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Increased psychiatric morbidity in non-heterosexual individuals

A study of 25,000 20-47 year-old twins

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Title (English)

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Abstract

This study is one of the world's largest analyses of the increased neuropsychiatric morbidity among non-heterosexual individuals. Not only did we elaborate on earlier research by finding increased rates of distress/depression, AD/HD and obsessive compulsive disorder, we also showed that while this could partly be explained by the minority stress hypothesis, there also appears to be some familial factors connecting non-heterosexuality to increased mental illness.

Keywords
Non-heterosexual, neuropsychiatry, mental health, twin design, sexual orientation

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Thomas Frisell

Sammanfattning

När homosexualitet 1979 ströks ur de officiella svenska listorna över mentala sjukdomar skedde det delvis som en följd av psykiatriska studier av icke-heterosexuella individer. Bakom dessa studier fanns ett tydligt syfte, de ville visa att en ”avvikande” sexualitet inte alls var kopplat till förekomsten av mentala sjukdomar, vilket den då rådande ”sjukdomsmodellen” av homosexualitet förutsade, och att därmed rättfärdiga att sjukdomsklassificeringen togs bort. Resultaten speglade forskarnas inställning och inga skillnader kunde påvisas mellan grupper med olika sexuell läggning.

I takt med att samhällsklimatet blivit mer accepterande har det dock påpekats att dessa tidiga studier led av alltför små studiepopulationer och en genomgående snedrekrytering av försökspersoner. Nyare studier som försökt undvika dessa fallgropar har konsekvent antytt att icke-heterosexuella individer faktiskt löper större risk än heterosexuella att utveckla depression, ångestsyndrom och missbruksproblem. De flesta av dessa studier har dock fortfarande haft relativt små studiepopulationer och därför haft svårt att uppskatta hur stor den faktiska riskökningen är, eller testa hypoteser som försöker förklara varför denna riskökning finns.

I denna studie genomfördes en av världens största studier av kopplingen mellan icke-heterosexualitet och mental ohälsa. Genom att använda data från STAGE (the Swedish Twin study on Adults: Genes and Environment), där alla svenskfödda tvillingar mellan 20 och 47 års ålder ombetts att besvara en utförlig enkät om deras fysiska och mentala hälsa, så har vi även kunnat ta hänsyn till familjära faktorer (effekter av genetik eller gemensam uppväxtmiljö).

Vi finner signifikant ökade nivåer av depression, ADHD, tvångssyndrom och andra former av mental ohälsa bland icke-heterosexuella individer jämfört med heterosexuella. Till viss del förklaras detta av den ökade utsattheten för de icke-heterosexuella individerna, som rapporterar en högre grad av diskriminering och hatbrott än heterosexuella. Det verkar dock även finnas familjära effekter som påverkar kopplingen mellan mentala sjukdomar och icke-heterosexualitet.

Civilingenjörsprogrammet i Molekylär bioteknik

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Introduction

Though less than thirty years have passed since the Swedish National Board of Health and Welfare (Socialstyrelsen) removed homosexuality from their list of diagnosable disorders, the situation for non-heterosexuals have improved considerably in that time. While prejudices certainly persist, the mainstream opinion has clearly shifted and the attitudes towards homosexuality is now much more tolerant, at least among women, the young, and those believing that homosexuality is rooted in biology [1]. The National Board of Health and Welfare's decision was influenced by changing international practice and growing support for gay and lesbian rights, but it was also supported by research determined to prove that there were no mental differences between heterosexuals and homosexuals. However, as research has moved away from the heated, and morally loaded, debate of whether homosexuality should be considered an illness, it has been acknowledged that this early research suffered from low sample power and severe sample bias. Indeed, more recent research, avoiding these pitfalls, has consistently found psychiatric differences of great clinical importance.

Most importantly, several population based surveys suggest that non-heterosexual individuals more often suffer from depression, substance abuse, anxiety disorders and self-injurious behavior than do heterosexual individuals. Though the results from these studies are in agreement, they are individually relatively weak and offer low precision in estimating the level of this increased mental illness. Also, while it is widely assumed that this increase is due to the discrimination, social stigma and self-loathing (the so called "minority stress") connected with being homo- or bisexual, the empirical evidence for this causal assumption is thin. In fact, only one study used the co-twin control method, which allows for testing if psychiatric ill-health is secondary to sexual orientation (e.g. according to the "minority stress" hypothesis) or if their association is confounded by genetic, other familial or additional socio-demographic factors.

In this study we used data from STAGE (the Study of Twin Adults: Genes and Environments), a 2005-2006 survey of all (N=42 582) 20-47 year-old twins in the Swedish twin registry (overall response rate 60%). This data contains information on mental health and sexual experience as well as a section concerned with traumatic and stressful life events. This enabled us to perform the largest, most reliable analysis of the increased mental health risk for non-heterosexual individuals in the world (the first in Sweden) and allowed us to check for perceived

discrimination and hate crime victimization, testing the minority stress hypothesis. Since the survey was based on twins it was also possible to check for familial confounders, such as genetic factors potentially influencing the association between non-heterosexuality and mental illnesses.

Even though attitudes are changing, research studying the connection between non-heterosexuality and mental illnesses has the unfortunate potential to be used by those embracing prejudice rather than science, or those working towards a political goal rather than enlightenment. In an attempt to counter-act this, an in-depth background will be provided, summarizing and discussing research addressing human sexual orientation, before the results from the present study is presented.

Background

Defining sexual orientation

Quoting The American Heritage Dictionary, sexual orientation is defined as "The direction of one's sexual interest toward members of the same, opposite, or both sexes" [2]. Sexual orientation is commonly categorized into homo-, hetero- and bisexuality according to these "directions of sexual interest". While these definitions are now widely recognized in society, one should bear in mind that they have only been around since the early 20th century. Historians as well as anthropologists continuously point out that while the presence of non-heterosexual sexual *orientation* might be universal, the prevalence of non-heterosexual sexual *behavior* is not.

During the later parts of the 20th century there was some scientific debate over what kinds of sexual orientation it was possible to have, and how this trait should be measured in surveys. While some argued that a simple question asking people what sexual orientation they identified themselves with was enough, others favored a complex definition where sexual orientation should be seen more as a continuous trait with several dimensions, such as "romantic feelings" separated from "sexual arousal", "future ideation" and "sexual experiences". With factor analysis showing that most variation in sexual orientation could indeed be captured in just a few questions [3], and the realization that a complex definition led to the need for even greater samples, this debate has largely ended. Today most researchers agree that sexual orientation should, if possible, be measured as three parameters, self-

labeling (which can range from “lesbian” or “straight” to the more nebulous “queer”), sexual feelings (often self-reported sexual attraction and fantasies) and past sexual activity (measured as number of past sexual partners of same and/or opposite sex).

Ever since Sigmund Freud’s early conceptualizations of sexual development, the mechanisms that determine a person’s sexual orientation have been a matter of great discussion. Freud considered all people innately bisexual and that homosexuality was a possible, albeit unwanted, outcome of the psychosexual development. In mainstream psychoanalysis this view soon fell out of popularity and for most of the 20th century non-heterosexual sexual orientation was considered to be an illness, occurring as an outlet for the need of sexual gratification when the patient felt too threatened by heterosexual sex [4]. After many years of empirical research failing to support the idea of homosexuality as a clinical entity and repeated failures to cure the condition, but perhaps most importantly, the growing support for the gay rights movement, the American Psychiatric Association removed homosexuality from their official list of diagnosable disorders in 1973. In 1979, after a rather undramatic occupation of the stairwell in their Stockholm office [5], the Swedish National Board of Health and Welfare followed suit and removed homosexuality from the Swedish version of the International Classification of Disorders. Today, the mainstream view in psychology is that non-heterosexual sexual orientation is a normal, though statistically relatively uncommon, expression of human sexuality and that treatment is not only unwarranted, but probably useless. However, while comforting for non-heterosexual individuals and a useful definition for civil rights activists, this does nothing to answer the basic questions: Why are there different sexual orientations? What determines which sexual orientation a person will develop?

For some American conservative Christians the answer is easy: children are purposefully recruited into homosexuality through childhood sexual abuse, all part of the sinister homosexual agenda [6]. For large parts of the gay community the answer is equally easy: we’re born this way and it can’t be changed; it’s probably all in the genes. But is it really?

The biology of human sexual orientation

Evolutionary speaking, it would seem probable that females’ sexual attraction to males and males’ sexual attraction to females is hardwired in our biology. Procreation is, after all, the most central tenet of evolutionary biology. Though there has been a lot of speculation concerning the possible evolutionary merits of

homosexuality [7], in order to evolutionarily motivate its existence, it is perfectly possible that a phenomenon as complex as sexual attraction, that is "supposed" to work separately for such biologically close entities as human males and females, is vulnerable and sometimes go "wrong". Independently of whether homosexuality is part of an "evolutionary strategy" or if it is just a sign of an inevitable instability resulting from the complexity of neurodevelopment, it seems reasonable that biology plays a part in determining a person's sexual orientation. But what part, and how important is it compared to other factors?

Researchers have mainly approached this question from two directions, behavioral genetics and proxy associations. Through behavioral genetics it is possible to get measures of heritability and to look for genes associated with non-heterosexual orientation. The second strategy is based on the theory that sexuality is determined during the prenatal neurodevelopment and looks for associations between sexual orientation and different traits known to be influenced by prenatal factors, such as handedness, finger length, birth weight and certain reflexes.

When considering research on human sexual orientation it is important to remember a few limitations. First, the prevalence of non-heterosexual sexual orientation is low, at least when behaviorally measured, at about 5% in the adult Swedish population [8], giving even large population based surveys low statistical power. On the other hand, when recruiting a community sample, for example through advertisements in gay bars or queer magazines, there is a great risk of biasing your sample. Not surprisingly, people who frequent bars, gay or otherwise, tend to drink more, have different attitudes towards life and are more often single than other people.

In the literature there are several ways to define non-heterosexuality. As have already been mentioned, most researchers agree that self identification, sexual attraction and sexual experience should be weighed together to form categories of sexual orientation, but there is no agreement on how this should be done. Also, for various reasons some studies do not include all measures of sexuality, and while the three parameters are correlated, they are not generally exchangeable.

Since we know so little about the mechanisms of sexual orientation, we cannot say whether there are different effects underlying homosexuality and bisexuality, and considering the obvious gender differences, the mechanisms might well be different between men and women. This gives us another problem since, due to low statistical power and vague definitions of sexual orientation, bisexuality and homosexuality are often put together into a single non-heterosexual category, and

in some smaller studies analyses are not performed separately for women and men. With these limitations in mind, I will attempt to sum up the research conducted so far.

Behavioral genetics

Family studies have found greater prevalence of homosexuality among relatives of homosexual probands. Some studies have also found increased rates of male homosexuality along maternal transmission lines, which could imply linkage to the X-chromosome or specific imprinting [9]. Most astonishingly, family studies have consistently found a fraternal birth order effect, i.e. gay men have a higher average number of older brothers than straight men do. Indeed, epidemiological statistics suggests that as many as one out of seven gay men owe their homosexuality to the fraternal birth order effect [9]. While this is a very reliable finding, the mechanism behind it is not known, and a theory of progressive maternal immunity to male specific antigens remains to be proven.

Several twin studies have found moderate heritability and no effect of shared environment [9], but they suffer from very small samples. In one study the small sample size (N=2907, including twins and siblings) made it impossible to analyze men and women separately, and though it showed that siblings to non-heterosexual individuals have clearly increased odds of being non-heterosexual themselves, the estimates of heritability compared to environmental effects are unreliable [10]. A slightly larger study (N=3498, including opposite sex twins) found moderate heritability among women (accounting for 50-60% of the variance) but substantially lower genetic effects among men. Although familial factors were found the low power made it impossible to separate between heritable factors and the effects of shared environment [11]. A recent Swedish population study (N = 2,320 monozygotic pairs and 1,506 same-sex dizygotic pairs) fails to reproduce these gender differences [8]. It found modest, as in previous studies, non-significant genetic contributions and relatively strong effects of the unique environment. Among men, structural equation modeling revealed that genetic effects accounted for 0%-39% of the variance, and unique environmental effects for 61%-73%. Among women, 13%-19% were explained by additive genetic factors, 64%-68% by unique environmental factors and 16%-19% was due to shared environment. These results raise questions about the validity of the earlier research, which was not, apart from two smaller studies, based on population samples.

Early linkage studies identified an association between homosexuality and an Xq28 marker, but this finding has been difficult to replicate [9]. In the largest linkage study so far, based on a sample of 146 families with two or more gay brothers, the Xq28 finding was not replicated but several other regions were found, 7q36, 8p12 and (of maternal origin) 10q26 [12]. Interestingly these regions contain genes such as *VIPR2* (vasoactive intestinal peptide receptor type II, a G-coupled receptor of VIP, a neurotransmitter), *SHH* (Sonic hedgehog, essential for early bilateral patterning of the embryo, i.e. left to right symmetry) and *GNRH1* (Gonadotropin-releasing hormone 1, involved in the expression on luteinizing hormone and follicle-stimulating hormone). Only two association studies have been performed on specific candidate genes, the androgen receptor gene and *CYP19A1* respectively, genes proved to play a role in mating behavior in several animal studies. Unfortunately both association studies produced null findings [9].

Perhaps surprising to some, non-heterosexuality appears to have a quite modest heritability. Also, no genes or quantitative trait loci that affect sexual orientation in humans have yet been consistently identified. While this indicates that environmental factors are important for determining a person's sexual orientation, one should remember that the environment also consists of biological influences.

Prenatal factors

Studies on animals have consistently shown that gonadal steroidal androgens play a large role in creating the sex difference in the model animals' brains and behavior [9]. It does not seem illogical to assume that they play a similar role in determining sexual behavior among humans. This reasoning gave birth to the "prenatal androgen model" which suggests that human sexual orientation is influenced by the prenatal levels of androgens present in the amniotic fluid and more specifically in the emerging fetal brain. The classical hypothesis is that attraction to men (heterosexuality among women) is the default state, whereas attraction to females (heterosexuality in men) is caused by increased levels of androgens (mainly testosterone). If these levels are altered so that a female fetus is subjected to increased levels of testosterone or a male fetus is subjected to lowered levels, the result would be homosexuality. Obviously research on human development is limited by ethical factors and this hypothesis has only been tested through animal models and the analysis of "proxy markers". In this context, a proxy marker is an easily measured trait that is known to be influenced by prenatal hormone exposure. Finding a difference in these traits between homosexuals and heterosexuals is thus

a proxy of finding a difference in hormone exposure, providing information concerning the effects of specific hormones at different stages of neurodevelopment.

Perhaps the most studied proxy marker is the ratio of the second to fourth finger lengths (the 2D:4D ratio). On average men has lower 2D:4D ratios than women and several studies indicate that this is mediated by prenatal androgen exposure [9]. As the prenatal androgen model would predict, self-defined lesbian women have lower 2D:4D ratios than straight women, indicating increased levels of androgen exposure in the former compared to the latter. Studies of gay men, however, show confusing results with some studies showing decreased ratios and some showing increased ratios compared to straight men. These gender differences in the patterns of results between non-heterosexual and heterosexual subjects are replicated through studies on other proxies, such as fingerprint patterning (females have an asymmetry, with more ridges on the left hand), handedness (males are more often left handed) and oto-acoustic emissions (spontaneous or reflex-triggered sound emissions within the ear, found to be more numerous in females). Even more confusion comes from studies on physical growth markers, where homosexual men report earlier onset of puberty and less long-bone growth than heterosexual men, but no significant differences have been found between lesbian and straight women. [9]

Overall, the most robust finding appears to be that homosexual women are exposed to more prenatal androgens than are heterosexual women. Studies on homosexual compared to heterosexual men, on the other hand, sometimes indicate decreased prenatal exposure to androgens and sometimes an increased exposure. Perhaps the development of non-heterosexuality in men could result from both higher and lower levels of androgens than average for male fetuses, respectively. Alternatively, patterns of shifting androgen levels over time during fetal development determine sexual orientation [9]. Then again, maybe these findings are just due to random variation, and androgen levels have no effect on male sexual orientation. While these results might sound confusing and unsatisfying, the research dealing with the prenatal androgen model has shown two things. First, there appears to be different mechanisms underlying male and female homosexuality and second, the fact that significant differences can be found implies that there truly is a connection between prenatal hormones and sexual orientation, at least among women. Little is known about the nature of this connection, but considering the nature of the androgens themselves and the proxies they are known to affect; it seems probable that androgen levels regulate the early developmental

pathway in a general sense rather than exclusively influencing sexual orientation in a direct manner.

Learning theories

In summary, non-heterosexuality is modestly heritable and no genes have yet been found that influences it. In addition, research indicates that prenatal androgens are involved, but the mechanism is unclear and androgen levels do not seem to explain all the variation in sexual orientation. From this, it would seem that environmental factors have a huge impact on sexual development. Perhaps sexual orientation is learnt rather than inborn? Some support for this can be found from animal studies that have shown that conditioning can influence mating behavior and sexual arousal. In humans, this kind of research is not possible, but anthropological studies on cultures where ritual homosexuality is practiced during childhood/adolescence (some New Guinean tribes, e.g. the Sambia tribe) imply that this behavior does not result in elevated levels of homosexuality among adults [9]. Epidemiological studies have shown that sibling sex-play does not explain the fraternal birth order effect and that children growing up with homosexual parents are not more prone to become homosexual adults themselves. On the whole, research on environmental factors affecting human sexual orientation is surprisingly thin, but the data available indicates that learning mechanisms are not very important for deciding a person's sexual orientation [9].

Is non-heterosexuality a mental illness?

For most of the 20th century, non-heterosexuality was considered, by professionals as well as by ordinary people, a mental illness. Indeed, even today there are many who consider it a contagion and who try to fight it, believing that it is unnatural and sick [6]. Since there is no universal definition of the concept "mental illness" some would argue that the truth lies in the eye of the beholder, maybe it should be considered a disease in one cultural context but not in another [13]. Nevertheless, when the American Psychiatric Association's Board of Trustees removed homosexuality from their Diagnostic and Statistical Manual of Mental Disorders (most commonly referred to as the DSM) in 1973, they did so for a reason.

The following account is largely based on *Psychoanalysis and the model of homosexuality as psychopathology: a historical overview* [14], in which Friedman and Downey gives an historical overview of homosexuality's status as an illness.

According to them, what needs an explanation is not why homosexuality was removed from the DSM, but rather why it was ever included there to begin with.

In post 2nd World War USA, psychoanalysis quickly became the most prominent psychological discipline. In part, this was because of the psychoanalysts' remarkable success in treating soldiers suffering from stress-induced mental problems during the war, but the influx of famous European psychoanalysts, some of whom had actually worked with Sigmund Freud himself, certainly did not hurt. After the war, psychoanalysis in America became a rigid structure, where an orthodox educational system supported an unquestioning belief in Freud's basic tenets [14]. This created a scientific tradition where general rules could be deducted from a handful of case studies, and skeptics demanding empirical research were ridiculed and frozen out. Advances in related disciplines such as psycho-pharmacology was treated with great suspicion and an unwarranted belief in the efficacy of the pure psychoanalytical method thrived. Even so, psychoanalysis helped many people to cope better with their problems and to live more rewarding lives. After all, the people who were able to engage in psychoanalysis were the ones who were well enough to partake in a discussion and who had an "observational ego" strong enough to analyze their own actions and motivations. In addition, they were also the ones who could afford the hundreds of hours in therapy thought to be required to get results. Many of these people suffered from disorders that even today could be treated with psychotherapy therapy sessions. However, the psychoanalytical approach did not work for homosexuality as well as it sometimes did for certain forms of depression or psychosomatic disorders.

While Sigmund Freud considered homosexuality a less than ideal outcome of psychosexual development, he did not consider it a treatable disease. According to Freud everyone had unconscious homosexual as well as heterosexual desires, but the homosexual ones were more likely to be denied by the conscious mind and were therefore more likely to cause mental problems. Freud suggested many mechanisms that could result in homosexuality in men, e.g. castration terror caused by the sight of the mother's genitals or oedipal rage at the father turned into homosexual love through reaction formation. Sandor Rado and his students elaborated on Freud's theories of sexuality stating that heterosexuality was the only normal outcome of psychosexual development. They postulated that trauma so serious that it could change this natural development would not only result in homosexuality but would also lead to substantial general damage to the person's mental functioning. According to Rado, treatment of homosexuals should focus on conquering their

irrational fears of heterosexual sex and relationships, thus letting their assumedly repressed, “natural” desires take over. During the 1940s to 1970s, models that stated that homosexuality was an illness associated with severe mental problems were quickly accepted and applied within mainstream psychoanalysis. With minimal or no empirical evidence, mental health professionals were convinced of the validity of these theories and psychoanalysis’ power to cure homosexuality. For all but a few of the homosexual patients who were administered this therapy the result was a great loss of money, time and self-esteem. Failure to be cured was usually chalked up to be the patients own fault, obviously he or she did not “want to change” or was not committed enough when going through the required courtship with people he/she had no sexual interest in.

A 1962 study made by the Committee of Medical Psychoanalysts, based only on information from the patients’ psychoanalysts and with no independent evaluation or follow up, found that 20% or less of homosexual patients were reported to have changed their sexual orientation to heterosexual [14]. While this kind of studies did not evoke any reaction from mainstream psychoanalysts, scientists from other disciplines were compiling a growing body of evidence showing that homosexuality was much more common than generally assumed and that empirical research on non-clinical samples of homosexuals and heterosexuals could not find any significant differences in mental traits or psychopathology [4].

Finally, in 1973, after mounting evidence that homosexuality was not curable (at least not through psychoanalysis) and not generally associated with mental disorders, homosexuality was removed from the Diagnostic and Statistical Manual’s list of mental disorders. Perhaps more important than the actual findings of researchers, attitudes were changing in the academic world, with strong criticism against the lack of scientific enquiry within psychoanalysis and a growing support for gay and lesbian rights. Of course these revisions did not pass without objections from traditional psychoanalysts as well as organizations guarding conservative values. In fact, the opposition has not given up yet [6]. As late as in May 2000, the American Psychiatric Association felt the need to issue a position statement reiterating their official view that homosexuality is not a diagnosable mental disorder and that treatments claiming to cure homosexuals are not backed up by empirical research [15].

Are non-heterosexuals mentally ill?

In the heated climate of the1960s and 1970s when sexual liberation collided with conservative (and often religious) values, mistakes where made on both sides of the debate. Since the ruling paradigm stated that homosexuality was an illness that, by its very nature, was associated with diverse mental problems, its critics claimed to show that this was not true, that in fact there was not an increased rate of mental illness among homosexuals. In response, supporters of the illness model tried to show the opposite. These early studies were small and suffered heavily from sampling bias, but even worse, the results seems to have been interpreted differently depending on what conclusion one preferred [4]. In hindsight, it is obvious that this debate was concerned with the wrong question. Increased levels of mental illness within the homosexual population say nothing about the causes of homosexuality. In fact, wouldn't we expect there to be increased mental illness among people who are ostracized by most of society?

During the last decade or so, attitudes in society (or rather the way these attitudes are perceived by researchers) have finally softened enough to enable larger, more reliable epidemiological studies of mental health taking sexuality into account, though many of these studies still suffer from biased sampling, low statistical power and diffuse definitions of sexuality. A short summary of the results will follow.

There are many studies showing that non-heterosexual men and women have increased rates of mood disorders (such as depression) and anxiety disorders, compared to heterosexual subjects of the same gender (e.g. [16] (N = 3648, only men); [17] (N = 5998); [18] (N = 5877)). It has also been shown that there are increased past and future suicide attempt rates among non-heterosexual adolescents of both sexes ([19], N = 2924) as well as increased life-time suicidality among adult non-heterosexual men ([20], N = 103 twin pairs discordant for heterosexuality). There is also some evidence that bisexuals are at a higher risk than homosexuals for anxiety disorders and depression ([21], N = 4824).

Among non-heterosexual females alcohol abuse is more common then among heterosexual women (e.g. [22], "snowball sample" N=2179, about 50% non-heterosexuals), and it seems that bisexual women are at a particular risk for drinking problems ([23], N= 10301). There is some indication that increased alcohol and drug use is connected to the coming out process and may later decrease to more "normal" levels ([24], N = 156, all non-heterosexual). While male non-heterosexuals do not show an equally dramatic increase in alcohol consumption

compared to heterosexual men, they do show a highly increased rate of eating disorders ([25], N = 788, 50% non-heterosexual; [26], N = 121, about 50% non-heterosexual). This increase in eating disorders has been connected to an increased body dissatisfaction among non-heterosexual men ([27], N = 169 heterosexuals and 70 non-heterosexuals, only men).

The conclusion from these studies is clear; there is indeed an elevated prevalence of mood and anxiety disorders among non-heterosexuals, compared to heterosexuals. With the exception of the increased rates of alcohol and drug abuse in women and of eating disorders in men, this elevated prevalence of mental illness seems to apply to both genders. In his *Archives of General Psychiatry* commentary, Bailey ([28]) suggests three different explanations to these findings. The first hypothesis is that the increased illness is caused by the increased discrimination, self-loathing and emotional pain that follow from being gay or lesbian in a hetero-normative society. In the literature, this hypothesis is now widely referred to as the *minority stress model*. The second hypothesis is that homosexuality is caused by developmental errors that are also associated with neurophysiologic problems, leading to an increased vulnerability to mental illnesses. This hypothesis is sometimes referred to as the *developmental instability model*. Lastly, Bailey points to prenatal androgen theories and the prevalence of sex-atypical traits among homosexuals and argues that maybe gay men are more susceptible to female typical forms of mental illness and vice versa.

Though there is some support for the prenatal androgen model (see above), Bailey's third hypothesis has been largely refuted. While homosexual men do show increased levels of "female-typical" disorders like depression and anxiety disorders, so does homosexual women. If the third hypothesis was true, one would instead expect to find a "male typical" decreased level of depression in lesbian relative to heterosexual women. Indeed, the only gender differentiated risk increases that have been found are the ones concerning eating disorders and alcohol abuse that has been mentioned above, and this might well reflect different attitudes about gender roles and socially expected behaviors, rather than different biological vulnerabilities.

In the literature, it is widely assumed that the minority stress model accounts for all of the increased mental illness (e.g. [4], [13]). It has indeed been indicated that homosexuals and bisexuals suffer increased levels of discrimination and physical and psychological abuse, during childhood and as adults ([29], N = 557 gay/lesbian, 163 bisexuals, 525 heterosexuals) and that non-heterosexual men (but not women) report a lower quality of life ([30], N = 5998). It has also been shown

that experiencing multiple episodes of anti-gay violence increases the level of distress in non-heterosexual men ([31], N = 2881, all non-heterosexual) and that perceived discrimination accounts for some of the increased risk for psychiatric disorders ([32], N = 2917). Though it seems highly plausible that the minority stress model can explain part of the increased mental illness, it should be pointed out that there is no empirical research to suggest that it explains all of it.

Then, what about the developmental instability model? While this theory seems to be a realistic explanation and fully compatible with e.g. the prenatal androgen model, it appears that the developmental instability theory has been equated to "an organism's level of vulnerability to environmental and genetic stresses during development", and the prediction that this is related to fluctuating asymmetries (FA), i.e. "random deviations from perfect symmetry in bilateral bodily features" [9]. These fluctuating asymmetries are thought to be related to an organism's fitness, with less fit organisms showing greater FA. The theory states that homosexuals should have greater FA than heterosexuals, because the instability causing homosexuality also reduces fitness. Not surprisingly, no such difference has been found [9]. I must confess that I'm a bit perplexed by this hypothesis, and the very thought that "genomic stability" is trait that can be measured through the level of symmetry in someone's face or hands. As far as I can see, this research has done nothing to disprove (or even test!) the hypothesis that homosexuality is caused by a developmental error. This research has, however, shown that even if homosexuality is caused by a developmental error, this error does not cause random physical deformities.

Methods

The Swedish twin registry and STAGE

Established in the late 1950s, the Swedish twin registry today encompasses all twins born in Sweden since 1886, i.e. more then 170 000 individuals of whom about 135 000 are still alive and currently residing in Sweden [33]. The original purpose of the registry was to enable epidemiological studies concerned with the effects of smoking and alcohol consumption on the risk for cancer and cardiovascular disease while taking genetic vulnerabilities into account. Today it is used to study a much wider range of illnesses and other outcomes with respect to many different exposures and risk factors. Since it contains monozygotic as well as same-sex and opposite-sex dizygotic twins it is possible to study heritability and to

obtain estimates of the relative effect of genetics compared to shared and unique family environment.

In the Study of Twin Adults: Genes and Environment (STAGE), all twins in the Swedish twin registry born between 1959 and 1985 (N = 42 582) were invited to participate in what was the world's largest web-based survey. The total response rate was 59.6% yielding an overall N of 25,364, though some questions had lower internal response rates. The questionnaire consisted of around 1300 questions, but many of these were follow-up questions not relevant for all respondents. Among these questions were sections concerned with physical and mental health, demographics, smoking, drinking habits and nutrition but also with sexual risk behavior. In this last section, two items addressed the lifetime number of individuals of the same and opposite sex, respectively, that the respondent had "been sexually together with". From these questions, two behaviorally defined measures of non-heterosexuality were constructed: having had any same sex sexual partner (Any same-sex experience) and having had equally many or more same sex sexual partners compared to opposite sex sexual partners (Same-sex partner predominance). Note that this means that the second category is nested within the first one.

Dependent variables

STAGE includes many diagnostic sections concerned with different disorders. In this study I used the sections concerning attention-deficit/hyperactivity disorder (AD/HD), current depression, lifetime major depression (DSM-IV MD) and obsessive compulsive disorder (OCD). The questions in the AD/HD section attempt to measure a respondent's level of impulsivity and inattentiveness. The items are scored and represent the DSM-IV symptoms, with a DSM-IV defined cut-off on the sum [34], i.e. if a person's score is higher than "N" the person is considered to have AD/HD. The version used here is not as strict as the clinical DSM-IV measure, since it accepts "maybe" as an answer, giving it half the score of a "yes". Though there has been a lot of discussion concerning the best way to assess AD/HD among adults ([35], [36]), studies has shown that self-reporting gives a valid measure of current AD/HD [37]. OCD was also measured continuously as a symptom count (not based on the DSM-IV), but no cut-off was used to get a dichotomous measure.

Depression was measured as a continuous trait according to the Center of Epidemiological Studies Depression scale, CES-D (current depression), and dichotomously according to the DSM-IV definition of Major Depression, MD (life-

time depression). The CES-D scale has been repeatedly validated ([38], [39]), though it has been pointed out that it should preferably be used in combination with some other measure of depression [40]. In STAGE, a shortened down version of the CES-D is used, but it is supplemented by the dichotomous measure of major depression. This measure of MD fulfills DSM criteria A (a certain amount of depressive symptoms must have been present for a period of at least two weeks), C (the depression must have impaired the subjects ability to work and function) and E (the episode of depression was not caused by bereavement). We have not taken into account criteria B (the depression is not an effect of another disorder, such as bipolar disorder) or D (the symptoms are not a direct effect of a drug or a somatic disorder).

In the statistical analysis all the "continuous" count measures have been transformed by adding one and taking the ten-logarithm (transf(x) = log10(x+1)), this gave a better approximation of the normal distribution, measured through lowered kurtosis and skewness. This transformation was chosen following recommendations from [41].

Apart from the diagnostic sections, STAGE also contains direct questions on the form "have you ever suffered from…" This list of illnesses includes 11 psychiatric disorders: depression, bipolar disorder, panic/anxiety disorders, phobia, problems with drugs or alcohol abuse, eating disorders, obsessive compulsive disorder, AD/HD, Tourette syndrome, schizophrenia and, finally, autism spectrum disorders. These items are included in the analysis, but they have not been validated, and may include numerous false positives.

Independent variables

Sexual orientation aside, several other independent variables were included in the analysis to account for possible confounders and to estimate the connection between perceived victimization and mental illness among non-heterosexuals. The possible confounders included were: age, relationship status and educational level. While the twin registry includes an exact measure of age, the other two had to be derived from several items of the questionnaire. Relationship status is defined as either being in a serious relationship, or being single. In contrast to some studies, this includes relationships where the partners are not cohabiting, and the "single" category includes widows and divorcées. Educational level was categorized as Low, Medium or High level, where Low equals having completed elementary school or lower, High equals undertaking or having finished university level education and

Medium level is everything that is higher then elementary but lower than university level of education. While level of education is a measure of a person's socioeconomic status, it is desirable to complement it with other measures, e.g. based on occupation or residential area. Unfortunately those measures are being derived by other groups, and have not yet been finished for STAGE.

Perceived victimization was measured by two items. The first asked whether the respondent had ever "been discriminated against in an insulting or disparaging way because of your race, ethnicity, gender, sexual orientation or religion?" The other question was whether the respondent had ever "been the victim of a hate crime? This means that you might have experienced violence directed at you due to your race, ethnicity, gender, sexual orientation or religion."

Regression and the logistic link function

Most ordinary statistical tests, such as t-tests, MANOVAs and regressions, can be described using Generalized Linear Models, or GLIMs. Generally we want to model a dependent variable (y) as a linear function of n independent variables (x_1, x_2,..., x_n) while adding a residual term (e) to account for the fact that the model is not a full representation of reality:

$$y = \beta_0 + \sum_{i=1}^{n} (\beta_i x_i) + e \qquad \text{[Eq. 1]}$$

To solve this we usually use more than one measurement. Say that we have k different ys; it is then helpful to write the model in matrix form:

$$\begin{pmatrix} y_1 \\ y_2 \\ \vdots \\ y_k \end{pmatrix} = \begin{pmatrix} 1 & x_{11} & \cdots & x_{1n} \\ 1 & x_{21} & & \\ \vdots & & \ddots & \\ 1 & x_{k1} & & x_{kn} \end{pmatrix} \begin{pmatrix} \beta_0 \\ \beta_1 \\ \vdots \\ \beta_n \end{pmatrix} + \begin{pmatrix} e_1 \\ e_2 \\ \vdots \\ e_k \end{pmatrix} \qquad \text{[Eq. 2]}$$

Or equivalently:

$$\vec{\mathbf{y}} = \mathbf{X}\vec{\boldsymbol{\beta}} + \vec{\mathbf{e}} \qquad \text{[Eq. 3]}$$

To estimate the βs (i.e. solving Eq. 2), most programs use the method of least squares. This is done by testing different values of the βs and choosing the combination that gives the lowest sum of the squared residuals.

The above model is only valid for dependent variables that are continuous and approximately normally distributed with constant variance; this means that it can not be used for the dichotomous (yes or no) data we have on different illnesses, where a person either has the disease or not. We can get around this by introducing the link function g(μ), where μ is the expected value, i.e. the mean, of y. We define g(μ) as:

$$g(\mu) = \mathbf{X}\vec{\boldsymbol{\beta}} \qquad \text{[Eq. 4]}$$

For the model above this means that:

$$g(\mu) = \mu \qquad \text{[Eq. 5]}$$

Dichotomous data follow the Bernoulli distribution, which is actually just the Binomial distribution where n = 1. It can be shown ([42]) that the link function then becomes:

$$g(\mu) = log\left(\frac{\mu}{(1-\mu)}\right) \qquad \text{[Eq. 6]}$$

Where "log" represents the natural logarithm. This is called the logit link function, and regression implementing it is called logistic regression. In the binomial distribution p = μ = the prevalence of the studied disease. This has important implications for calculating the statistic known as the odds ratio, or OR, but let us first write out the equation used when solving models with logistic regression:

$$log\left(\frac{p}{(1-p)}\right) = \beta_0 + \sum_{i=1}^{n}(\beta_i x_i) \qquad \text{[Eq. 7]}$$

Odds ratios

If the probability that something will happen is p, its odds is:

$$\text{Odds} = \frac{p}{(1-p)} \qquad \text{[Eq. 8]}$$

Two statistics commonly used in epidemiology are the odds ratio, OR, and the relative risk, RR. They are defined as:

$$\text{OR} = \frac{\frac{p_1}{(1-p_1)}}{\frac{p_2}{(1-p_2)}} \qquad \text{RR} = \frac{p_1}{p_2}$$

Here the p:s usually represent the risks of having a certain disease in two different groups, e.g. the risk for lung cancer among smokers and non-smokers. While the RR might seem more intuitive than the OR, there are some cases where it cannot be calculated. However, it is easily seen that for small p:s the OR is very close to the RR. A handy characteristic of logistic regression is that its link function is the natural logarithm of the odds. When one of the independent variables (let's say x_1) is binary, representing group membership (e.g. relationship status), this means that the OR can easily be calculated by exponentiating the regression coefficient:

$$OR(x_1) = \frac{\exp(\beta_0 + \beta_1 + \sum_{i=2}^{n} \beta_i x_i)}{\exp(\beta_0 + \sum_{i=2}^{n} \beta_i x_i)} = e^{\beta_1} \qquad \text{[Eq. 9]}$$

GEE

The data from STAGE is based on twins. While this allows us to perform twin controlled analysis, it also introduces a problem since the observations in the dataset will have a pair wise correlation, i.e. twins are more similar to each other than to a randomly selected person from the dataset. This can be compensated for using General Estimating Equations, GEE. This uses the basic model of the GLIMs but also solves the GEE equation, which on twin data looks like:

$$\sum_{\mathbf{t=1}}^{\mathbf{2}} \frac{\partial \boldsymbol{\mu}_\mathbf{t}}{\partial \boldsymbol{\beta}} \mathbf{V}_\mathbf{t}^{-1} (\mathbf{Y}_\mathbf{t} - \boldsymbol{\mu}_\mathbf{t}(\boldsymbol{\beta})) = 0 \qquad \text{[Eq. 10]}$$

Here the vector $\mathbf{Y_t}$ holds measurements on the twins within each pair, the vector $\boldsymbol{\beta}$ contains the regression parameters, $\boldsymbol{\mu}$ contains the means to the traits measured in $\mathbf{Y_t}$ and $\mathbf{V_t}$ is the covariance matrix of $\mathbf{Y_t}$ defined by the degree of correlation between twins.

Paired t-test and co-twin controls

The object of a co-twin control is to compare twins within a pair to check for familial confounders. The analysis can only be performed on pairs where the twins are discordant, i.e. they differ with respect to a certain binary variable, usually exposure to some risk factor. In this study the relevant variable is sexual orientation, and twin pairs discordant for sexual orientation are selected for a paired t-test, on continuous measures of illness, or a conditional logistic regression, on dichotomous measures. In a paired t-test one simply calculates the difference in a trait, e.g. depression counts, within each twin pair, and then performs a t-test to see if this difference is significantly different from zero. A conditional logistic regression on twins is a logistic regression where the regression coefficients are first calculated within each pair and then weighed together for the entire dataset. If the analysis is performed separately on dizygotic and monozygotic pairs one can also differentiate between purely environmental effects (accounting for the difference among monozygotic twins) and mixed environmental and genetic differences (accounting for the difference among dizygotic twins). A problem with co-twin controls on rare phenotypes is that even for such a big sample as the one used in STAGE, the number of discordant twin pairs where both twins have answered all the relevant questions is low. This is especially troublesome in the conditional logistic regression since most of the studied disorders are rare and only pairs where the twins are discordant for the studied disorder as well as for sexual orientation contribute to the result. In our study this meant that I could not use the conditional logistic regression to study AD/HD, and that the results for major depression was highly unreliable (for men, we found only 12 informative twin pairs). In the end I chose not to include the results from the conditional logistic regression, relying only on the paired t-tests as twin control analysis.

SAS

The calculations have been performed using SAS v.9.1.3. For the regression with GEE, Proc Genmod was primarily used. The conditional logistic regression was performed using Proc Logistics. For the descriptive statistics Proc Freq, Proc

Univariate and Proc Means was used, and for the paired t-test, Proc Means. The macros are attached in Appendix 1, but not the full scripts, since they are excruciatingly long and repetitive.

Results

Demographics

Of the 25,364 respondents, 11,229 were men (response rate: 53.2%) and 14,096 were women (response rate: 65.9%). STAGE was directed only at adult twins from the twin registry, where "adult" was defined as 20-47 years (mean=33.7, SD=7.7). There were no significant differences in age between men and women, or between heterosexual men compared to non-heterosexual men. Women reporting any same-sex experience were significantly younger than women who did not, but the difference was very small (mean=32.2 years compared to 33.5 years, $p<0.0001$). All respondents were born in Sweden, which means that none were 1st generation immigrants. The internal response rate was lower for the sexual risk section, resulting in 7,231 and 6,488 men and 10,676 and 9,425 women that could be included in the analysis of any same-sex experience and same-sex partner predominance, respectively. Of these, 5.6% of men and 7.8% of women reported having had any same-sex partner, and 4.3% of men and 4.1% of women fulfilled the criterion for same-sex partner predominance. For any same-sex partner, this gave us 303 discordant female twin pairs, and 102 discordant male twin pairs; for same-sex partner predominance it gave us 147 female pairs and 73 male pairs. The prevalence of the possible confounders and the perceived victimization is shown in *Tables 1 & 2*.

While females reported a higher frequency of "being in a relationship", than

Table 1: Female demographics	**No same-sex experience (n=9714)α**	**Any same-sex experience (n=819)α**	**Not same-sex partner predominance (n=8749)α**	**Same-sex partner predominance (n=375)α**
Currently in a relationship	74.7%	71.6%	74.8%	81.1%
Low level of education	4.1%	4.0%	3.8%	3.3%
Medium level of education	46.0%	49.1%	45.2%	48.2%
High level of education	50.0%	47.0%	51.1%	48.5%
Perceived discrimination	6.8%	17.6%	7.5%	15.2%
Hate crime victimization	0.7%	3.5%	0.8%	3.4%

α) n for discrimination and victimization was 9191; 781; 8327 and 355, respectively.

Table 2: Male demographics	**No same-sex experience (n=6750)γ**	**Any same-sex experience (n=400)γ**	**Not same-sex partner predominance (n=6013)γ**	**Same-sex partner predominance (n=267)γ**
Currently in a relationship	68.5%	61.3%	68.4%	62.9%
Low level of education	5.5%	5.8%	4.8%	6.4%
Medium level of education	52.6%	50.4%	51.5%	48.5%
High level of education	41.9%	43.8%	43.7%	45.1%
Perceived discrimination	3.3%	16.8%	3.5%	21.0%
Hate crime victimization	1.4%	7.3%	1.4%	8.8%

γ) n for discrimination and victimization was 6204; 369; 5548 and 253, respectively.

males did (75% and 68% respectively), there was also an effect of sexual orientation. Females who had had predominately same-sex partners reported a higher frequency of relationships than other females (81.1%) while men who had had predominately same-sex partners reported lower frequency of relationships than other males (62.9%). Lowest frequency of relationships was found when considering the category reporting any lifetime same-sex experience, 71.6% (females) and 61.3% (males). Women consistently showed a higher level of education than men (50% compared to 42% reported High level of education). The differences between heterosexual and non-heterosexual was small, but non-heterosexual females were more often of Medium level and less often of High level than heterosexual females. The opposite was found among men; non-heterosexual men were slightly more often of either Low or High level and less often of Medium level of education than heterosexual men.

Over all, heterosexual women reported more discrimination, but less hate crime victimization than heterosexual men. The difference between heterosexual and non-heterosexual, however, was considerable. Among heterosexual women, about 7% reported being discriminated against, a figure that was more than doubled among non-heterosexual women (17.6% or 15.2%, depending on definition). Hate crime victimization was five times higher among women with any lifetime same-sex sexual experience (3.5%) compared to women with no same-sex experience (0.7%). Among men these differences were even stronger, with non-heterosexual men reporting six times more perceived discrimination (16.8% or 21%) than heterosexual men (3.3%). Perceived hate crime victimization was generally higher for men than for women, but still showed a more than five fold increase among non-heterosexuals (7.3% or 8.8% compared to 1.4%). Among women, using the narrow definition of non-heterosexuality (same-sex partner predominance) lowered the perceived discrimination and hate crime victimization compared to using the wider definition. Interestingly, the opposite applied to non-heterosexual men, where using the narrow definition provided even higher levels of victimization than the wide did.

Dichotomous measures of illness

Table 3 shows the results of the logistic regression using GEE on dichotomous AD/HD and major depression (MD) data. The prevalence of AD/HD is high, due to it being defined using wide criterions, and it should be interpreted as “possible AD/HD” rather than an actual diagnosis. As expected females have about twice the

male prevalence of MD, while males have a slightly higher prevalence of AD/HD than females do. The prevalence of both AD/HD and MD is significantly higher among non-heterosexual individuals than among heterosexual individuals. This is true for both genders and for both definitions of non-heterosexuality. The crude odds ratios reflect this, and are all clearly above one, with only same-sex partner predominance as a predictor for AD/HD failing to reach significance. Checking for the possible confounders (adjustment 1) only slightly changes the results, but when also checking for perceived discrimination and hate crime victimization (adjustment 2), all odds ratios are lowered, and several fail to reach significance. Without exception, the wide definition of non-heterosexuality (any same-sex experience) results in higher odds ratios than the narrow definition (same-sex partner predominance).

Continuous measures of illness

The continuous measures of depression (using the CES-D scale), AD/HD and OCD (based on symptom counts) are actually count measures with highly skewed distributions. The variables were therefore transformed by adding one and applying the 10-logarithm. While this gives numbers that might seem less intuitively interpretable, the scales are actually arbitrary even to begin with. This lack of normality is especially troublesome for the obsessive compulsivity scale, where a majority of respondents score zero. In *Table 4* the mean values of the variables are presented. For both men and women non-heterosexuals have a higher mean value of all three measures than heterosexuals do. This applies to both definitions of non-heterosexuality, but in all cases the mean value is higher for the "any same-sex experience" category than for the "same-sex partner predominance" category. Over all, women score higher than men on the depression and obsessive compulsivity

Table 3: Dichotomous measures	**MD**				**AD/HD**			
	Female		**Male**		**Female**		**Male**	
	Any same-sex experience (n=9300)	**Same-sex partner predominance (n=8139)**	**Any same-sex experience (n=6219)**	**Same-sex partner predominance (n=5505)**	**Any same-sex experience (n=9411)**	**Same-sex partner predominance (n=8223)**	**Any same-sex experience (n=6275)**	**Same-sex partner predominance (n=5551)**
Prevalence among heterosexuals	16.4%	17.3%	7.5%	8.1%	1.9%	1.8%	2.1%	2.3%
Prevalence non-heterosexuals	27.9%	22.2%	13.6%	11.9%	3.2%	2.7%	4.3%	3.7%
Crude OR	*1.9 (1.6-2.3)*	*1.3 (1.0-1.8)*	*1.9 (1.4-2.7)*	*1.6 (1.0-2.3)*	*1.7 (1.0-2.6)*	1.5 (0.8-3.0)	*2.1 (1.2-3.5)*	1.7 (0.8-3.3)
Adjusted OR 1	*1.9 (1.6-2.3)*	*1.4 (1.1-1.8)*	*1.8 (1.3-2.5)*	1.5 (1.0-2.2)	*1.6 (1.0-2.5)*	1.6 (0.8-3.1)	*2.1 (1.2-3.6)*	1.6 (0.8-3.2)
Adjusted OR 2	*1.8 (1.5-2.2)*	1.3 (1.0-1.7)	*1.5 (1.0-2.1)*	1.1 (0.7-1.7)	1.3 (0.8-2.1)	1.4 (0.7-2.7)	1.5 (0.8-2.7)	1.1 (0.5-2.2)

Adjustment 1: relationship status, age, level of education.
Adjustment 2: relationship status, age, level of education, perceived discrimination, hate crime victimization.
Numbers in italics denote significans at α = 0.05.

scales, but lower on the AD/HD scale.

Table 5 summarizes the results from the regression analysis using GEE. The betas are all non-negative, are stable to the first adjustment (adjusting for possible confounders) and are lowered by the second adjustment (adjusting for the same possible confounders and also for perceived discrimination and hate crime victimization). The betas are significant for AD/HD and depression among females using both definitions of non-heterosexuality, and among men when using the any same-sex experience definition. Only for "any same-sex experience" among females, are the betas for the OCD scale significant. This relative lack of significant results might in part be due to the OCD scale's extreme skewness, which gives it a high standard deviation compared to its actual score. As before, the effect of non-heterosexuality is larger when considering the "any same-sex experience" category than when considering the "same-sex partner predominance" category. In fact, among males, no betas for the "same-sex partner predominance" category are significant, though they still follow the general trends, i.e. relatively stable to adjustment 1 and lowered by adjustment 2.

Table 4: Continuous measures	**CES-D**		**AD/HD**		**OCD**	
Female	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
No same-sex experience (n=8815)	0,73	0,38	0,59	0,38	0,14	0,24
Any same-sex experience (n=739)	0,82	0,38	0,70	0,37	0,18	0,26
Not predominantly same-sex experience (n=7992)	0,73	0,38	0,60	0,37	0,14	0,24
Predominantly same-sex experience (n=332)	0,77	0,38	0,65	0,37	0,16	0,25
Male						
No same-sex experience (n=6007)	0,68	0,36	0,61	0,37	0,11	0,21
Any same-sex experience (n=353)	0,75	0,38	0,67	0,38	0,13	0,25
Not predominantly same-sex experience (n=5372)	0,68	0,36	0,61	0,37	0,11	0,21
Predominantly same-sex experience (n=243)	0,72	0,39	0,64	0,37	0,12	0,24

The result of the paired t-test is presented in *Table 6*. Strikingly, only one significant difference is found, concerning depression among females when using the narrow "same-sex partner predominance" definition of non-heterosexuality (mean difference =-0.08). This means that the depression score is actually *lower* for the non-heterosexual twin than it is for the heterosexual twin. In all other comparisons, no significant increase or decrease in depression, AD/HD or OCD can be found.

Table 5: Regression analysis

		CES-D			AD/HD			OCD		
		β	SE	p	β	SE	p	β	SE	p
Female: Any same-sex experience (n=9554)	**Crude**	*0.08*	0.01	<0.0001	*0.09*	0.14	<0.0001	*0.04*	0.01	<0.0001
	Adjusted 1	*0.08*	0.01	<0.0001	*0.08*	0.01	<0.0001	*0.04*	0.01	0.0002
	Adjusted 2	*0.06*	0.01	<0.0001	*0.07*	0.01	<0.0001	*0.03*	0.01	0.0019
Female: Same-sex partner predominance (n=8324)	**Crude**	*0.04*	0.02	0.0460	0.03	0.02	0.1023	0.02	0.01	0.1755
	Adjusted 1	*0.04*	0.02	0.0355	*0.04*	0.02	0.0258	0.02	0.01	0.1437
	Adjusted 2	0.03	0.02	0.0931	0.03	0.02	0.1055	0.01	0.01	0.2775
Male: Any same-sex experience (n=6360)	**Crude**	*0.07*	0.02	0.0005	*0.05*	0.02	0.0105	0.02	0.01	0.0803
	Adjusted 1	*0.06*	0.02	0.0023	*0.06*	0.02	0.0047	0.02	0.01	0.0857
	Adjusted 2	0.04	0.02	0.0658	0.04	0.02	0.0860	0.01	0.01	0.2795
Male: Same-sex partner predominance (n=5615)	**Crude**	0.04	0.03	0.1009	0.03	0.02	0.1820	0.01	0.02	0.3450
	Adjusted 1	0.03	0.02	0.1842	0.04	0.02	0.1283	0.01	0.02	0.3570
	Adjusted 2	0.00	0.02	0.9590	0.01	0.02	0.7197	0.00	0.02	0.8431

Adjustment 1: relationship status, age, level of education.
Adjustment 2: relationship status, age, level of education, perceived discrimination, hate crime victimization.
Numbers in italics denote significans at α = 0.05.

Table 6: Paired t-test

		Number of pairs	Mean	SE	t	p
Female: Any same-sex experience	**CES-D**	307	0.04	0.03	1.64	0.1024
	AD/HD	299	-0.01	0.02	-0.32	0.7519
	OCD	299	0.03	0.02	1.44	0.1502
Female: Same-sex partner predominance	**CES-D**	*144*	*-0.08*	*0.03*	*-2.48*	*0.0144*
	AD/HD	147	-0.02	0.04	-0.53	0.5942
	OCD	141	0.00	0.02	0.13	0.8984
Male: Any same-sex experience	**CES-D**	102	-0.01	0.05	-0.3	0.7613
	AD/HD	99	-0.01	0.04	-0.33	0.7455
	OCD	102	0.01	0.03	0.4	0.6896
Male: Same-sex partner predominance	**CES-D**	73	0.00	0.06	-0.06	0.9541
	AD/HD	72	0.01	0.05	0.27	0.7915
	OCD	73	-0.01	0.03	-0.25	0.8003

Self-reported illness

In *Tables 7-10* the results of the logistic regression using GEE on the answers to the "have you ever suffered from…" questions are presented. While these answers have not been validated and represent perceived illnesses rather than actual diagnoses, they show a striking concordance with the previous analysis. For almost every disorder the prevalence is clearly higher among the non-heterosexual group than among the heterosexual group, though this is a bit unstable for some rare disorders like schizophrenia and autism. For many of the disorders, such as depression, bipolar disorder and anxiety disorders, the results are clearly significant in every analysis. In almost every case where the OR is over one, it is slightly lowered by the first adjustment and then lowered again by the second adjustment; though there is some gender difference in this. Among females, using the predominately same-sex partner definition, the odds ratios are increased by the first adjustment rather than lowered, due to this groups increased frequency of relationships. The effect of the second adjustment is most remarkable among men, using the same-sex partner predominance definition, leaving significantly increased odds only for depression and eating disorders. Consistently, the odds ratios are higher when using the "any same-sex experience" definition of non-heterosexuality compared to using the "same-sex partner predominance" definition.

Table 7: Female	**No same-sex Experience (n=7829)[a]**	**Any same-sex Experience (n=650)[a]**	**Crude OR**	**95% CI**	**Adjusted OR 1**	**95% CI**	**Adjusted OR 2**	**95% CI**
Depression	23.4%	38.4%	*2.0*	*1.7-2.3*	*1.9*	*1.6-2.3*	*1.8*	*1.5-2.1*
Bipolar disorder	0.5%	1.5%	*3.5*	*1.7-7.1*	*3.3*	*1.7-6.7*	*2.7*	*1.3-5.6*
Panic/anxiety	13.7%	26.1%	*2.1*	*1.8-2.5*	*2.1*	*1.8-2.5*	*2.0*	*1.6-2.4*
Phobia[a]	10.1%	14.9%	*1.5*	*1.2-2.0*	*1.4*	*1.1-1.8*	*1.3*	*1.0-1.7*
Drug or alcohol abuse	1.4%	8.7%	*6.4*	*4.5-9.0*	*6.5*	*4.6-9.3*	*5.9*	*4.1-8.4*
Eating disorders	8.3%	15.0%	*1.9*	*1.5-2.4*	*1.8*	*1.5-2.3*	*1.7*	*1.3-2.1*
OCD	3.5%	8.4%	*2.3*	*1.6-3.2*	*2.2*	*1.6-3.0*	*1.9*	*1.4-2.7*
AD/HD	0.2%	0.3%	2.0	0.4-9.0	2.0	0.5-8.9	1.7	
Tourette	0.2%	0.6%	2.8	1.0-8.5	2.7	0.9-8.1	2.0	0.6-7.3
Schizophrenia	0.1%	0.0%						
ASD	0.1%	0.2%	2.4	0.3-20.7	2.5	0.3-21.2	2.4	

a) For Phobia, n = 6833 & 542, respectively.
Adjustment 1: relationship status, age, level of education.
Adjustment 2: relationship status, age, level of education, perceived discrimination, hate crime victimization
Numbers in italics denote significans at α = 0.05.

Table 8: Male	No same-sex experience (n=5383)[a]	Any same-sex experience (n=315)[a]	Crude OR (95% CI)	Adjusted OR 1	95% CI	Adjusted OR 2	95% CI
Depression	14.8%	26.8%	*2.1 (1.6-2.7)*	*2.0*	*1.5-2.6*	*1.7*	*1.3-2.2*
Bipolar disorder	0.5%	2.2%	*4.9 (2.1-11.3)*	*4.3*	*1.7-10.6*	2.5	0.9-6.5
Panic/anxiety	8.3%	16.5%	*2.2 (1.6-3.0)*	*2.1*	*1.5-2.8*	*1.8*	*1.3-2.5*
Phobia[a]	4.6%	8.9%	*1.9 (1.2-3.1)*	*2.0*	*1.3-3.2*	1.5	0.9-2.4
Drug or alcohol abuse	3.0%	7.6%	*2.7 (1.8-4.2)*	*2.6*	*1.7-4.1*	*1.9*	*1.2-3.1*
Eating Disorders	0.6%	3.5%	*6.5 (3.2-13.0)*	*6.1*	*3.0-12.2*	*3.8*	*1.8-8.1*
OCD	2.8%	3.2%	1.2 (0.6-2.2)	1.1	0.6-2.2	0.9	0.4-1.7
AD/HD	0.3%	1.0%	3.1 (1.0-12.0)	3.1	0.8-11.2	1.8	0.3-9.8
Tourette	0.4%	0.6%	1.5 (0.4-6.4)	1.4	0.3-5.8	1.0	0.2-4.2
Schizophrenia	0.2%	1.0%	*6.5 (1.7-24.5)*	*5.8*	*1.4-23.8*	*5.3*	*1.4-20.3*
ASD	0.2%	0.3%	2.1 (0.3-17.2)	2.1	0.2-17.6	1.3	0.0-35.0

a) For Phobia, n = 4615 & 270, respectively.
Adjustment 1: relationship status, age, level of education.
Adjustment 2: relationship status, age, level of education, perceived discrimination, hate crime victimization.
Numbers in italics denote significans at α = 0.05.

Table 9: Female	Not same-sex partner predominance (n=7082)[a]	Predominately same-sex partners (n=295)[a]	Crude OR	95% CI	Adjusted OR 1	95% CI	Adjusted OR 2	95% CI
Depression	23.8%	35.1%	*1.7*	*1.3-2.1*	*1.7*	*1.3-2.2*	*1.6*	*1.2-2.0*
Bipolar disorder	0.5%	2.0%	*4.2*	*1.7-10.0*	*4.4*	*1.8-10.4*	*3.6*	*1.5-8.9*
Panic/anxiety	14.2%	20.7%	*1.5*	*1.1-2.0*	*1.5*	*1.1-2.0*	*1.4*	*1.0-1.8*
Phobia[a]	10.5%	13.0%	1.3	0.9-1.8	1.3	0.9-1.8	1.2	0.8-1.7
Drug or alcohol abuse	1.8%	4.4%	*2.5*	*1.4-4.6*	*2.7*	*1.5-4.9*	*2.3*	*1.2-4.7*
Eating disorders	8.7%	9.5%	1.1	0.7-1.6	1.1	0.7-1.6	1.0	0.6-1.4
OCD	3.8%	7.2%	1.6	0.9-2.8	*1.7*	*1.0-2.9*	1.5	0.9-2.5
AD/HD	0.2%	0.3%	2.2	0.3-17.0	2.2	0.3-16.8	1.8	
Tourette	0.2%	0.7%	3.0	0.7-13.2	3.2	0.7-14.6	2.5	0.5-12.8
Schizophrenia	0.0%	0.0%						
ASD	0.1%	0.0%						

a) For Phobia, n = 6213 & 254, respectively.
Adjustment 1: relationship status, age, level of education.
Adjustment 2: relationship status, age, level of education, perceived discrimination, hate crime victimization.
Numbers in italics denote significans at α = 0.05.

Table 10: Male	Not same-sex partner predominance (n=4815)[a]	Predominately same-sex partners (n=221)[a]	Crude OR	95% CI	Adjusted OR 1	95% CI	Adjusted 2 OR	95% CI
Depression	15.4%	27.7%	*2.1*	*1.6-2.9*	*2.1*	*1.5-2.8*	*1.7*	*1.2-2.3*
Bipolar disorder	0.5%	1.8%	*3.7*	*1.3-10.7*	*3.2*	*1.1-9.0*	1.5	0.5-*4.2*
Panic/anxiety	8.7%	14.0%	*1.7*	*1.2-2.5*	*1.6*	*1.1-2.4*	1.4	0.9-2.1
Phobia[a]	4.7%	7.3%	1.6	0.9-2.8	1.6	0.9-2.8	1.0	0.5-2.0
Drug or alcohol abuse	3.2%	4.1%	1.3	0.7-2.6	1.2	0.6-2.4	0.7	0.4-1.5
Eating disorders	0.6%	3.6%	*5.8*	*2.6-12.8*	*5.3*	*2.5-11.6*	*2.8*	*1.1-7.1*
OCD	2.9%	2.3%	0.8	0.3-1.9	0.8	0.3-1.9	0.5	0.2-1.3
AD/HD	0.3%	0.5%	1.6	0.2-12.0	1.3	0.2-10.1	0.5	0.1-3.9
Tourette	0.4%	0.5%	1.1	0.1-8.2	1.0	0.1-7.5	0.6	0.1-3.6
Schizophrenia	0.2%	0.0%						
ASD	0.2%	0.0%						

a) For Phobia, n = 4201 & 193, respectively.
Adjustment 1: relationship status, age, level of education.
Adjustment 2: relationship status, age, level of education, perceived discrimination, hate crime victimization.
Numbers in italics denote significans at α = 0.05.

Discussion

Increased psychiatric morbidity

In agreement with earlier studies (e.g. [13]) we find increased rates of depression among non-heterosexual individuals compared to heterosexual individuals. People who have ever had sex with a person of the same gender are at an almost doubled risk to have ever had an episode of major depression. They also have significantly increased scores of current depression, compared to people with no same-sex sexual experience. Though many different measures of mental illnesses have been associated with non-heterosexuality; this is the first study to include AD/HD. We find that men who have ever had sex with another man is at a doubled risk to have developed AD/HD, which is slightly higher than the increased risk for AD/HD among women who have ever had sex with another woman compared to women who have not. This increased risk is also evident when looking at the scores continuously.

Though the self-reported illnesses lack validation, and at least the prevalence of depression seems a bit high, the odds ratios for depression and AD/HD are comparable to the odds ratios from the results using the diagnostic sections of STAGE. The increased level of anxiety disorders among non-heterosexuals mirror earlier findings [13], and so does the gender specific increases; of problems with drugs and alcohol among non-heterosexual females [23] and of eating disorders among non-heterosexual men [27].It is interesting then to note the previously unreported increased rate of obsessive compulsive disorder among non-heterosexual compared to heterosexual females and, conspicuous by its absence, the *lack* of an increased risk for OCD among non-heterosexual men. This result is supported by the analysis of the obsessive compulsive symptom count, which only found significant results for “any same-sex experience” females.

The results for some of the self-reported disorders should be treated with caution. Very few people reported to have suffered from AD/HD, Tourette syndrome, autism spectrum disorders or schizophrenia. While schizophrenia and autism are indeed rare disorders, probably even rarer among respondents to voluntary questionnaires, adults suffering from Tourettes and AD/HD might simply not be aware of their disorder, or the diagnostic name for it. This means that the analysis rely on very few people, reflected in wide confidence intervals, but this also makes findings difficult to interpret. Though the crude odds ratios for autism spectrum disorders are about 2 (not significant) for both men and women using the “any same-sex experience” definition, in fact each of these results are based on a single

non-heterosexual man respectively woman reporting to have suffered from ASD. Among men who reported any same-sex experience, three individuals reported having suffered from schizophrenia, resulting in a significant finding (OR = 6.5, CI = 1.7-24.5). It is possible that in the individual case, the illness might have affected the person's propensity for non-heterosexual behavior rather than the other way around.

The difference between occasional and predominant same-sex sexual partners

Consistently, for every disorder studied, we find that using the wide rather than the narrow definition of non-heterosexuality gives higher odds ratios and higher βs. In many cases, e.g. eating disorders among women and drug or alcohol problems among men, the results suggest that there is no real difference among heterosexual and non-heterosexual when using the narrow, equal number or more same-sex sexual partners, definition of non-heterosexuality. At the same time, in both these examples, we see odds ratios significantly higher than one when using the wide definition, any lifetime same-sex sexual experience. It appears that people with some homosexual experience, but with predominately heterosexual partners, are at a particular risk for developing mental disorders. Though it is tempting to put this in connection to research suggesting that bisexuals are at an increased risk for some disorders [21], it bears reminding that we have used purely behavioral definitions of sexual orientation. Since we have no measures of self-identification or self-perceived sexual attraction, we cannot confidently talk about people as homosexual, bisexual or even heterosexual. Perhaps this increased mental illness is indeed somehow connected to being bisexual; maybe reflecting a lack of support from both the gay community's and mainstream heterosexual society's social networks. But then again, maybe those who consider themselves heterosexual and, for various reasons, are at an increased risk for mental disorders, are also more prone to experiment sexually.

Minority stress

In all analyses the odds ratios and betas were lowered by the second adjustment, i.e. checking for perceived discrimination and hate crime victimization. While correlation is never proof of causality, a reasonable interpretation of this is that the increased stress of discrimination and victimization leads to increased mental illness among non-heterosexual individuals. The perceived discrimination and hate

crime victimization can be thought to reflect some mixture of objective and subjective stress. While it seems probable that it represents actual victimization, it also seems probable that it in part represents a person's propensity for perceiving situations as discriminatory and victimizing, and subsequently remembering such situations. Though it might seem likely that non-heterosexual individuals would be extra perceptive to discriminatory behavior, some researchers suggests that members of minority groups actually underestimate the degree of discrimination they are subjected to, in order to avoid false alarms that might otherwise put a strain on social relations [13]. The self-reported perceived discrimination and victimization does not cover all aspects on which "minority stress" might act, we have no direct measure on for example internalized homophobia. For these reasons it could be argued that "minority stress" might account for even more of the increased mental illness than these results indicate. While this seems likely, we would do well to remember that the causality is not really proven. The results could also indicate that homosexual men with eating disorders and phobias attract more discrimination and hate crime victimization than other homosexual men do.

Familial factors

While adjusting for victimization did lower the odds ratios and betas, there were many cases where the increased risks were still significant. Even among the results that were not significant after the second adjustment, almost all odds ratios were higher than one, and all betas were non-negative. In contrast, when looking within twin pairs using the paired t-test and not even compensating for perceived discrimination or victimization, no significant betas could be found. The sole exception was for female twin pairs discordant with respect to "same-sex partner predominance" where the beta was significant at -0.08, meaning that the non-heterosexual twin was, on average, less depressed than the heterosexual one. Apparently even if one twin is non-heterosexual and subject to "minority stress", it does not suffer from more mental illness than its heterosexual twin does. This is truly remarkable compared to the results from the other analysis and indicates that there is some familial factor influencing the connection between homosexuality and mental illness. Whether this familial factor is genetic, an effect of unmeasured socioeconomic confounders or an effect of the shared family environment, we cannot say.

Only one previous study of the connection between sexual orientation and mental health analyzed differences within twin pairs, a 1999 co-twin control study

performed on 103 male twin-pairs from the Vietnam Era Twin Registry (VET) [20]. The registry consists of twin pairs where both brothers served in the US military between 1965 and 1975, in Vietnam or elsewhere. In the conditional logistic regression, significant odds ratios were found for “any adult same-gender partner”, for the four analyzed measures of suicidality. While we did not measure suicidality per se, it seems reasonable that this should be somewhat correlated to an increased level of depression and distress. These results might then seem to contradict the results from the present study, but there are a few interesting points to make.

A possible interpretation could be that the effect of “minority stress” is lower for civilians living in present day Sweden than it has been for these American war veterans. After all, homosexuals were still supposedly banned from US military service during this time, and unable to be open with their sexual orientation in such a hetero-normative atmosphere, they might have been more vulnerable to the extreme stress of war. The effect of familial factors influencing this connection might be weak compared to this increased stress. It is also interesting to compare the prevalence of suicidal symptoms between the heterosexuals with non-heterosexual twin brothers and the heterosexuals with heterosexual twin brothers (Table 1 in [20]). For all four measures of suicidality the former have higher prevalence than the latter, though this is significant at the 95% level only for “suicidal ideation”. We suggest then, that the familial factors evident in the present study can also be glimpsed through this earlier co-twin control study, where it was overshadowed by the effects of “minority stress”.

Caveats

This study is subject to several limitations. First, we have used a purely behavioral definition of sexual orientation; to more fully capture the complexity of human sexuality it would have been interesting to compare these results with definitions based on self-identification and sexual attractions. It would have been particularly interesting to analyze the people reporting any same-sex sexual partner, but not fulfilling the criteria for same-sex partner predominance, and see how their self-image correlate to the increased mental illness found in this group.

Second, we used crude measures of minority stress. In only asking about particular stressful occasions such as discrimination and victimization we get no measure of constant stress such as internalized homophobia, or feelings of “not fitting in”. This might lead to an underestimation of the effects of minority stress.

We also lack information on HIV status, but since Sweden has relatively low prevalence of HIV/AIDS [43] this should not be a concern.

Third, the "have you ever suffered from…" questions are not validated and it would be preferable to replace them with classifications based on the diagnostic sections, the way we did with depression and AD/HD. While diagnostic information is available for most of the disorders, many of the necessary algorithms are being written in collaboration with American colleagues. Unfortunately, they have not been finished in time to be incorporated in this study.

Conclusions

In conclusion then, this study opens up new areas of research. It seems clear that there is indeed an increase of mental illness among non-heterosexual individuals compared to heterosexuals. It also seems highly likely that this is, at least in part, mediated by discrimination and minority stress. However, we also find that the increased mental illness can be explained by familial factors, without even checking for discrimination and victimization. This reminds us that we understand very little about what really influences the development of sexual orientation and mental disorders. More research is needed to identify the familial factor. Is it genetic or due to unmeasured socioeconomic factors? Is it caused by the similar pre-natal environment of the twins, or is it rather an effect of the similar upbringing? More research is also needed to understand the specifics of the increased risks. Why are the risks for substance abuse and eating disorders so sex-atypically increased? And why are non-heterosexual women at an increased risk for OCD, while there is no such increase for non-heterosexual men?

Although this research raises many new questions, it does appear that the increased risks are largely mediated by increased discrimination and hate crime victimization. Perhaps the most important conclusion of this research is then that even in Sweden, a relatively liberal country, efforts aimed towards changing attitudes and a growing acceptance of homosexuality is warranted, and will lead to less illness and lowered health care costs. In combating prejudice against non-heterosexuality; we are literally creating a saner world.

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I also read some books concerned with basic concepts:

Ahlbom, A. et al. Grunderna i Epidemiologi, tredje upplagan. ISBN: 91-44-03712-0. *Studentlitteratur.* 2006.

Blom, G. Sannolikhetsteori och statistikteori med tillämpningar. *Studentlitteratur*. ISBN: 91-44-03594-2. 1989.

Plomin, R. et al. Behavioral Genetics, 4th Ed. ISBN: 0-7167-5159-3. *Worth Publishers,* New York. 2001.

Appendix 1: SAS macros

```
%macro printORs;  * prints Odds Ratios, used by the macro dicgee;;
  data one;
    set geeest;
    if parm='INTERCEPT' or parm='SCALE' then delete;
    OR=exp(estimate);
    Lower=exp(estimate-1.96*stderr);
    Upper=exp(estimate+1.96*stderr);
  run;
  title 'GEE';
  proc print data=one;
    var parm level1 estimate z probz OR Lower Upper;
  label OR='Odds ratio';
  run;
%mend printORs;

%macro twintest(infile, outcome); /*Paired t-test on mz+dz twins*/
data twina;
set &infile;
if tvab=1 and zyg<=3;
run;

data twinb;
set &infile;
if tvab=2 and zyg<=3;
run;

data twinat;
set twina (rename=(&outcome=toutcome anyss=tanyss
more_or_equal_ss=tmore_or_equal_ss));
label toutcome='Twin' &outcome;
label tanyss='Twin any same sex experience';
label tmore_or_equal_ss='Twin same sex predominance';
keep pairnr toutcome tanyss tmore_or_equal_ss;
run;

proc sort data=twinat;
by pairnr;
run;

data twinbt;
set twinb (rename=(&outcome=toutcome anyss=tanyss
more_or_equal_ss=tmore_or_equal_ss));
label toutcome='Twin' &outcome;
label tanyss='Twin any same sex experience';
label tmore_or_equal_ss='Twin same sex predominance';
keep pairnr toutcome tanyss tmore_or_equal_ss;
run;

proc sort data=twinbt;
by pairnr;
run;

data twinc;
merge twina (in=in1) twinbt (in=in2);
by pairnr;
if in1=1 and in2=1;
run;
```

```
data twind;
merge twinb(in=inf) twinat (in=inet);
by pairnr;
if inf=1 and inet=1;
run;

proc sort data=twind;
by twinnr;
run;

proc sort data=twinc;
by twinnr;
run;

data twine;
merge twinc twind;
by twinnr;
run;

data cotwinanydiff;
set twine;
if anyss = 1 and tanyss = 0;
anydisdiff = &outcome-toutcome;
run;

data cotwinpredomdiff;
set twine;
if more_or_equal_ss=1 and tmore_or_equal_ss = 0;
predomdisdiff = &outcome-toutcome;
run;

proc means n mean stderr t prt data=cotwinanydiff (where=(sex=1));
title 'Paired t-test for mz+dz twins; Male' &outcome;
var anydisdiff;
run;

proc means n mean stderr t prt data=cotwinanydiff (where=(sex=2));
title 'Paired t-test for mz+dz twins; Female' &outcome;
var anydisdiff;
run;

proc means n mean stderr t prt data=cotwinpredomdiff (where=(sex=1));
title 'Paired t-test for mz+dz twins; Male; Predominance' &outcome;
var predomdisdiff;
run;

proc means n mean stderr t prt data=cotwinpredomdiff (where=(sex=2));
title 'Paired t-test for mz+dz twins; Female; Predominance' &outcome;
var predomdisdiff;
run;
%mend;




%macro contgee(infile, outcome, samesex); /*GEE on continous outcomes*/
           proc genmod data=&infile(where=((&outcome ^=.) and (&samesex
^=.) and (sex=1)));
                      title 'Male, Cont GEE' &outcome &samesex;
```

```
                        class pairnr x_edulevel(desc) relstatus(descending)
&samesex(descending);
                        model &outcome = inputdate_age &samesex relstatus
x_edulevel/ dist=nor link=id type3;
                        repeated subject=pairnr / type=exch corrw;
            run;

            proc genmod data=&infile(where=((&outcome ^=.) and (&samesex
^=.) and (sex=2)));
                        title 'Female, Cont GEE' &outcome &samesex;
                        class pairnr relstatus(descending)
&samesex(descending) x_edulevel(desc);
                        model &outcome = inputdate_age &samesex relstatus
x_edulevel/ dist=nor link=id type3;
                        repeated subject=pairnr / type=exch corrw;
            run;
%mend;



%macro fullcontgee(infile, outcome, samesex); /*GEE on continous outcomes*/
            proc genmod data=&infile(where=((&outcome ^=.) and (&samesex
^=.) and (sex=1)));
                        title 'Male, Full Cont GEE' &outcome &samesex;
                        class pairnr x_edulevel(desc) relstatus(descending)
&samesex(descending) discrim_1(desc) hatecrim_1(desc);
                        model &outcome = inputdate_age &samesex relstatus
discrim_1 hatecrim_1 x_edulevel/ dist=nor link=id type3;
                        repeated subject=pairnr / type=exch corrw;
            run;

            proc genmod data=&infile(where=((&outcome ^=.) and (&samesex
^=.) and (sex=2)));
                        title 'Female, Full Cont GEE' &outcome &samesex;
                        class pairnr relstatus(descending)
&samesex(descending) discrim_1(desc) hatecrim_1(desc) x_edulevel(desc);
                        model &outcome = inputdate_age &samesex relstatus
discrim_1 hatecrim_1 x_edulevel/ dist=nor link=id type3;
                        repeated subject=pairnr / type=exch corrw;
            run;
%mend;



%macro crudecontgee(infile, outcome, samesex); /*GEE on continous outcomes,
without covariates*/
            proc genmod data=&infile(where=((&outcome ^=.) and (&samesex
^=.) and (sex=1)));
                        title 'Male, Crude cont GEE' &outcome &samesex;
                        class pairnr &samesex(descending);
                        model &outcome = &samesex / dist=nor link=id type3;
                        repeated subject=pairnr / type=exch corrw;
            run;

            proc genmod data=&infile(where=((&outcome ^=.) and (&samesex
^=.) and (sex=2)));
                        title 'Female, Crude cont GEE' &outcome &samesex;
                        class pairnr &samesex(descending);
                        model &outcome = &samesex / dist=nor link=id type3;
                        repeated subject=pairnr / type=exch corrw;
            run;
```

```
%mend;



%macro dicgee(infile, outcome, samesex); /*GEE on dichotomous outcomes*/
           proc genmod data=&infile(where=((&outcome ^=.) and (&samesex
^=.) and (sex=1))) descending;
                       title 'Male, Dic GEE' &outcome &samesex;
                       class pairnr relstatus(descending)
&samesex(descending)  x_edulevel(desc);
                       model &outcome = inputdate_age &samesex relstatus
x_edulevel / dist=bin link=logit type3;
                       repeated subject=pairnr / type=exch corrw;
                       ods output GEEEmpPEst=GEEEst;
           run;
           %printORs
           ods output close;
           proc genmod data=&infile(where=((&outcome ^=.) and (&samesex
^=.) and (sex=2))) descending;
                       title 'Female, Dic GEE'&outcome &samesex;
                       class pairnr relstatus(descending)
&samesex(descending) x_edulevel(desc);
                       model &outcome = inputdate_age &samesex relstatus
x_edulevel / dist=bin link=logit type3;
                       repeated subject=pairnr / type=exch corrw;
                       ods output GEEEmpPEst=GEEEst;
           run;
           %printORs
           ods output close;
%mend;



%macro fulldicgee(infile, outcome, samesex); /*GEE on dichotomous
outcomes*/
           proc genmod data=&infile(where=((&outcome ^=.) and (&samesex
^=.) and (sex=1))) descending;
                       title 'Male, Full Dic GEE ' &outcome &samesex;
                       class pairnr relstatus(descending)
&samesex(descending) discrim_1(desc) hatecrim_1(desc) x_edulevel(desc);
                       model &outcome = inputdate_age &samesex relstatus
discrim_1 hatecrim_1 x_edulevel / dist=bin link=logit type3;
                       repeated subject=pairnr / type=exch corrw;
                       ods output GEEEmpPEst=GEEEst;
           run;
           %printORs
           ods output close;
           proc genmod data=&infile(where=((&outcome ^=.) and (&samesex
^=.) and (sex=2))) descending;
                       title 'Female, Full Dic GEE '&outcome &samesex;
                       class pairnr relstatus(descending)
&samesex(descending) discrim_1(desc) hatecrim_1(desc) x_edulevel(desc);
                       model &outcome = inputdate_age &samesex relstatus
discrim_1 hatecrim_1 x_edulevel / dist=bin link=logit type3;
                       repeated subject=pairnr / type=exch corrw;
                       ods output GEEEmpPEst=GEEEst;
           run;
           %printORs
           ods output close;
%mend;
```

```
%macro crudedicgee(infile, outcome, samesex); /*GEE on dichotomous
outcomes, without covariates*/
          proc genmod data=&infile(where=((&outcome ^=.) and (&samesex
^=.) and (sex=1))) descending;
                    title 'Male, crude dic GEE' &outcome &samesex;
                    class pairnr &samesex(descending);
                    model &outcome = &samesex / dist=bin link=logit
type3;
                    repeated subject=pairnr / type=exch corrw;
                    ods output GEEEmpPEst=GEEEst;
          run;
          %printORs
          ods output close;
          proc genmod data=&infile(where=((&outcome ^=.) and (&samesex
^=.) and (sex=2))) descending;
                    title 'Female, crude dic GEE'&outcome &samesex;
                    class pairnr &samesex(descending);
                    model &outcome = &samesex / dist=bin link=logit
type3;
                    repeated subject=pairnr / type=exch corrw;
                    ods output GEEEmpPEst=GEEEst;
          run;
          %printORs
          ods output close;
%mend;



%macro twincontrol (infile, outcome, samesex); /*Conditional logistic
regression on MZ+DZ, MZ twins*/
data disc_pair;
          set &infile;                    /* Creating a dataset with same-
sex discordant co-twins */
          if &outcome ^=.;
          if &samesex ^=.;
          if (zyg=1 | zyg=2 | zyg=3);
run;
proc sql;
          create table cotwin as
          select a.*
          from disc_pair as a, disc_pair as b
          where a.pairnr=b.pairnr
          and a.&samesex ^= b.&samesex
          and a.sex=b.sex;
quit;
proc sort data=cotwin;
          by pairnr;
run;

proc logistic data=cotwin descending;                /* Conditional
logistic regression with both MZ & DZ */
          where(sex=1);
          strata pairnr;
          model &outcome = &samesex;
          title 'Co-twin control MZ & DZ: Male';
run;
```

```
proc logistic data=cotwin descending;                /* Conditional
logistic regression with both MZ & DZ */
          where(sex=2);
          strata pairnr;
          model &outcome = &samesex;
          title 'Co-twin control MZ & DZ: Female';
run;
data cotmz;
          set cotwin(where=(zyg=1));
proc sort;
          by pairnr;
run;
proc logistic data=cotmz descending;       /* Conditional logistic
regression with MZ only */
          where(sex=1);
          strata pairnr;
          model &outcome = &samesex;
          title 'Co-twin control MZ only: Male';
run;
proc logistic data=cotmz descending;       /* Conditional logistic
regression with MZ only */
          where(sex=2);
          strata pairnr;
          model &outcome = &samesex;
          title 'Co-twin control MZ only: Female';
run;
title;

/* Delete intermediate datasets */
proc datasets; delete disc_pair cotwin cotmz ; run;
quit;
%mend;
```