain the energy levels needed to maintain normal reproductive function, and identify the factors associated or predictive of individual differences in energy requirements. It is also important to understand the connection between energy availability, endocrine changes and connection to morphological changes of the pelvic organs.

C) Low Environmental Temperature Modifies Fecundability Through Increased Need to Divert Energy to Maintain Bodily Temperature

The question posed here is whether low temperature might affect fecundability by turning the energy balance negative in women who restrict their diet. This is a complex area. Approximately 10 percent of daily energy expenditure is used to maintain bodily temperature (Ravussin, 2002). This can be altered through the metabolic rate and its reaction to food intake, cold and heat exposure, stress, fear, and admission of drugs or hormones that increase

metabolic rate. Several factors contribute. For example, if the indoor temperature drops from 24 Degrees Celsius to 16 Degrees, a person wearing normal clothing will use about 2 percent more energy (Astrup, 1999). Homeostatic mechanisms, originating from centres in the hypothalamus, will perhaps motivate the woman to put on more clothes or turn up the heat in a room. A more dramatic situation arises if the woman falls into water of 15 degrees. The energy expenditure may increase 100-400 percent depending on the amount of subcutaneous tissue. The cold water will make her muscles shiver, and activate the sympathetic nervous system, which by noradrenalinic activation will increase the metabolism in several tissues and organs (Astrup, 1999).

It is possible that other factors may moderate the relationship between environmental temperature, energy balance and fecundability. Socio-cultural influences such as the desire of younger women to wear light clothing during colder periods of the year may contribute.

This premise raises several questions that are hard to answer. First, does low environmental temperature contribute to a negative energy balance in some women? And how is low environmental temperature defined in terms of degrees? How low does the temperature need to be for the reproductive system is affected?

Secondly, for how long of time does the energy to maintain bodily temperature need to be on the expense of the reproductive system before fecundability is down graded? And what are the individual differences that determine this? Is this related to the length of winter?

Third, when extra energy is needed to maintain bodily temperature, do the women at some point feel cold? Is there an association to subjective experience of cold or warm? Do they feel cold, but ignore it?

Fourth, will there have to be other features present for the ambient temperature and low energy availability to affect the reproductive functions? Features that override or make it possible to ignore the bodies attempt to maintain temperature and restore the energy balance? For example, personality traits such as obsessiveness or drive for thinness that is something else than dieters wish to lose weight, maintain a low weight or prevent gaining weight? Is there reduced body sensation awareness, or deficiencies in the thermoregulation that should have activated the hypothalamus in order to motivate the woman to put on more clothes? –Or made her seek a warmer place, or made her eat more?

In conclusion, it is possible that there is an association between low environmental temperature, low weight and fecundability. However, the association is complex, and raises questions that are difficult to answer at this point. A crucial factor seems to involve the

individual differences, thereby also complicating the research that needs to be conducted in an attempt to answer the questions posed.

D) Unhealthy Eating Patterns are Intergenerationally Transmitted

This premise is well supported in the literature. Relatives of patients with AN and BN have a higher probability of suffering from EDs themselves. The rate of ED-NOS is about 7-12 times in close relatives (Lilenfeld et al., 1998), with sisters and mothers being most represented (Stein et al., 1999). This is further supported by the increasing consensus that ED psychopathology constitutes a continuum, where AN represents the furthest extreme (Walter & Kendler, 1995). Although the extent and nature of genetic and environmental contributions to the intergenerational transmission of ED remain unclear (Fariburn, Cowen, & Harrison, 1999).

Some mother-daughter behaviours are associated with an increased risk of familial ED. For example, mothers of schoolgirls scoring high on distorted eating were more critical towards their daughter in terms of her attractiveness than the daughters were towards themselves (Pike & Rodin, 1991). In addition, these mothers thought their daughters should lose weight, in contrast to the attitudes held by mothers of schoolgirls without the distorted eating. Interestingly, even though the majority of the mothers had dieted, the mothers of the distorted eating group had begun dieting at an earlier age (Pike & Rodin, 1991). Benedikt, Werheim, and Love (1998) supported this observation having found that maternal encouragement was significantly associated with the daughters dieting behaviour. In addition, they found that modelling was an important factor for extreme weight control behaviours, such as fasting, crash dieting and skipping meals, but not for moderate weight control behaviours like dietary restrain, exercise and body dissatisfaction.

Childhood and infant feeding problems are associated with the development of AN (Nicolls, 2007). Mothers of children with feeding problems are more likely to have had both current and past ED (Whelan & Cooper, 2000). Mothers with ED also behave differently towards the child during mealtime compared to play time, with more negative comments during mealtimes (Cooper, Whelan, Woolgar, Morrell, & Murray, 2004). Also mothers of the infants with feeding disorders showed less dyadic reciprocity, less maternal contingency, more dyadic conflict and struggle for control. The latter have been related to lowered ability to self-regulate energy intake (Park, Senior & Stein, 2003).

Additional support for this hypothesis, and this premise, is given by Crisp (2006). He highlighted the relationship between excessive maternal concerns about weight and shape,

and abnormal weight control behaviour, in regard to the SoBB for patients with AN. From 16 background variables, the abnormal weight control behaviour was the only factor significantly related to SoBB, indicating a role for maternal behaviour in the SoBB for patients with AN.

In summary, there is still controversy about why there is a familial aggregation of EDs, including what the transmitting behaviours may be, but there is a consensus that some form of intergenerational transmission occurs.

Evaluation of the hypothesis

This section evaluates the hypothesis according to the five criteria stated on p. 32.

Necessary: The hypothesis does propose mechanisms that are necessary in order to explain the observed SoBB. These mechanisms are necessary, even though they do not specify all the other factors that contribute to the development of AN. This criterion is fulfilled.

Sufficient: This hypothesis includes all the variables needed to explain the SoBB in AN. Even though alternative hypothesis also could account for the SoBB, this hypothesis proposes a sufficient explanation on its own.

Specific: This hypothesis fulfils this criterion, as it predicts that the child born from the thin, food restricting mothers, will be vulnerable for AN.

Empirically derived: Despite the lack of empirical knowledge regarding premise C), the other premises are supported by empirical evidence. The criterion can therefore be considered as fulfilled.

Refutable: Some implications of the model have already been tested, and the findings did not falsify the hypothesis. The model predicts that there should be an excess of births during spring months in both hemispheres, but no variation in the SoBB on the equator. The reviewed papers support this. Although just one paper has investigated the SoBB in Australia, the results showed that fewer patients with restrictive AN were conceived in the colder months (Willoughby et al., 2002). The same situation appears for the equator; just one study has investigated the SoBB (Willoughby et al., 2005), but the lack of SoBB supports this hypothesis

In sum, this hypothesis has good explanatory power. It explains why the SoBB for AN is the way it is.

Summary and Proposals for Future Research

The environmental temperature of conception hypothesis explains the observed SoBB in AN by stating that these patients are the daughters of mothers whose fecundability fluctuate seasonally. Conceiving would be easier in the warmer months of the year, because they then do not need to divert extra energy to maintain bodily temperature. The vulnerability for AN in their daughters is increased by environmental and genetic factors.

For most healthy women, a restrictive diet will contribute to weight loss, prevent weight gain or maintain a low weight. It might have been an evolutionary advantage to avoid conceiving when food availability was scarce. Restrictiveness seams to interfere with the endocrine regulation of fecundability, and over time, the lowered weight lead to morphological changes in the pelvic organs. Even though the specific mechanisms are not identified, there is a consensus that some form of intergenerational transmission occurs.

Further research could focus on assessing the prevalence of subclinical ED, or describe the dimension of ED. The field would also benefit from a clarification of the terms used to describe people who diet and people who are restrictive. What are the differences? If both groups restrict their intake because of weight and shape reasons, are there nuances here that are important? Is the restrictiveness ego-syntonic? Will this matter? Future research could be done in collaboration with fertility clinics. By assessing eating patterns, exercise habits, endocrine status and body temperature, more information could be generated. A focus on what factors contribute to the individual differences is also needed. One direction could be assessing the length of the luteal phase.

SUNLIGHT EXPOSURE AND SEASON OF BIRTH BIAS

A common ending phrase in the literature on SoB is statements about the need of further research to "disentangle the confounded influences of socio-cultural, geophysical and genetic factors" (for example Nilesen, 1992 p. 33; Rezaul et al., 1996 p. 60). The higher prevalence of affective disorders in families of ED patients and the possible connection through 5-HT, is noted by two of the 11 reviewed papers (Rezaul et al., 1996; Crisp, 2006). However, they interpret this association in different ways. Rezaul et al., (1996) suggest that the SoBB in AN may be accounted for by patients with AN and comorbid AD, whilst Crisp (2006), in an subordinate clause, mentions the possibility that the mother's fecundability may fluctuate through the seasons due to changes in her mood. These ideas have not been further explored.

Acknowledging that there are many ways in which the sunlight might exert its influence on SoBB, one of the aims of this dissertation is to develop this further. This will be done by proposing three hypotheses about how the sunlight might be involved in the SoBB in AN. These will be referred to as the sun hypotheses.

In brief, the sun hypotheses propose that increased levels of sunlight contribute to the SoBB in AN either directly by causing abnormal neurodevelopment in the developing foetus, through the sunlight's direct effect on the mother by affecting her mood or indirectly through affecting the interaction between the mother and child. Three hypotheses will be explored separately.

Sun hypothesis nr 1: Neurodevelopment and Sunlight Exposure

Description of the Hypothesis

This hypothesis states that high levels of sunlight exposure during the first trimester of gestation may interfere with normal neurological development for some foetuses. This can lead to a vulnerability for AN in some females born in the spring. AN may develop when these neurodevelopmental deficiencies interact with familial and socio-cultural influences. The premises this hypothesis is build on are:

A) Neurodevelopmental disturbances predispose some individuals to AN

B) Sunlight exposure cause stress that interferes with embryonic development

Discussion of the Premises

A) Neurodevelopmental Disturbances Predispose some Individuals to AN

This premise is supported by empirical evidence from cognitive assessments and neurological imagining studies. There are consistent reports of cognitive impairment in AN which appear to be primary rather than secondary to malnutrition (Frampton & Hutchinson, 2007) These include cognitive rigidity, weak central coherence and impaired visuo-spatial memory. These findings appear to be associated with abnormalities on brain imaging (Lask, 2005). In general, brain imaging findings indicate a fronto-striatal circuitry abnormality in up to 70 percent of young people with AN. The current hypothesis about sunlight influence on the SoBB in AN proposes that sunlight exposure contributes to this neurodevelopmental abnormality. As yet, information is not available on SoB differences between those with and without such abnormalities.

B) Sunlight Exposure Causes Stress that Interferes with Embryonic Development

This hypothesis claims that sunlight exposure may affect neurodevelopment. This could happen through increased levels of sunlight exposure during the first trimester of gestation, causing either oxidative stress or DNA damage separately or in combination.

The rationale for this premise is supported by findings from other parts of SoBB research. As briefly mentioned on p.16, neural tube defects and neurodevelopment have been linked to season of conception (Marzullo & Fraser, 2004). The hypothesised explanations was maternal oxidant stress caused by increased levels sunlight exposure, as both neural tube closure and the development of lateral asymmetry share some common pathways that can be disrupted by oxidant stress. The specific response to this stress is influenced by the embryo's own genetic makeup (Marzullo & Fraser, 2004). This could be relevant for AN as oxidative stress might interfere with the part of the ectoderm that eventually results in the limbic system, for example by causing cell death in some circuits in the medial temporal cortex.

Alternatively, one could speculate if there is asymmetrical activity favouring the frontal lobe, as this part is involved with some of the features found to persist in recovered patients (Tchanturia et al., 2004; Treasure, Tchanturia, & Schmidt, 2005). Unfortunately, these studies might be criticised for the lack of clarity about the definition of "recovered", and small sample size, indication that interpretations must be done with reservations, until replications confirm the findings.

In addition, it is not unlikely that some women are more vulnerable to develop higher levels of oxidant stress than others. Given the potential higher incidence of subclinical maternal ED, in mothers of patients with AN, the potential stress of becoming pregnant (James, 2001) may increase cortisone levels and thereby decrease the chance of counteracting the oxidant stress (Knardahl, 2002). This links the oxidative stress to reduced immune system; which is influenced directly by UV radiation (Schmitt & Ullrich, 2000).As this gets more complicated, and outside the scope of this dissertation, it is interesting to note that psychological disorders have been associated with altered T-cell function (Schwarz, Chian, Müller, & Ackenheil, 2001). The close interconnections between the psyche, the neurotransmitters, the endocrine system, and the immune system will probably illuminate this further in the future (Schwarz et al., 2001).

The second pathway to this premise is that ultraviolet radiation (UVR) from the sun cause mutations in the DNA of the developing foetus. This pathway is based on a study by Davis and Lowell (2006). They found that the births of patients who later develop psychological disorders are associated to eleven-year cyclic variation of solar activity. This activity is caused by magnetic storms on the Sun´s surface, visible as sunspots. In periods of high activity, peak years, the UVR in the earths upper atmosphere increase up to a three-fold, but just 1-2 percent on ground level. Even though, this increase of UVR on ground level is a significant stress to organism's DNA-repair mechanisms (Ries et al., 2000). This could support the premise now under discussion; that sunlight might cause stress that interferes with embryonic development. Increased sunlight, particularly in peak years of the sun cycle, may interfere with the normal neurodevelopment in some foetus. The vulnerability for AN will depend upon genetic factors, in addition to environmental stresses after birth, during childhood, and adolescence.

One argument against this pathway is that damage early in the embryonic development would have profound effects (Bukatko & Daehler, 1998). A AN vulnerability might not be classified as such. Even though the claim, put forward by Davis and Lowell (2006), is that the ectodermic tissues (the tissue in the neural tube forms the central nervous system) are "susceptible to mutation by UVR and may not have fully developed epigenetic modulation of these genetic alterations" (p. 455). This links to the complex interaction between the environment and the genes in the embryonic development, which is still very much of a puzzle. However, even though the mutations at this early stage of development might cause profound abnormalities, the effect of the mutation depends upon where the damage is situated and how the embryo might counteract it integrates it in the further development (Davis &

Lowell, 2006). New insights and understanding of this early development is still emerging leaving the possibilities open for this hypothesis. What is certain is that these issues are very complicated, and exploring it in greater detail is beyond the aims of this dissertation. The point of including this any how, is that it help highlight the need for more research on the association between sunlight exposure and neurodevelopment, and the possible role that could have in explaining the observed SoBB in AN.

Other explanations for the neurodevelopmental abnormalities are competing with the hypothesis of sunlight exposure influence. For example, genetic influences or pre-or perinatal environmental brain insults have been suggested (Tchanturia et al., 2004). Emerging evidence show that perinatal complications like premature birth (before week 32), cephalhematoma (bleeding in the skull because of insults) and breech delivery may be implicated in the aetiology of AN, probably by causing neurodevelopmental abnormalities (Bakan, Birmingham, & Goldner, 1990; Cnattingius Hultman, Dahl, & Sparen, 1999). However, they may only account for a small subset of the cases (Lindberg & Hjern, 2003). As other psychological disorders also have been related to pre- and perinatal complications, there is a question of specificity (Verdoux & Sutter, 2002) as well as a question the implication of increased of numbers of complication, the severity or type of complications (Feingold, Sheir-Neiss, Melnychuk, Brachrach, and Paul, 2002)

A recent study by Favaro, Tenconi, and Santonastaso (2006), using a different methodology from previous studies, showed that specific obstetric complications, such as maternal anaemia, diabetes mellitus, and preemclampsia, are more related to AN than to BN and to controls. They also found that the higher the level of complications the greater the risk for AN. In addition, unpublished data indicates that there is a SoBB for perinatal complications, with an excess of spring births (personal communication with Dr. Favaro, 21st of March, 2007).

This pathway to the premise that sunlight exposure affects neurodevelopment suggests that increased amount of sunlight in the first trimester can cause oxidative stress or cause mutations that interfere with normal neurodevelopment. The alternative hypothesis, that perinatal complications may be involved is a strong contestant, as disconnections in the brain's circuits may result from perinatal insults (Bear, Connors, Paradiso, 2001). Or perhaps the sunlight exposure causes oxidative stress or mutations in the period straight after birth?

Evaluation of hypothesis

Necessary: Neurodevelopmental abnormalities may arise as a result of various teratogenic influences. The possible vulnerability for inducing AN is determined by the site of damage and of individual differences in genetic makeup. Therefore increased levels of sunlight exposure during the first trimester are not necessary for the abnormal neurodevelopment to occur, and consequently may not be necessary for the SoBB in AN to occur. This criterion is not fulfilled.

Sufficient: If it is correct that there is a specific damage that causes the abnormal development then this hypothesis would fulfil this criterion.

Specific: This hypothesis is specific because, it presupposes that there must be a specific insult that cause a specific abnormality in the neurodevelopment, and that this increases the vulnerability for AN. However, it is possible that damage at other locations, and combined with other genes, will lead to different psychopathology. Depending on the stage of gestation, the genes and amount sunlight exposure, different psychopathology might arise. The observed SoBB with excess in the late winter/early spring for other disorders supports this, and adds support for this hypothesis.

Empirically derived: There is increasing evidence that some features associated with AN, do not disappear with weight recovery. Based on this, it is possible that these features are caused by abnormal neurodevelopment. The mechanisms behind this are not known. This hypothesis proposes that detrimental effects from oxidative stress or mutations from UVR exposure could cause them. These claims are built on empirical evidence, and the hypothesis fulfils this criterion.

Refutable: This hypothesis fulfils this criterion as an absence or negative relationship between the abnormal findings that persist after weight gain and UVR exposure at the early stage of gestation would disprove it.

In summary, the hypothesis that increased levels of sunlight exposure during the first trimester has good explanatory power. It might also explain why not all the patients with AN are born in the spring, and why the majority of them have changes in that persist after weight gain. The question that remains is weather the hypothesis is necessary to explain the SoBB.

Discussion and Proposals for Future Research

This hypothesis state that increased sunlight exposure during the first trimester might cause neurological damage that increases the vulnerability for AN.

The consistent reports of impairments from cognitive assessments and neurological imaging studies that appear to be primary rather than secondary to malnutrition, supports the premise of a neurodevelopmental abnormality associated with AN. This neurodevelopmental abnormality may be caused by oxidative stress or mutations from increased levels of sunlight exposure.

Many questions still need to be explored. Is the SoBB in AN related to increases in the intensity of different kinds of sunlight; UVA, UVB, or daylight. Would vacation habits be involved?

Sun Hypothesis nr 2:

Maternal Affective Disorder and Sunlight Exposure

Description of Sun Hypothesis nr 2

This hypothesis suggests that affective disorders or subclinical affective disorders in the mother might lead to the observed SoBB for AN patients (Crisp, 2006).

The hypothesis goes like this: Affective disorders, like major depression, bipolar depression or seasonal affective disorder (SAD) is less severe in the summer because of greater levels of sunlight exposure. This increases the chance that the mother will be more sexually active, leading to a higher possibility of conception in the summer, and a spring birth. This hypothesis rests on three premises:

A) There is a high degree of affective disorders in the close relatives of patients with AN

B) Symptoms of affective disorders diminish as a result for more sunshine exposure during the summer

C) Less severe symptoms of affective disorders increase the chance of sex and more severe symptoms reduce the likelihood of sex

Discussion of the Premises

A) There is a High Degree of Affective Disorders in Close Relatives of Patients with AN

This premise is supported by several studies showing a high degree of familial aggregation of affective disorders and ED (like Mangweth, et al, 2003; Lilenfeld et al, 1998; McElroy et al, 2005; Grigoroiu-Serbanescu, Magureanu, Milea, Dobrescu, & Marinescu, 2003). A history of major depression has been reported in 10 percent of mothers of patients AN (Nilsson, Gillberg, & Råstam, 1998). It is further established that affective disorders is

commonly comorbid in patients with ED (Blouin et al, 1992), and vice versa (Gruber & Dilsaver, 1996). Different symptoms of affective disorders have been connected to the two ED subgroups (Kennedy et al, 1994). Some studies suggest that BN is more closely related to affective disorders, than AN, because of a higher level of comorbidity between the two (Ghadirian, Marini, Jabalpurwala, & Steiger, 1999), a seasonal worsening of eating-related symptoms in both disorders (carbohydrate craving for SAD and bingeing for BN) (Kräuchi, Wirz-Justice, & Graw, 1993; Blouin et al, 1992), changes in serotonin levels in response to medication, and relieved signs of mood and binge-purge symptoms from light therapy (Lam, Lee, Tam, Grewal, & Yatham, 2001).

AN, BN and affective disorders are probably close interlinked, as shown by a meta-analysis that found more studies showing a higher frequency of BN in the relatives of AN patients, than compared to comparison groups (Strober, Freeman, Lampert, Diamond, & Kaye, 2000). This could suggest that the higher degree of affective disorders in families of AN, could be additionally enhanced by the close relationship between AN and BN.

The most obvious challenge for this premise, is the question of why the child, conceived in the summer because the mother is suffering less from affective disorders, goes on to develop AN and not affective disorders. Perhaps, instead of explaining SoBB in AN, this premise is better at explaining the overlap in SoBB for affective disorders with excess in winter/ early spring and AN with SoBB excess in spring?

B) Symptoms of Affective Disorders Diminish as a Result of More Sunshine Exposure

Again, a question of definition is relevant in order to discuss the premise. What are affective disorders, and will that matter to the relationship between SoBB in AN and sunlight exposure? Do all symptoms of affective disorders diminish as a result of greater level of sunshine exposure, or is there subtypes of affective disorders that improves after sunshine exposure.

According to DSM-IV, but not ICD-10, recurrent depressive episodes with a seasonal pattern are identified as seasonal affective disorder (SAD) (APA, 1994). In many respects it is similar to other depressive episodes, like low mood, loss of interest, anhedonia, anergia, poor motivation, low libido, anxiety, irritability and social withdrawal (Eagles et al., 2004). However, characteristic for SAD patients is the increased need for sleep, and an increase in weight and appetite, especially for carbohydrate rich food and chocolate. Episodes of SAD usually start in the autumn or winter, and spontaneously remit in the spring (Gruber &

Dilsaver, 1996). In the North of Norway, one-third of the women and one-fifth of the men experience problems with sleep, mood or energy related to season (Hansen, Lund, & Smith-Sivertsen, 1998). Also eating pattern, especially for younger people, varies through the seasons (Perry, Silvera, Rosenvinge, Neilands, & Holte, 2001). Reduction in sunlight exposure is the likely cause. This is supported by the spontaneous recovery in spring and studies showing an association between melatonin, circadian rhythm and depression (for example Wirz-Justice, 2006). Specifically, recovery is associated with shorter wavelength, as this blue light, outperform light of longer wavelengths, in terms of reducing depressive symptoms (Glickman, Byrne, Pineda, Haucks, & Brainard, 2005).

There might be a biological vulnerability, perhaps caused by a mutation that previously had beneficial qualities in terms of survival (Levitan et al, 2004). This might explain the lack of simple relationship between SAD and latitude of living (Hansen et al., 1998). Differing from people who do not experience SAD, for SAD patients, the reduction in light might generate a signal of seasonal change that resembles that of other mammals (Wehr et al., 2001). This signal might involve melatonin or serotonergic functioning (Davis & Levitan, 2005; Johnson & Everitt, 2000). The deficiencies in serotonergic functioning can be linked to the carbohydrate craving, indicating that the sweets might function as "self-medication" (Sher, 2001). Intake of sweets in the second half of the day is a primary predictor of the therapeutic response to light (Kräuchi et al., 1993). Relevant to the hypothesis under discussion, is that women are more at risk for mood disorders, than men, and SAD is most common in women of child-bearing age (Eagles, 2003).

There is still controversy regarding the validity of a separate diagnostic entity for recurrent depression showing seasonal variations (Hansen et al., 1998). It is possible that the types of depression showing increased need for sleep and weight gain is a milder form of depression. Alternatively, that it is an initial stage of depression (personal conversation, Professor Kenneth Nunn, 15th March 2007).

C) Less Severe Symptoms of Affective Disorders Increase the Chance of Sex and More Severe Symptoms Reduce the Likelihood of Sex

One of the biggest challenges in research is drawing conclusions, especially about causality, based on observations. This is also the case regarding depression and sexual intimacy as although depression have been linked to relationship problems, the cause-effect direction is unclear (Evans & Wertheim, 1998). In addition, there is limited amount of research on this topic.

What has been shown is that sexual dysfunction and depression often co-occur (Dobkin, Leiblum, Rosen, Menza, & Marin, 2006). However, a close, intimate relationship is protective against depression, and predict faster response for treatment (Waring & Patton, 1984). A close association probably exists between how a woman perceives her relationship and how satisfied she is with her relationship, and depressive symptoms and depressed mood (Murtagh, 1998). Luckily, there is no relationship between a romanticized view of love and depression (Carr, 2002).

Cyranowski, Frank, Cherry, Houck, and Kupfer, (2004) found, while controlling for other variables, that depressive symptoms were associated with decrements in sexual desire, sexual cognition/fantasy, sexual arousal, orgasmic function and global evaluation of sexual function. Because the reduction in sexual function outlasted recovery from the depressive episode, the authors interpreted their findings to indicate a trait-like physiological phenomenon.

In sum, this means that there is a negative correlation between severity of symptoms of depression and sexual activity. The hard question is whether this is because of the depressive episode or because of other factors. There is a possibility that women prone to depression might have more problems in relationships, and experience less pleasure from, and interest, in sex. If this is true, this premise is not valid, but for now, the question remains open.

Evaluation of the Hypothesis

Necessary: This hypothesis is close to fulfilling this premise. The observed SoBB in AN could be caused by diminishing symptoms of affective disorders increasing the likelihood of sexual activity for the mother. But as it may not fulfil some of the other criteria, it is not that convincing, and therefore does not pass this criterion.

Sufficient: This hypothesis embraces several unspecified mechanisms, for example the vagueness of the relationship between AN and affective disorders, thereby complicating the evaluation of sufficiency. Therefore it does not fulfil this criterion.

Specific: The greatest weakness with this hypothesis is the lack of specificity. Even thought the close relationship between affective disorders and AN is plausible, the hypothesis does not give a sufficient account for why the child should be vulnerable for AN. For example, why do not the BN group show a similar SoBB?. This criterion is not fulfilled.

Empirically derived: The first premise, which suggests a close association between affective disorders and ED, is empirically based. Preferably, more about the specific

mechanisms and relationship between affective disorders and ED knowledge should be added. There are disagreements about how to subdivide affective disorders, but there is evidence that some people suffering from depression characterised by increased need for carbohydrates and sleep, do better in the spring and the summer. In addition, more research is needed to establish the extent to which the depressive symptoms decrease these women's level of intimacy. Even though more information and replications of studies are needed, this criterion is fulfilled.

Refutable: This hypothesis predicts that significantly more of the mothers of the patients with AN born in the spring should have had a history of affective disorders around year of the conception of the child, compared to the patients with AN not born in the spring. If this is not the case, the hypothesis is refuted. This means that the hypothesis could be refuted given future research, and the hypothesis fulfils the fifth criterion.

This hypothesis has low explanatory power. It do explain why the SoBB for AN must be the way it is, but it does not specify why some of the children born in the spring should develop AN and not BN. The necessity and sufficiency of this hypothesis is also unclear.

Summary and Proposals for Future Research

This hypothesis states that symptoms of affective disorders diminish in the spring and summer, making it more probable that women suffering from affective disorders have sex. Due to the close relationship between affective disorders and ED, and in addition to yet unknown influences, there is a SoBB in AN.

Both AN and BN show high levels of comorbidity, and there is a high level of affective disorders in the families of AN. Symptoms of some forms of affective disorders diminish as a result of greater levels of sunshine exposure during the summer. As the symptoms of affective disorders diminishes, the chance of sex increases.

Questions that need further exploration to increase the understanding of this hypothesis are: what makes the children of a women with affective disorders prone to AN? Is there a SoBB for children of mothers with affective disorders? And are affective disorders more common in mothers of patients with AN born in the spring?

Morgan and Lacey (2000) showed that the there was a group of BN who previously had AN, this group had a SoBB with peak in the spring. Could the affective disorders mothers be more representative for this group? The reviewed papers also showed that the SoBB was most evident in the younger group, the early-onset AN and the restrictive AN group. Is it possible that some of these later develop BN symptoms?

Sun hypothesis nr 3: Big Baby and Sunlight Exposure

Description of the Hypothesis

This hypothesis states that more sunlight exposure in the first trimester increases the birth weight of the baby. For some mothers, this may trigger certain behaviours influencing the mother-child interaction, in such a way that the child will be more vulnerable to develop AN. This hypothesis is based on three premises:

A) More exposure to sunlight during the first trimester will lead to babies with higher birth weight
B) The baby's size will affect the mother-child interaction
C) Some forms of early interaction styles contribute to AN vulnerability

The last premises will not be discussed, as it is included in the discussion of the last premise for the Environmental temperature of conception hypothesis, page 39.

Discussion of the Premises

A) More Exposure to Sunlight During the First Trimester will Lead to Babies with Higher Birth Weight

This premise is based on a study by Tustin, Gross and Hayne (2004). They found that sunlight exposure has different effects on birth weight depending upon the trimester of gestation. Babies whose first trimester was during sunnier months were heavier at birth than babies who spent their second or third trimester in the sunnier months.

One implication of this is that there might be a SoBB for the weight of babies. Most, but not all, papers published show that the highest frequencies of high birth weight do occur in the winter/spring (McGrath, Barnett, & Eyles, 2005). However, these studies are also flawed by lack of definitions, and suffer from the same methodological issues as discussed in this dissertation.

Assuming that there is a spring SoBB for high birth weight, can it be explained by sunlight exposure? Birth weight is dependent upon duration of gestation and foetal growth (Smith, Stenhouse, Crossley, Cameron, & Conner, 2002). Average gestational age does not differ as a function of ambient temperature during the gestation, nor as a function of variations in sunlight exposure. In contrast, foetal growth is influenced by sunlight exposure (Tustin et al., 2004) through its effect on several systems in the human body that in turn can affect foetal growth. For example, the level of insulin growth factor – 1 (IGF-1) is positively associated with high levels of sunlight exposure in animals (Webster, Corson, Littlejohn,

Stuart, & Suttie, 1998). IGF-1 affects foetal growth by favouring the foetus over the placenta when distributing nutrition (Tustin et al., 2004). That means that high level of sunshine will lead to higher level of IGF-1 and the developing foetus will therefore receive more nutrition.

The conclusion for this premise is that information is needed from studies that deal effectively with methodological issues, specifically the definitions of seasons and sunlight levels.

An advantage with this premise is that it proposes a specific mechanism for why the baby born in the spring should be bigger.

B) The Baby's Size will Affect the Mother-Child Interaction

Appearance makes a difference and influence interaction with other people. For example, leaders are often older, taller and heavier than the average group member (Forsyth, 1998). This may due to a heuristic mode of thought were height is associated with power. The same mechanisms may come in play when different traits and characteristics is associated to a baby's gender. Depending on external clues, like colour on the baby's clothes, the expectation of a little girl or boy evokes different behaviours in adults, including how they describe and talk to the baby (Butatko & Daehler, 1998). It is therefore not unlikely that some women will respond in a certain way to a big baby and that this will evoke a different interaction pattern than a small baby could.

To avoid ethical propitiations to investigate this, new mothers could be asked to interact with children of varying sizes. For example, the design could randomly assign women to either interact with the small or the bigger children first. Observed differences between the interactions with smaller versus bigger babies could be due to the size. The women could also be assessed for eating disorder psychopathology, as a relationship between that and interaction toward bigger babies could shed light on the intergenerational transmission of eating disorders.

Evaluation of the Hypothesis

Necessary: If the babies born in the spring are heavier, this could trigger some mothers to behave in ways that are thought to increase the vulnerability for AN in the child. But as this behaviour might be triggered by other factors as well, this premise is not fulfilled.

Sufficient: This hypothesis could, if all the premises are valid, sufficiently account for the SoBB.

Specific: This hypothesis fulfils this criterion as the big babies will trigger behaviour that is associated to later development of AN.

Empirically derived: There are reports of higher birth weight in the spring, but they are inconsistent. It is known that appearance and traits in people evoke specific responses in other people, therefore not unlikely that some women will respond in certain ways to a big baby. However, this is still speculative and needs to be investigated in more detail. Therefore this is not criterion fulfilled.

Refutable: This criterion is fulfilled. If there is not a higher proportion of patients with AN born in the spring with a higher birth weight, compared to patients born in the rest of the year, this hypothesis would be refuted. There should also be a positive correlation between the sunlight at conception and a high birth weight for the patients with AN born in the spring.

In summary, this hypothesis have intermediate explanatory power, as it is highly specific and explains why the SoBB is the way it is, but probably not necessary. It also need more empirical support.

Summary and Proposals for Future Research

The bigger baby hypothesis states that a big baby might alter the interaction style between some mothers and babies, in a negative direction. The baby is big because it spent its first trimester in the sunnier months of the year.

The premises discussed indicate a possibility that there is a spring birth bias for bigger babies and that a big baby will trigger certain behaviours in some women. However, these premises that this hypothesis is based on need to be investigated further.

Future research needs to investigate why the SoBB for birth weight differ and if the differences follow any pattern. Measuring IGF-1 levels through the pregnancy, and correlating that with birth weight and sunlight would further contribute to the evaluation of this hypothesis.

SUMMARY

The aetiology of most diseases, especially psychological disorders, is poorly understood. This almost certainly contributes to their poor prognosis. This is also true for ED. Hippocrates advised that the effect of the seasons should be investigated. It seams appropriate to do so for AN given the SoBB.

Two hypotheses aiming to explain the observed SoBB in AN have been presented and discussed in-depth, in this dissertation. The first hypothesis is a well-formulated model which has undergone some empirical exploration. It proposes that the SoBB in AN is a consequence of the effect that fluctuating ambient temperature has on the fecundability in thin, food-restricting women. This is a strong hypothesis, with good explanatory power. The second hypothesis proposes that variations in sunlight, which are correlated with environmental temperature, could contribute to the SoBB in AN. This hypothesis has received very little empirical evaluation. In an attempt to shed some light, this dissertation has developed three subsidiary hypothesis that proposes different mechanisms for how sunlight exposure might be involved in the observed SoBB in AN.

The first of subsidiary hypothesis highlights the potential damage to foetal neurodevelopment as a result of increased levels of sunlight early in the gestation. This is also a strong (subsidiary) hypothesis, with good explanatory power. Its greatest challenge is the question of necessity, as abnormal neurodevelopment might be caused by other factors, such as obstetric complications. The second subsidiary hypothesis suggests that sunlight might relieve the symptoms of maternal affective disorders, thereby increasing the chance of sexual activity and conception during sunnier months. This subsidiary hypothesis has the lowest explanatory power, as it lacks specificity, and is probably not necessary nor sufficient. The last subsidiary hypothesis proposes that increased sunlight exposure might lead to higher birth weight, with subsequent maternal concerns about feeding too much to her daughter. This has intermediate explanatory power; its greatest weakness is lack of empirical support. Each of the three mechanisms in which the sun can cause the SoBB has some logical and empirical support, but there is much more work to be done.

Detailed consideration needs to be given to methodological issues; such as definitions of seasons, sampling and sample size. In addition, there need to be better control for variables such as comorbidity and statistical methods.

Conclusions- Facts and Fictions

At this point it is not possible to conclude if the SoBB is a fact or a fiction. What is a fact is that more research is needed and is going to be done. That this research is as easy and straightforward as it may first seem, is a fiction. A fact is that the greatest obstacle is the rarity of AN. A fiction is that the answer will be simple.

APPENDIX

Table 7

Note: In this table, information about the samples, comparison groups and findings are presented from each of the 11 papers that are reviewed. The information is stated using almost the same phrases as in the original papers. In addition, some comments about methodological issues for each study are included in the column to the right. To simplify the table, a couple of additional abbreviation is included.
R-AN= Restrictive Anorexia Nervosa
BP-AN= Binge-purge Anorexia Nervosa
EO-AN= Early-Onset Anorexia Nervosa

Detailed Review of the 11 Papers on Season of Birth Bias in Eating Disorders

Authors:	**Sample:**	**Comparison group**	**Findings; presented according to the statistical analysis used:**	**Methodological issues:**	
				Strengths	**Weaknesses**
• Nielsen, • 1992, • Denmark	1 Selected sample from Rigshospitalet 1960-1976; • 140 f; • 54 under & 86 over 15 years 2 Nationwide sample from Danish National Psychiatric Demography, Patients treated for AN in the years 1973-1987; • 593 f; • 105 under & 144 over 15 years	National population data Danish statistical Year books, for nr of live born birth pr month for 1935-1988.	<u>Jones´ method (1988)</u> • No SoBB in age group under 15 years in unselected nationwide sample. • SoBB *trend* for f 15 years or over born, in 1959-1964, amplitude 25% , peak in April • *Significant S*oBB for f over 15 years, born 1963-1968, amplitude 40%, peak in April • One harmonic without a trend. • Normal population of Danish women have two harmonics with trend, peak in April 9% and August, and a minimum/trough in November of 7%.	• First to analyse SoBB in AN sample • Used only females as index and controls • Separate analysis for onset over and under 15 years • Good description of data processing and analysis used	• Does not discuss sample size or power calculations. • No p values given for non-significant findings • Diagnostic manual not stated • Info on comorbid diagnosis was available, but not mentioned later in paper. • Not clear what analysis gave which results. • Duplication of subject count not addressed • Does not define “season” • No rationale for making the groups “over and under 15 years” • Two years are overlapping in the groups 1959-1964 and 1963-1968

Authors:	Sample:	Comparison group	Findings; presented according to the statistical analysis used:	Methodological issues:	
				Strengths	**Weaknesses**
• Rezaul et al., • 1996 • UK	Unselected nationwide sample of 1937 f referred from 1979 to Maudsley Hospital ED Unit; • Younger patients (born after 1963): 882 • Older patients (born in or before 1963): 1057	National population data from Kingdom Office of Population Censuses and Surveys.	Edwards´ test (1961) • SoBB significant different from general population for unselected nationwide sample; peak in May ($X^2= 14.65$, $p<0.05$) • Not significant different SoBB from general population for f born before 1963, but peak in June ($X^2=4.38$, $p=0.92$) • SoBB significant different from general population, for younger patients, born after 1963, peak in March ($X^2=14.87$, $p<0,05$)	• Relatively big sample for Edwards´ test, and for quarterly chi-squared analysis. Not for months. • Offers several hypotheses that can guide future research • The comorbidity of ED to schizophrenia and AD is very central to discussion.	• Not mentioned if comparison group include all births or just live births • Does not provide information about onset (e.g. early or late) for the older patients. Not valid to conclude that older patients not could have early- onset • Diagnostic manual not stated. • Duplication of subject count not addressed • No definition of “seasons” nor “winter birth effect”
• Morgan & Lacey, • 2000 • UK	St.George´s Hospital ED unit; 934 referred subjects • Older patients (born in or before 1963) 389, • Younger patients (born in 1964 or after) 546 • 227 BN arising from AN	National population data from Kingdom Office of Population Censuses and Surveys. And comparisons of subgroups.	Edwards´ test (1961) • Not SoBB in whole sample ($X^2=2.333$,$p>0.03$) • BN arising from AN significant SoBB; peak in March ($X^2= 7.85$, $p<0.05$) • SoBB for older patients with BN; peak in July ($X^2=42.44$,$p <0.01$). • No significant different younger patients with BN ($X^2=1.57$, $p>0.50$)	• First study to investigate BN • States diagnostic manual: DSM-IV	• Although consistent with methods of previous 2 papers regarding year split, no rationale for why they use this year split. • Does not specify sex of subjects • Does not define “season” • The authors seem to define the findings of peak in July for older patients as anomalous, without explaining why. • Duplication of subject count is not addressed. • Comorbidity not mentioned

Authors:	Sample:	Comparison group	Findings; presented according to the statistical analysis used:	Methodological issues:	
				Strengths	**Weaknesses**
• Eagls et al., • 2001 • Northeast Scotland	446 f from case records for patients presenting at secondary services in years 1965-1991 • AN 287 • AN strict criteria 159	5.766 f control births from Aberdeen maternity and neonatal databank for years 1951,1961,1971,1981	<u>Edwards´ test (1961)</u> • No seasonality detected for AN or controls <u>Nonparametric method of Hewitt</u> • When comparing first 6 months to second 6 month, significant excess in first 6 months for AN compared to controls. 54,7% vs 48,9% • Excess of births in first 6 months of year (p=0.013), (X^2=5.67, df=1, p=0.017). • Most evident excess in 2nd quarter, 28,3% for An vs 24% for controls • Largest excess in June.	• Used only females as controls • Tightly defined AN diagnosis • No other comorbidity at presentation of illness • Comparison of local birth • Uses several analysing methods	• No age stated nor subtypes of AN used • Diagnostic manual not stated • Duplication of subject count issue is not addressed. • No definition of “seasonal variation” or “seasonal effect”, nor “season” which seams to be used to refer to single months.
• Watkins et al., • 2002 • Uk	Case records 408 f, born between 1970 and 1990at three hospitals: St.George´s, Huntercoumbe Manor, Great Ormond Street. • 259 EO-AN • 149 other childhood-onset ED	Uk general population, 306.700 live monthly births rates for 1981 from England and Wales 149 children with other childhood-onset ED (not AN)	<u>Seasonal chi squared for cyclic trends (Rogers)</u> • April as peak month for AN birth rates relative to UK normative trend (angle=-56.52), but this was not significant (X^2=14.16,df=11;p=0.20) • No significant seasonality effect monthly or quarterly (X^2=5.41,df=11,p=0.14), but peak period April to June (angle=-29.47) • Monthly births pattern for AN vs other ED significant differences (X^2=24.43,df=1, p=0.01); AN peak month of birth in April (angle=-81.94) and through in October. • When comparing other ED vs normative data, July to September were peak quarter (angle= -83.03), and September peak month (angle= 78.21). But these were not significant findings for quarters (X^2=1.11,df=3,p=0.77) or months (X^2=7.39,df=11;p=7.6). <u>Non-seasonal chi-squared</u> • No significant association between diagnosis and month (X^2=14.89,df=11;two-tailed p=0.18) or for quarter of year (X^2= 3.48,df=3; two-tailed p=0.32) • Higher rate of birth for AN in April-June compared to other ED (X^2=3.15,df=11,one-tailed p=0.03)	• First to look at just peaks • Hypothesis driven; investigating the environmental temperatures role at conception • Diagnostic manual stated: Great Ormond Street Hospital criteria • States a need for studies including place of birth/ and mothers habitant before conceiving	• Did not split AN in subgroups R-AN and BP-AN. • Duplication of subject count issue is not addressed. • Comorbidity not mentioned

Authors:	Sample:	Comparison group	Findings; presented according to the statistical analysis used:	Methodological issues:	
				Strengths	Weaknesses
			Mann-Whitney test • Temperature (treated dimensionally) at assumed time of conception higher for EO-AN than other ED (z=2.26, one-tailed p=0.02) • Temperature (treated categorically) at assumed time of conception showed significantly more EO-AN than other ED conceived in warmer months (X^2 (Yate´s correction) =4.48,df=1,one-tailed p=0.017)		
• Waller et al., • 2002 • Uk	Case records of 195 f at the three hospitals: St.George´s, Huntercoumbe Manor, Great Ormond Street; • 117 R-AN • 78 BP-AN	Age mached Uk population birth patterns • Comparison group • R-AN and BP-AN	Nonparametric chi-squared, one-tailed for directional hypotheses • Not different SobP for sample compared to normal population • No significant SobB for entire sample in month (X^2= 10.2,df=11,NS) or quarter (X^2=3.62,df=3,NS) • Significantly more R-AN born in April-June than BP-AN (X^2=2.91,df01, one-tailed p<0.05) • R-AN slightly higher temperature at conception than BP-AN, but not significantly (p=0.12) • Restrictive attitudes correlated significantly with temp at conception in R-AN only (X^2 (Yate´s correction) =3.18,df=1, one-tailed p<0.04) Mann-Whitney • No association between temperature at conception and BMI (z=0.41, NS).	• Diagnostic manual stated: DSM-IV • Strict criteria	• No control group in method however findings indicate some comparisons to normal population norms • Not reported p-values for not significant samples • Duplication of subject count issue is not addressed.
• Willoughby et al., • 2002 • Australia	Australia: Wesley Private hospital, Northside clinic, Concorde Hospital, 198 subjects Born between 1970-90;	Australia general population; 230.000 for 1987 • -Age matched Uk population birth patterns	Rogers (1977) seasonal chi-squared • Peak for AN in December, but not significant according to chi-squared goodness of fit (X^2=13.1, df=11,p=0.28) • No seasonality for quarters (X^2= 5.94,df=3,p=0.11), but peak in October –December.	• First study done on ED in southern hemisphere • Diagnostic manual stated: DSM-IV and GOS	• Duplication of subject count issue is not addressed.

Authors:	Sample:	Comparison group	Findings; presented according to the statistical analysis used:	Methodological issues:	
				Strengths	Weaknesses
	• 142 R-AN • 56 BP-AN Uk: Same 259 AN subjects as in Watkins et al 2002.	• Comparison group • R-AN and BP-AN	<u>Standard chi-squared</u> • No significant associations between diagnoses (R-AN vs BP-AN) and month of birth(X^2=7.68,df=11, two-tailed p=0.74) • Not significant associations between diagnoses (R-AN vs BP-AN or quarter (X^2=4.45,df=3, two-tailed p=0.21), but association trend between diagnosis and the hypothesized high-risk period (Oct-Dec) vs rest of year (X^2=2.01,df=1, one-tailed p=0.07) • No significant association between country of birth and month X^2=12.74,df=11, one-tailed p=0.31) • Not significant association between country of birth or quarter of year (X^2=4.94,df=3, one-tailed p=0.17) • Significantly fewer R-AN (40/134;30%) conceived in cooler months relative to BP-AN conceived in cooler month (23/54;43%) (X^2(Yate´s correction)=2.81,df=1, one-tailed p=0.04) <u>Mann-Whitney</u> • No significant difference between temperatures at assumed conception for R-AN and BP-AN (z=0.07, one-tailed p=0.93)		
• Willoughby et al., • 2005 • Singapore	102 patients born between 1971-1990 from Institute of Mental Health and Woodbringe Hospital. Singapore. 93f + 9 m • -68 R- AN • -63 BP-AN	General population monthly live births form Population Statistics Section, Singapore Department of Statistics. Uses 1981 as index year before consistency in the range of births	<u>Standard chi-squared, one-tailed</u> • No significant difference between general population and AN, monthly (X^2=18.88,df=11,p=0.06) of quarterly and (X^2=5.71,df=3, p=0.12) • No significant difference between R-AN and BP-AN for months (X¨”=12.86,df=11, p=0.30) or quarters (X¨”=3.54, df=3, p=0.31).	• First study to look at AN in equator • States diagnostic manual, DSM-IV.	• Is not clear about source of the retrospective data • Duplication of subject count issue is not addressed.

Authors:	Sample:	Comparison group	Findings; presented according to the statistical analysis used:	Methodological issues:	
				Strengths	Weaknesses
• Pena-Lledo et al., • 2003 • South West Spain	Case notes 105 f to an eating disorder service in Spain. • 47 R-AN • 17 BP-AN • 41 BN	Compares the subgroups of ED	Standard chi-squared, one-tailed • Not significant association of diagnosis and month of birth (X¨"=16.4,df=11,p=0.06) • Not significant association between diagnosis and quarter of birth (X^2= 5.46, df=1, p=0.07), but R-AN most likely to be born during June - August. • Association of diagnosis and high risk period, June-August, and diagnosis was significant (X^2=4.02, df=1, p=0.03) • R-AN more likely than BP-AN to be born June-August, 42,6% vs 24,1%.	• Specifying birth place • Researcher blinded month of birth reviewed case notes, and determined diagnosis • Diagnostic manual stated; DSM-IV • Uses quarter of year analysis based on mean daytime temperature measures from National Spanish Meteorological institute.	• Does not specify specialist level of name of eating disorder service name. • So small sample for chi-squared analysis. • Does not define day-time temperature.
• Crisp, • 2006 • UK	980 f with AN from the St.George´s database.	Uk Office for National Statistics (ONS)	Edwards´ method (1961) • No significant findings. • Older patients (born before 1964): trough in their season of birth in respect of February and peaks in March/April • For younger patients (born in 1964 of later) peak in March/April with other fluctuations.	• Focus on the parental background variable.	• Does not state when patients are born, or when they are treated. • Diagnostic manual: not stated • Does not state other methods used than Edwards´s (1961) • Does not report any p values
• Brewerton et al, • in press • USA	3006 f from national, representative sample. BN 85 Non-BN 2898	Non-BN group from normal population	Chi-square test • Significant differences between BN and controls across seasons (p<0.03) and months (p<0.03). • Fall was highest relative number of BN. The lowest was spring, followed by summer • Peaks of births: October -January, through; March - July.	• Diagnostic manual stated: DSM-IV. • States which definition or season is used.	• To small sample for chi-squared analysis.

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