studies consisted of clinically referred samples of children, which was not the case for the earlier studies. For example, in the study by Green (1987) the sample of feminine boys was recruited through advertisement.

Secondly, and in line with the intensity explanation, there are possible cultural differences in referral: As described earlier, the sex ratios of child referrals in Canada are historically in greater favour of boys than girls as compared to the Netherlands. This may indicate that femininity in boys is experienced as more problematic in Canada –resulting in more referrals of boys with less extreme GD than in the Netherlands. As a result, the persistence rates are higher in the Netherlands compared to Canada.

Thirdly, we can consider the time of follow-up: As can be seen in Table 1, the time of follow-up differed across the studies and one could hypothesize that the studies with a later follow-up age (of older adolescents or adults) and those having a longer follow-up time, would report higher persistence rates than the studies where the follow-up took place at a younger age (i.e. shorter follow-up time). This trend is however not observed over the reported studies. To test this hypothesis, Steensma & Cohen-Kettenis (2015) recently published a report on the first 150 childhood cases from Amsterdam, the Netherlands, and checked whether a longer follow-up period would result in higher persistence rates. The children were at the time of first assessment – between 5 to 12 years old and between 19 to 38 years of age at the time of follow-up. Out of the 150 cases, 40 re-entered the clinic during adolescence (12–18 years of age) and turned out to be persisters (26.7%). However, after checking the files of the adult clinic (which sees nearly all adults with gender dysphoria in the Netherlands), it appeared that five individuals applied for treatment after the age of 18, raising the persistence rate to 30% and showing the importance of long-term follow-ups. Based on this information, it seems reasonable to conclude that the persistence of GD may well be higher than 15%. However, desistence of GD still seems to be the case in the majority of children with GD.

Two other clinically relevant questions are (1) whether we know anything with regard to the factors that are associated with the persistence or desistence of childhood GD and (2) how the process of persistence or desistence is experienced.

As to the factors associated with the persistence of GD, knowledge is still limited but fortunately slowly increasing. A central finding from all quantitative studies focusing on the topic is that the persistence of GD is most closely linked to the intensity of the GD in childhood and the amount of reported cross-gendered behaviour; in other words the more intense GD is in childhood, and the more cross-gendered behaviour is reported by parents or through self-report, the higher the chance that the GD persists (Drummond et al., 2008; Singh, 2012; Steensma, McGuire, Kreukels, Beekman, & Cohen-Kettenis, 2013; Wallien & Cohen-Kettenis, 2008). In addition to this, several other factors are linked to persistence of GD: For example, Steensma et al. (2013) and Wallien & Cohen-Kettenis (2008) showed that the persistence rate is generally higher in natal girls than in natal boys; And Steensma et al. (2013) and Singh (2012) found that the assessment age in childhood was higher in children where the GD persisted than for desisters; Further, Singh (2012) reported a higher social class in the parents of desisters compared to the parents of persisters.

In addition, Steensma et al. (2013) found that a social transition in childhood, especially in natal boys, and verbal identification with the desired/experienced gender was predictive for the persistence of GD. Interestingly, the identification finding was reported in an earlier qualitative study by Steensma, Biemond, de Boer & Cohen-Kettenis (2011) who observed differences in reported experiences of GD between persisters and desisters who were interviewed. For example, the persisters explicitly indicated that they felt they *were* the 'other' sex and the desisters indicated that they only *wished* they were the 'other' sex. The primary aim of the Steensma et al. (2011) study was to get a better understanding of the processes that contribute to the persistence and desistence of childhood GD. By interviewing adolescents (14 persisters, 11 desisters) who all fulfilled the DSM-IV or DSM-IV-TR criteria of a gender identity diagnosis in childhood (APA, 1994, 2000), it became clear that the period between 10 and 13 years was considered crucial. Both persisters and desisters stated that the changes in their social environment, the anticipated and actual feminization or masculinization of their bodies, and the first experiences of falling in love and sexual attraction in this period, contributed to an increase (in the persisters) or decrease (in the desisters) of their gender related interests, behaviours, and feelings of gender discomfort.

Treatment and counselling of children with GD

Over the last decade, the care for prepubescent children with GD has been rapidly changing and there is a growing number of specialized gender clinics for young people (Hsieh & Leininger, 2014; Khatchadourian, Ahmed, & Metzger, 2014; Riittakerttu, Sumia, Työläjärvi, & Lindberg, 2015). Best clinical practice in gender referred children is still controversial and raises debates among dedicated professionals. General agreement does, however, exist that the care for children with

GD should be focused on reducing the child's distress related to their GD; on help with other psychological difficulties; and optimizing psychological adjustment and wellbeing (e.g. Byne et al., 2012; Coleman et al., 2011). As for the counselling of the gender dysphoric feelings in children with GD; empirical treatment models do not exist and general consensus between clinicians is not always easy to obtain (Byne et al., 2012). In the current professional literature, three treatment models for the care of gender variant children can be distinguished (e.g. Byne et al., 2012; Drescher, 2013) and it is these to which we now turn.

The first approach focuses on working with the child and caregivers to lessen cross-gender behaviour and identification, to persuade the child that the 'right gender' is the one assigned at birth (Giordano, 2012), to decrease the likelihood that GD will persist into adolescence, and prevent adult transsexualism. Critics of this approach have linked it to 'reparative therapy', a term more commonly used to describe efforts to change same sex attraction to heterosexuality in gay adults or 'pre-homosexual' children (Drescher, 2013). In the past, such behavioural and psychodynamic therapies to lessen the GD have been largely used in children with GD with overall unsatisfactory results (Byne et al., 2012; Möller, Schreier, Li, & Romer, 2009). Instead, children often seem to become distressed if their preferences and/or behaviours are blocked (Richardson, 1999). At present, interventions aimed to lessen GD are referred to as unethical by the World Professional Association for Transgendered Health (WPATH: Coleman et al., 2011) and many other international professional organizations. The American Academy of Child & Adolescent Psychiatry, for example, has explicitly formulated their position against any psychological treatment aimed to change gender nonconforming behaviours (Adelson, 2012).

The second approach is focused on dealing with the potential social risks for the child (Byne et al., 2012). Because its aim is to allow the progress of the GD in the child to unfold in a natural way, it is often referred to as 'watchful waiting' (Drescher, 2013). Counselling based on this approach may include interventions that focus on the co-existing problems of the child and/or the family; helping parents and the child to bear the uncertainty of the child's psychosexual outcome; and providing psycho-education to help the child and the family to make balanced decisions regarding topics such as the child's coming out, early social transitioning, and/or how to handle peer rejection or social ostracism. In practice, the child and parents are encouraged to find a balance between an accepting and supportive attitude toward GD, while at the same time protecting the child against any negative reactions and remaining realistic about the chance that GD feelings may desist in the future. Parents are encouraged to provide enough space for their child to explore their gender dysphoric feelings, while at the same time keeping all future outcomes open (e.g., de Vries & Cohen-Kettenis, 2012; Di Ceglie, 1998, 2014).

The third approach is focused on affirming the child's (trans)gender identification and helps the child to build a positive self-identity and gender resilience. In particular, the child is supported in transitioning to the desired/experienced gender role. The rationale for supporting social transition before puberty is that children can revert to their originally assigned gender if necessary since the transition is solely at a social level and without medical intervention (e.g. Byne et al., 2012; Drescher, 2013; Hill, Menvielle, Sica, & Johnson, 2010). Critics of this approach believe that supporting gender transition in childhood may indeed be relieving for children with GD but question the effect on future development. The debate thereby focuses on whether a transition may increase the likelihood of persistence because, for example, a child may 'forget' how to live in the original gender role and therefore will no longer be able to feel the desire to change back; or that transitioned children may repress doubts about the transition out of fear that they have to go through the process of making their desire to socially (re)transition public for a second time (Steensma, 2013). The fact that transitioning for a second time can be difficult was indeed shown in the qualitative study by Steensma et al. (2011) where children who transitioned early in childhood reported a struggle with changing back to their original gender role when their feelings desisted, with the fear of being teased or excluded by their peers reported as the main reason for this.

Unfortunately, empirical answers about the best way to counsel children with GD and their caregivers are currently not available. The WPATH have therefore formulated a balanced position in their Standards of Care (Coleman et al., 2011), where clinicians are encouraged to help families by providing information about what is known about the development of children with GD and to help them to make decisions where the potential benefits and challenges of particular choices are weighted.

Conclusion

According to the DSM-5 diagnostic criteria for gender dysphoria, children with GD experience clinically significant distress because of the incongruence between their assigned gender at birth and experienced gender (APA, 2013). The clinical presentation of children who present with gender identity issues is characterized by gender-nonconformity and a vulnerability to having psychological problems – primarily of an internalized nature (e.g. Cohen-Kettenis et al., 2003; Steensma et al., 2014), and an increased likelihood of ASD symptomatology (de Vries et al., 2010; VanderLaan et al., 2015). The extent and intensity of all three characteristics can be variable.

When considering the development of children with GD; studies show that gender dysphoric feelings eventually desist for the majority of children with GD, and that their psychosexual outcome is strongly associated with a lesbian, gay, or bisexual sexuality which does not require any medical intervention, instead of an outcome where medical intervention is required (e.g. Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008; Singh, 2012). Factors predictive for the persistence of GD have been identified on a group level, with higher intensity of GD in childhood identified as the strongest predictor for a future gender dysphoric outcome (Steensma et al., 2013). The predictive value of the identified factors for persistence are, however, on an individual level less clear cut, and the clinical utility of currently identified factors is low.

Taken together this shows that there can be a great variability with regard to presentation of children with GD and their psychosexual outcome. The counselling of children with GD can therefore be complex and clinically challenging. To date, there is general agreement that the care for children with GD should not be aimed at avoiding adult same sex attraction or transsexualism; that no medical intervention should be provided in childhood (before puberty); that counselling should therefore be focused on reducing the child's distress related to the GD, on help with other psychological difficulties, and on optimizing psychological adjustment and wellbeing (e.g. Byne et al., 2012; Coleman et al., 2011).

However, besides these basic clinical values, there is currently no general consensus about the best approach to dealing with the (uncertain) future development of children with GD, and making decisions that may influence the functioning and/or development of the child – such as a social transition. Different clinical approaches are presented in the literature, and indeed taking the variability in presentation of children with GD into account, it seems important to underline that a 'one size fits all' approach is not best practice for children with GD. Therefore, different kinds of treatment options should be available which respect the unique needs of every child. In particular, the child's clinical psychological profile and gender development, as well as the contextual psychosocial characteristics of the child's family (e.g. belief system, supportive behaviours, access to health care) should always be taken into account in order to make balanced decisions. Currently, the limited empirical evidence in favour of a particular treatment makes treatment of teenagers with GD a controversial issue that raises intense, and often polarized, debate. Therefore, studies comparing different psychological treatment options are needed as well as research which aims to identify the factors involved in the persistence process of GD on an individual level. The primary goal is therefore to determine the safest and most efficacious mental and medical approach for the individual child with GD.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Achenbach, T.M., & Edelbrock, C.S. (1981). Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen. *Monographs of the Society for Research in Child Development*, 46(1), Serial No.188.

Achenbach, T.M., & Edelbrock, C.S. (1983). *Manual for the child behavior checklist and revised child behavior profile*. Burlington, VT: University of Vermont, Department of Psychiatry.

Adelson, S.L. (2012). Practice parameter on gay, lesbian, or bisexual sexual orientation, gender nonconformity, and gender discordance in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, 51, 957–974.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: American Psychiatric Press.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: American Psychiatric Press.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (fifth edition). Washington, DC: American Psychiatric Press.

Bakwin, H. (1968). Deviant gender-role behavior in children: Relation to homosexuality. *Pediatrics*, 41, 620–629.

Bates, J.E., Bentler, P.M., Thompson, S.P. (1973). Measurement of deviant gender development in boys. *Child Development*, 44, 591–598.

Bates, J.E., Bentler, P.M., Thompson, S.P. (1979). Gender-deviant boys compared with normal and clinical control boys. *Journal of Abnormal Child Psychology*, 7, 243–259.

Blakemore, J. E. O. (2003). Children's beliefs about violating gender norms: Boys shouldn't look like girls, and girls shouldn't act like boys. *Sex Roles*, 48, 411–419.

Byne, W., Bradley, S.J., Coleman, E., Eyler, A.E., Green, R., Menvielle, E.J., … Tompkins, D.A. (2012). Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. *Archives of Sexual Behavior*, 41, 759–796.

Carter, D.B., & McCloskey, L.A. (1984). Peers and the maintenance of sex-typed behavior: The development of childrens' conceptions of cross-gender behavior in their peers. *Social Cognition*, 2, 294–314.

Coates, S., & Person, E.S. (1985). Extreme boyhood femininity: Isolated behavior or pervasive disorder? *Journal of the American Academy of Child Psychiatry*, 24, 702–709.

Cohen-Kettenis, P.T., Owen, A., Kaijser, V.G., Bradley, S.J., & Zucker, K.J. (2003). Demographic characteristics, social competence, and problem behavior in children with gender identity disorder: A cross-national, cross-clinic comparative analysis. *Journal of Abnormal Child Psychology*, 31, 41–53.

Coleman, E., Bockting, W., Botzer, M., Cohen-Kettenis, P., DeCuypere, G., Feldman, J., . . . Zucker, K. (2011). Standards of care for the health of transsexual, transgender and gender non-conforming people, version 7. *International Journal of Transgenderism*, 13, 165–232.

Davenport, C.W. (1986). A follow-up study of 10 feminine boys. *Archives of Sexual Behavior*, 15, 511–517.

de Vries, A. L. C., Noens, I.L., Cohen-Kettenis, P.T., van Berckelaer-Onnes, I.A., & Doreleijers, T. A. H. (2010). Autism spectrum disorders in gender dysphoric children and adolescents. *Journal of Autism and Developmental Disorders*, 40, 930–936.

de Vries, A.L., & Cohen-Kettenis, P.T. (2012). Clinical management of gender dysphoria in children and adolescents: The Dutch approach. *Journal of Homosexuality*, 59, 301–320.

Di Ceglie, D. (1998). Management and therapeutic aims with children and adolescents with gender identity disorders and their families. In: D. Di Ceglie & D. Freedman (Eds.), *A Stranger in my own body: Atypical gender identity development and mental health*. London: Karnac Books, pp. 185–197.

Di Ceglie, D. (2014). Care for Gender-Dysphoric Children. In: B.P.C. Kreukels, T.D. Steensma, A.L.C. de Vries (Eds.), *Gender dysphoria and disorders of sex development: Progress in Care and Knowledge*. New York: Springer Science + Business Media, pp. 151–169.

Drescher, J. (2013). Controversies in Gender Diagnoses. *LGBT Health*, 1, 10–14.

Drescher, J. (2014). Gender identity diagnoses: History and controversies. In: B.P.C. Kreukels, T.D. Steensma, A.L.C. de Vries (Eds.), *Gender dysphoria and disorders of sex development: Progress in Care and Knowledge*. New York: Springer Science + Business Media, pp. 137–150.

Drescher, J., Cohen-Kettenis, P., & Winter, S. (2012). Minding the body: situating gender identity diagnoses in the ICD-11. *International Review of Psychiatry*, 24, 568–577.

Drummond, K.D., Bradley, S.J., Peterson-Badali, M., Zucker, K.J. (2008). A follow-up study of girls with gender identity disorder. *Developmental Psychology*, 44, 34–45.

Fombonne, E. (2005). Epidemiology of autistic disorder and other pervasive developmental disorders. *Journal of Clinical Psychiatry*, 66(Suppl 10), 3–8.

Giordano, S. (2012). *Children with gender identity disorder, a clinical, ethical and legal analysis*. London and New York: Routledge.

Green, R. (1987). *The 'sissy boy syndrome' and the development of homosexuality*. New Haven, CT: Yale University Press.

Hill, D.B., Menvielle, E., Sica, K.M., & Johnson, A. (2010). An affirmative intervention for families with gender variant children: Parental ratings of child mental health and gender. *Journal of Sex and Marital Therapy*, 36, 6–23.

Hsieh, S., & Leininger, J. (2014). Resource list: Clinical care programs for gender-nonconforming children and adolescents. *Pediatric Annals*, 43, 238–244.

Khatchadourian, K., Ahmed, S., & Metzger, D.L. (2014). Clinical management of youth with gender dysphoria in Vancouver. *The Journal of Pediatrics*, 164, 906–911.

Kosky, R.J. (1987). Gender-disordered children: Does inpatient treatment help? *Medical Journal of Australia*, 146, 565–569.

Lebovitz, P.S. (1972). Feminine behavior in boys: Aspects of its outcome. *American Journal of Psychiatry*, 128, 1283–1289.

Levy, G.D., Taylor, M.G., & Gelman, S.A. (1995). Traditional and evaluative aspects of flexibility in gender roles, social conventions, moral rules, and physical laws. *Child Development*, 66, 515–531.

Möller, B., Schreier, H., Li, A., & Romer, G. (2009). Gender Identity Disorder in Children and Adolescents. *Current Problems in Pediatric and Adolescent Health Care*, 39(5), 117–143.

Money, J., & Russo, A.J. (1979). Homosexual outcome of discordant gender identity/role: Longitudinal follow-up. *Journal of Pediatric Psychology*, 4, 29–41.

Rekers, G.A., & Morey, S.M. (1989). Relationship of maternal report of feminine behaviors and extraversion to clinician's rating of gender disturbance. *Perceptual and Motor Skills*, 69, 387–394.

Richardson, J. (1999). Response: finding the disorder in gender identity disorder. *Harvard Review of Psychiatry*, 7, 43–50.

Riittakerttu, K., Sumia, M., Työläjärvi, M., & Lindberg, N. (2015). Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development. *Child and Adolescent Psychiatry and Mental Health*, 9, 9–9.

Ruble, D.N., Taylor, L., Cyphers, L., Greulich, F.K., Lurye, L.E. & Shrout, P.E. (2007). The role of gender constancy in early gender development. *Child Development*, 78, 1121–1136.

Signorella, M.L., Bigler, R.S., & Liben, L.S. (1993). Developmental differences in children's gender schemata about others: A meta-analytic review. *Developmental Review*, 13, 147–183.

Singh, D. (2012). A follow-up study of boys with gender identity disorder. Unpublished doctoral dissertation, University of Toronto.

Singh, D., Bradley, S.J., & Zucker, K.J. (2011). Commentary on 'An Affirmative Intervention for Families with Gender Variant Children: Parental Ratings of Child Mental Health and Gender' by Hill, Menvielle, Sica, and Johnson (2010). *Journal of Sex and Marital Therapy*, 37, 151–157.

Steensma, T.D. (2013). From gender variance to gender dysphoria: Psychosexual development of gender atypical children and adolescents. Dissertation, VU University, Amsterdam, the Netherlands.

Steensma, T.D., Biemond, R., de Boer, F., & Cohen-Kettenis, P.T. (2011). Desisting and persisting gender dysphoria after childhood: A qualitative follow-up study. *Clinical Child Psychology and Psychiatry*, 16, 499–516.

Steensma, T.D., & Cohen-Kettenis, P.T. (2015). More than two developmental pathways in children with gender dysphoria? *Journal of the American Academy of Child and Adolescent Psychiatry*, 54, 147–148.

Steensma, T.D., McGuire, J.K., Kreukels, B.P., Beekman, A.J., & Cohen-Kettenis, P.T. (2013). Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 52, 582–590.

Steensma, T.D., Zucker, K.J., Kreukels, B. P. C., VanderLaan, D.P., Wood, H., Fuentes, A., & Cohen-Kettenis, P.T. (2014). Behavioral and emotional problems on the Teacher's Report Form: A cross-national, cross-clinic comparative analysis of gender dysphoric children and adolescents. *Journal of Abnormal Child Psychology*, 42, 635–647.

Stoddart, T., & Turiel, E. (1985). Childrens'concepts of cross-gender activities. *Child Development*, 56, 1241–1252.

Van Beijsterveldt, C.E., Hudziak, J.J., & Boomsma, D.I. (2006). Genetic and environmental influences on cross-gender behavior and relation to behavior problems: A study of Dutch twins at ages 7 and 10 years. *Archives of Sexual Behavior*, 35, 647–658.

VanderLaan, D.P., Postema, L., Wood, H., Singh, D., Fantus, S., Hyun, J., ... Leef, J., (2015). Do Children With Gender Dysphoria Have Intense/Obsessional Interests? *Journal of Sex Research*, 52, 213–219.

Verhulst, F.C., van der Ende, J., & Koot, H.M. (1996). *Handleiding voor de CBCL/4-18 [Manual for the CBCL/4-18]*. Erasmus University, Department of Child and Adolescent Psychiatry, Sophia Children's Hospital: Rotterdam, Netherlands.

Wallien, M.S., & Cohen-Kettenis, P.T. (2008). Psychosexual outcome of gender-dysphoric children. *Journal of the American Academy of Child and Adolescent Psychiatry*, 47, 1413–1423.

Wallien, M. S. C., Veenstra, R., Kreukels, B. P. C., & Cohen-Kettenis, P.T. (2010). Peer Group status of gender dysphoric children: A sociometric study. *Archives of Sexual Behavior*, 39, 553–560.

Wood, H., Sasaki, S., Bradley, S.J., Singh, D., Fantus S., Owen-Anderson, A., & Singh, D. (2013). Patterns of referral to a gender identity service for children and adolescents (1976–2011): age, sex ratio, and sexual orientation. *Journal of Sex & Marital Therapy*, 39, 1–6.

World Health Organization (1992). *International statistical classification of diseases and related health problems* (10th edition). Geneva: World Health Organization.

Zucker, K.J., & Bradley, S. (1995). *Gender identity disorder and psychosexual problems in children and adolescents*. New York: Guilford Press.

Zucker, K.J., Bradley, S.J., Owen-Anderson, A., Kibblewhite, S.J., Wood, H., Singh, D., & Choi, K. (2012). Demographics, behavior problems, and psychosexual characteristics of adolescents with gender identity disorder or transvestic fetishism. *Journal of Sex and Marital Therapy*, 38, 151–189.

Zucker, K.J., Bradley, S.J., & Sanikhani, M. (1997). Sex differences in referral rates of children with gender identity disorder: Some hypotheses. *Journal of Abnormal Child Psychology*, 25, 217–227.

Zucker, K.J., Wilson-Smith, D.N., Kurita, J.A., & Stern, A. (1995). Children's appraisals of sextyped behavior in their peers. *Sex Roles*, 33, 703–725.

Zucker, K.J., Wood, H., & VanderLaan, D.P. (2014). Models of psychopathology in children and adolescents with gender dysphoria. In: B.P.C. Kreukels, T.D. Steensma, A.L.C. de Vries (Eds.), *Gender dysphoria and disorders of sex development: Progress in Care and Knowledge*. New York: Springer Science + Business Media, pp. 171–192.

Zuger, B. (1984). Early effeminate behavior in boys. Outcome and significance for homosexuality. *Journal of Nervous and Mental Disease*, 172, 90–97.

OPEN ACCESS Freely available online

PLoS one

Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden

Cecilia Dhejne[1], Paul Lichtenstein[2], Marcus Boman[2], Anna L. V. Johansson[2], Niklas Långström[2,3], Mikael Landén[1,2,4]*

1 Department of Clinical Neuroscience, Division of Psychiatry, Karolinska Institutet, Stockholm, Sweden, **2** Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, **3** Centre for Violence Prevention, Karolinska Institutet, Stockholm, Sweden, **4** Institute of Neuroscience and Physiology, The Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden

Abstract

Context: The treatment for transsexualism is sex reassignment, including hormonal treatment and surgery aimed at making the person's body as congruent with the opposite sex as possible. There is a dearth of long term, follow-up studies after sex reassignment.

Objective: To estimate mortality, morbidity, and criminal rate after surgical sex reassignment of transsexual persons.

Design: A population-based matched cohort study.

Setting: Sweden, 1973-2003.

Participants: All 324 sex-reassigned persons (191 male-to-females, 133 female-to-males) in Sweden, 1973–2003. Random population controls (10:1) were matched by birth year and birth sex or reassigned (final) sex, respectively.

Main Outcome Measures: Hazard ratios (HR) with 95% confidence intervals (CI) for mortality and psychiatric morbidity were obtained with Cox regression models, which were adjusted for immigrant status and psychiatric morbidity prior to sex reassignment (adjusted HR [aHR]).

Results: The overall mortality for sex-reassigned persons was higher during follow-up (aHR 2.8; 95% CI 1.8–4.3) than for controls of the same birth sex, particularly death from suicide (aHR 19.1; 95% CI 5.8–62.9). Sex-reassigned persons also had an increased risk for suicide attempts (aHR 4.9; 95% CI 2.9–8.5) and psychiatric inpatient care (aHR 2.8; 95% CI 2.0–3.9). Comparisons with controls matched on reassigned sex yielded similar results. Female-to-males, but not male-to-females, had a higher risk for criminal convictions than their respective birth sex controls.

Conclusions: Persons with transsexualism, after sex reassignment, have considerably higher risks for mortality, suicidal behaviour, and psychiatric morbidity than the general population. Our findings suggest that sex reassignment, although alleviating gender dysphoria, may not suffice as treatment for transsexualism, and should inspire improved psychiatric and somatic care after sex reassignment for this patient group.

Citation: Dhejne C, Lichtenstein P, Boman M, Johansson ALV, Långström N, et al. (2011) Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden. PLoS ONE 6(2): e16885. doi:10.1371/journal.pone.0016885

Editor: James Scott, The University of Queensland, Australia

Received September 30, 2010; **Accepted** January 9, 2011; **Published** February 22, 2011

Funding: Financial support was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and the Karolinska Institutet, and through grants from the Swedish Medical Research Council (K2008-62x-14647-06-3) and the Royal Swedish Academy of Sciences (Torsten Amundson's Foundation). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study and the final responsibility for the decision to submit for publication was made by the corresponding author.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: mikael.landen@neuro.gu.se

Introduction

Transsexualism (ICD-10),[1] or gender identity disorder (DSM-IV),[2] is a condition in which a person's gender identity - the sense of being a man or a woman - contradicts his or her bodily sex characteristics. The individual experiences gender dysphoria and desires to live and be accepted as a member of the opposite sex.

The treatment for transsexualism includes removal of body hair, vocal training, and cross-sex hormonal treatment aimed at making the person's body as congruent with the opposite sex as possible to alleviate the gender dysphoria. Sex reassignment also involves the surgical removal of body parts to make external sexual characteristics resemble those of the opposite sex, so called sex reassignment/confirmation surgery (SRS). This is a unique intervention not only in psychiatry but in all of medicine. The present form of sex reassignment has been practised for more than half a century and is the internationally recognized treatment to ease gender dysphoria in transsexual persons.[3,4]

Despite the long history of this treatment, however, outcome data regarding mortality and psychiatric morbidity are scant. With respect to suicide and deaths from other causes after sex reassignment, an early Swedish study followed 24 transsexual persons for an average of six years and reported one suicide.[5] A subsequent Swedish study recorded three suicides after sex reassignment surgery of 175 patients.[6] A recent Swedish follow-up study reported no suicides in 60 transsexual patients, but one death due to complications after the sex reassignment surgery.[7] A Danish study reported death by suicide in 3 out of 29 operated male-to-female transsexual persons followed for an average of six years.[8] By contrast, a Belgian study of 107 transsexual persons followed for 4–6 years found no suicides or deaths from other causes.[9] A large Dutch single-centre study (N = 1,109), focusing on adverse events following hormonal treatment, compared the outcome after cross-sex hormone treatment with national Dutch standardized mortality and morbidity rates and found no increased mortality, with the exception of death from suicide and AIDS in male-to-females 25–39 years of age.[10] The same research group concluded in a recent report that treatment with cross-sex hormones seems acceptably safe, but with the reservation that solid clinical data are missing.[11] A limitation with respect to the Dutch cohort is that the proportion of patients treated with cross-sex hormones who also had surgical sex-reassignment is not accounted for.[10]

Data is inconsistent with respect to psychiatric morbidity post sex reassignment. Although many studies have reported psychiatric and psychological improvement after hormonal and/or surgical treatment,[7,12,13,14,15,16] other have reported on regrets,[17] psychiatric morbidity, and suicide attempts after SRS.[9,18] A recent systematic review and meta-analysis concluded that approximately 80% reported subjective improvement in terms of gender dysphoria, quality of life, and psychological symptoms, but also that there are studies reporting high psychiatric morbidity and suicide rates after sex reassignment.[19] The authors concluded though that the evidence base for sex reassignment "is of very low quality due to the serious methodological limitations of included studies."

The methodological shortcomings have many reasons. First, the nature of sex reassignment precludes double blind randomized controlled studies of the result. Second, transsexualism is rare [20] and many follow-ups are hampered by small numbers of subjects.[5,8,21,22,23,24,25,26,27,28] Third, many sex reassigned persons decline to participate in follow-up studies, or relocate after surgery, resulting in high drop-out rates and consequent selection bias.[6,9,12,21,24,28,29,30] Forth, several follow-up studies are hampered by limited follow-up periods.[7,9,21,22,26,30] Taken together, these limitations preclude solid and generalisable conclusions. A long-term population-based controlled study is one way to address these methodological shortcomings.

Here, we assessed mortality, psychiatric morbidity, and psychosocial integration expressed in criminal behaviour after sex reassignment in transsexual persons, in a total population cohort study with long-term follow-up information obtained from Swedish registers. The cohort was compared with randomly selected population controls matched for age and gender. We adjusted for premorbid differences regarding psychiatric morbidity and immigrant status. This study design sheds new light on transsexual persons' health after sex reassignment. It does not, however, address whether sex reassignment is an effective treatment or not.

Methods

National registers

The study population was identified by the linkage of several Swedish national registers, which contained a total of 13.8 million unique individuals. The Hospital Discharge Register (HDR, held by the National Board of Health and Welfare) contains discharge diagnoses, up to seven contributory diagnoses, external causes of morbidity or mortality, surgical procedure codes, and discharge date. Discharge diagnoses are coded according to the 8th (1969-1986), 9th (1987–1996), and 10th editions (1997-) of the International Classification of Diseases (ICD). The register covers virtually all psychiatric inpatient episodes in Sweden since 1973. Discharges that occurred up to 31 December 2003 were included. Surgical procedure codes could not be used for this study due to the lack of a specific code for sex reassignment surgery. The Total Population Register (TPR, held by Statistics Sweden) is comprised of data about the entire Swedish population. Through linkage with the Total Population Register it was possible to identify birth date and birth gender for all study subjects. The register is updated every year and gender information was available up to 2004/2005. The Medical Birth Register (MBR) was established in 1973 and contains birth data, including gender of the child at birth. National censuses based on mandatory self-report questionnaires completed by all adult citizens in 1960, 1970, 1980, and 1990 provided information on individuals, households, and dwellings, including gender, living area, and highest educational level. Complete migration data, including country of birth for immigrants for 1969–2003, were obtained from the TPR. In addition to educational information from the censuses, we also obtained highest educational level data for 1990 and 2000 from the Register of Education. The Cause of Death Register (CDR, Statistics Sweden) records all deaths in Sweden since 1952 and provided information on date of death and causes of death. Death events occurring up to 31 December 2003 are included in the study. The Crime Register (held by the National Council of Crime Prevention) provided information regarding crime type and date on all criminal convictions in Sweden during the period 1973–2004. Attempted and aggravated forms of all offences were also included. All crimes in Sweden are registered regardless of insanity at the time of perpetration; for example, for individuals who suffered from psychosis at the time of the offence. Moreover, conviction data include individuals who received custodial or non-custodial sentences and cases where the prosecutor decided to caution or fine without court proceedings. Finally, Sweden does not differ considerably from other members of the European Union regarding rates of violent crime and their resolution.[31]

Study population, identification of sex-reassigned persons (exposure assessment)

The study was designed as a population-based matched cohort study. We used the individual national registration number, assigned to all Swedish residents, including immigrants on arrival, as the primary key through all linkages. The registration number consists of 10 digits; the first six provide information of the birth date, whereas the ninth digit indicates the gender. In Sweden, a person presenting with gender dysphoria is referred to one of six specialised gender teams that evaluate and treat patients principally according to international consensus guidelines: Standards of Care.[3] With a medical certificate, the person applies to the National Board of Health and Welfare to receive permission for sex reassignment surgery and a change of legal sex status. A new national registration number signifying the new gender is assigned after sex reassignment surgery. The National

Board of Health and Welfare maintains a link between old and new national registration numbers, making it possible to follow individuals undergoing sex reassignment across registers and over time. Hence, sex reassignment surgery in Sweden requires (i) a transsexualism diagnosis and (ii) permission from the National Board of Health and Welfare.

A person was defined as exposed to sex reassignment surgery if two criteria were met: (i) at least one inpatient diagnosis of gender identity disorder diagnosis without concomitant psychiatric diagnoses in the Hospital Discharge Register, and (ii) at least one discrepancy between gender variables in the Medical Birth Register (from 1973 and onwards) or the National Censuses from 1960, 1970, 1980, or 1990 and the latest gender designation in the Total Population Register. The first criterion was employed to capture the hospitalization for sex reassignment surgery that serves to secure the diagnosis and provide a time point for sex reassignment surgery; the plastic surgeons namely record the reason for sex reassignment surgery, i.e., transsexualism, but not any co-occurring psychiatric morbidity. The second criterion was used to ensure that the person went through all steps in sex-reassignment and also changed sex legally.

The date of sex reassignment (start of follow-up) was defined as the first occurrence of a gender identity disorder diagnosis, without any other concomitant psychiatric disorder, in the Hospital Discharge Register after the patient changed sex status (any discordance in sex designation across the Censuses, Medical Birth, and Total Population registers). If this information was missing, we used instead the closest date in the Hospital Discharge Register on which the patient was diagnosed with gender identity disorder without concomitant psychiatric disorder prior to change in sex status. The reason for prioritizing the use of a gender identity disorder diagnosis *after* changed sex status over *before* was to avoid overestimating person-years at risk of sex-reassigned person.

Using these criteria, a total of 804 patients with gender identity disorder were identified, whereof 324 displayed a shift in the gender variable during the period 1973–2003. The 480 persons that did not shift gender variable comprise persons who either did not apply, or were not approved, for sex reassignment surgery. Moreover, the ICD 9 code 302 is a non specific code for sexual disorders. Hence, this group might also comprise persons that were hospitalized for sexual disorders other than transsexualism. Therefore, they were omitted from further analyses. Of the remaining 324 persons, 288 were identified with the gender identity diagnosis *after* and 36 *before* change of sex status. Out of the 288 persons identified *after* changed sex status, 185 could also be identified *before* change in sex status. The median time lag between the hospitalization *before* and *after* sex change for these 185 persons was 0.96 years (mean 2.2 years, SD 3.3).

Gender identity disorder was coded according to ICD-8: 302.3 (transsexualism) and 302.9 (sexual deviation NOS); ICD-9: 302 (overall code for sexual deviations and disorders, more specific codes were not available in ICD-9); and ICD-10: F64.0 (transsexualism), F64.1 (dual-role transvestism), F64.8 (other gender identity disorder), and F64.9 (gender identity disorder NOS). Other psychiatric disorders were coded as ICD-8: 290-301 and 303-315; ICD-9: 290-301 and 303-319; and ICD-10: F00-F63 as well as F65-F99.

Identification of population-based controls (unexposed group)

For each exposed person (N = 324), we randomly selected 10 unexposed controls. A person was defined as unexposed if there were no discrepancies in sex designation across the Censuses, Medical Birth, and Total Population registers *and* no gender identity disorder diagnosis according to the Hospital Discharge Register. Control persons were matched by sex and birth year and had to be alive and residing in Sweden at the estimated sex reassignment date of the case person. To study possible gender-specific effects on outcomes of interest, we used two different control groups: one with the same sex as the case individual at birth (birth sex matching) and the other with the sex that the case individual had been reassigned to (final sex matching).

Outcome measures

We studied mortality, psychiatric morbidity, accidents, and crime following sex reassignment. More specifically, we investigated: (1) all-cause mortality, (2) death by definite/uncertain suicide, (3) death by cardiovascular disease, and (4) death by tumour. Morbidity included (5) any psychiatric disorder (gender identity disorders excluded), (6) alcohol/drug misuse and dependence, (7) definite/uncertain suicide attempt, and (8) accidents. Finally, we addressed court convictions for (9) any criminal offence and (10) any violent offence. Each individual could contribute with several outcomes, but only one event per outcome. Causes of death (Cause of Death Registry from 1952 and onwards) were defined according to ICD as suicide (ICD-8 and ICD-9 codes E950-E959 and E980-E989, ICD-10 codes X60-X84 and Y10-Y34); cardiovascular disease (ICD-8 codes 390-458, ICD-9 codes 390-459, ICD-10 codes I00-I99); neoplasms (ICD-8 and ICD-9 codes 140-239, ICD-10 codes C00-D48), any psychiatric disorder (gender identity disorders excluded); (ICD-8 codes 290-301 and 303-315, ICD-9 codes 290-301 and 303-319, ICD-10 codes F00-F63 and F65-F99); alcohol/drug abuse and dependence (ICD-8 codes 303-304, ICD-9 codes 303-305 (tobacco use disorder excluded), ICD-10 codes F10-F16 and F18-F19 (x5 excluded); and accidents (ICD-8 and ICD-9 codes E800-E929, ICD-10 codes V01-X59).

Any criminal conviction during follow-up was counted; specifically, violent crime was defined as homicide and attempted homicide, aggravated assault and assault, robbery, threatening behaviour, harassment, arson, or any sexual offense.[32]

Covariates

Severe psychiatric morbidity was defined as inpatient care according to ICD-8 codes 291, 295-301, 303-304, and 307; ICD-9 codes 291-292, 295-298, 300-301, 303-305 (tobacco use disorder excluded), 307.1, 307.5, 308-309, and 311; ICD-10 codes F10-F16, F18-F25, F28-F45, F48, F50, and F60-F62. Immigrant status, defined as individuals born abroad, was obtained from the Total Population Register. All outcome/covariate variables were dichotomized (i.e., affected or unaffected) and without missing values.

Statistical analyses

Each individual contributed person-time from study entry (for exposed: date of sex reassignment; for unexposed: date of sex reassignment of matched case) until date of outcome event, death, emigration, or end of study period (31 December 2003), whichever came first. The association between exposure (sex reassignment) and outcome (mortality, morbidity, crime) was measured by hazard ratios (HR) with 95% CIs, taking follow-up time into account. HRs were estimated from Cox proportional hazard regression models, stratified on matched sets (1:10) to account for the matching by sex, age, and calendar time (birth year). We present crude HRs (though adjusted for sex and age through matching) and confounder-adjusted HRs [aHRs] for all outcomes. The two potential confounders, immigrant status (yes/no) and history of severe psychiatric morbidity (yes/no) prior to sex reassignment, were chosen based on previous research[18,33] and different prevalence across cases and controls (Table 1).

Gender-separated analyses were performed and a Kaplan-Meier survival plot graphically illustrates the survival of the sex reassigned cohort and matched controls (all-cause mortality) over time. The significance level was set at 0.05 (all tests were two-sided). All outcome/covariate variables were without missing values, since they are generated from register data, which are either present (affected) or missing (unaffected). The data were analysed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Ethics

The data linking of national registers required for this study was approved by the IRB at Karolinska Institutet, Stockholm. All data were analyzed anonymously; therefore, informed consent for each individual was neither necessary nor possible.

Results

We identified 324 transsexual persons (exposed cohort) who underwent sex reassignment surgery and were assigned a new legal sex between 1973 and 2003. These constituted the sex-reassigned (exposed) group. Fifty-nine percent (N = 191) of sex-reassigned persons were male-to-females and 41% (N = 133) female-to-males, yielding a sex ratio of 1.4:1 (Table 1).

The average follow-up time for all-cause mortality was 11.4 (median 9.1) years. The average follow-up time for the risk of being hospitalized for any psychiatric disorder was 10.4 (median 8.1).

Characteristics prior to sex reassignment

Table 1 displays demographic characteristics of sex-reassigned and control persons prior to study entry (sex reassignment). There were no substantial differences between female-to-males and male-to-females regarding measured baseline characteristics. Immigrant status was twice as common among transsexual individuals compared to controls, living in an urban area somewhat more common, and higher education about equally prevalent. Transsexual individuals had been hospitalized for psychiatric morbidity other than gender identity disorder prior to sex reassignment about four times more often than controls. To adjust for these baseline discrepancies, hazard ratios adjusted for immigrant status and psychiatric morbidity prior to baseline are presented for all outcomes [aHRs].

Mortality

Table 2 describes the risks for selected outcomes during follow-up among sex-reassigned persons, compared to same-age controls of the same birth sex. Sex-reassigned transsexual persons of both genders had approximately a three times higher risk of all-cause mortality than controls, also after adjustment for covariates. Table 2

Table 1. Baseline characteristics among sex-reassigned subjects in Sweden (N = 324) and population controls matched for birth year and sex.

Characteristic at baseline	Sex-reassigned subjects (N = 324)	Birth-sex matched controls (N = 3,240)	Final-sex matched controls (N = 3,240)
Gender			
Female at birth, male after sex change	133 (41%)	1,330 (41%)	1,330 (41%)
Male at birth, female after sex change	191 (59%)	1,910 (59%)	1,910 (59%)
Average age at study entry [years] (SD, min-max)			
Female at birth, male after sex change	33.3 (8.7, 20–62)	33.3 (8.7, 20–62)	33.3 (8.7, 20–62)
Male at birth, female after sex change	36.3 (10.1, 21–69)	36.3 (10.1, 21–69)	36.3 (10.1, 21–69)
Both genders	35.1 (9.7, 20–69)	35.1 (9.7, 20–69)	35.1 (9.7, 20–69)
Immigrant status			
Female at birth, male after sex change	28 (21%)	118 (9%)	100 (8%)
Male at birth, female after sex change	42 (22%)	176 (9%)	164 (9%)
Both genders	70 (22%)	294 (9%)	264 (8%)
Less than 10 years of schooling prior to entry vs. 10 years or more			
Females at birth, males after sex change	49 (44%); 62 (56%)	414 (37%); 714 (63%)	407 (36%); 713 (64%)
Males at birth, females after sex change	61 (41%); 89 (59%)	665 (40%); 1,011 (60%)	595 (35%); 1,091 (65%)
All individuals with data	110 (42%); 151 (58%)	1,079 (38%); 1,725 (62%)	1,002 (36%); 1,804 (64%)
Psychiatric morbidity* prior to study entry			
Female at birth, male after sex change	22 (17%)	47 (4%)	42 (3%)
Male at birth, female after sex change	36 (19%)	76 (4%)	72 (4%)
Both genders	58 (18%)	123 (4%)	114 (4%)
Rural [vs. urban] living area prior to entry			
Female at birth, male after sex change	13 (10%)	180 (14%)	195 (15%)
Male at birth, female after sex change	20 (10%)	319 (17%)	272 (14%)
Both genders	33 (10%)	499 (15%)	467 (14%)

Note:
*Hospitalizations for gender identity disorder were not included.
doi:10.1371/journal.pone.0016885.t001

Table 2. Risk of various outcomes among sex-reassigned subjects in Sweden (N = 324) compared to population controls matched for birth year and birth sex.

	Number of events cases/ controls 1973–2003	Outcome incidence rate per 1000 person-years 1973–2003 (95% CI)		Crude hazard ratio (95% CI) 1973–2003	Adjusted* hazard ratio (95% CI) 1973–2003	Adjusted* hazard ratio (95% CI) 1973–1988	Adjusted* hazard ratio (95% CI) 1989–2003
		Cases	Controls				
Any death	27/99	7.3 (5.0–10.6)	2.5 (2.0–3.0)	2.9 (1.9–4.5)	2.8 (1.8–4.3)	3.1 (1.9–5.0)	1.9 (0.7–5.0)
Death by suicide	10/5	2.7 (1.5–5.0)	0.1 (0.1–0.3)	19.1 (6.5–55.9)	19.1 (5.8–62.9)	N/A	N/A
Death by cardiovascular disease	9/42	2.4 (1.3–4.7)	1.1 (0.8–1.4)	2.6 (1.2–5.4)	2.5 (1.2–5.3)	N/A	N/A
Death by neoplasm	8/38	2.2 (1.1–4.3)	1.0 (0.7–1.3)	2.1 (1.0–4.6)	2.1 (1.0–4.6)	N/A	N/A
Any psychiatric hospitalisation‡	64/173	19.0 (14.8–24.2)	4.2 (3.6–4.9)	4.2 (3.1–5.6)	2.8 (2.0–3.9)	3.0 (1.9–4.6)	2.5 (1.4–4.2)
Substance misuse	22/78	5.9 (3.9–8.9)	1.8 (1.5–2.3)	3.0 (1.9–4.9)	1.7 (1.0–3.1)	N/A	N/A
Suicide attempt	29/44	7.9 (5.5–11.4)	1.0 (0.8–1.4)	7.6 (4.7–12.4)	4.9 (2.9–8.5)	7.9 (4.1–15.3)	2.0 (0.7–5.3)
Any accident	32/233	9.0 (6.3–12.7)	5.7 (5.0–6.5)	1.6 (1.1–2.3)	1.4 (1.0–2.1)	1.6 (1.0–2.5)	1.1 (0.5–2.2)
Any crime	60/350	18.5 (14.3–23.8)	9.0 (8.1–10.0)	1.9 (1.4–2.5)	1.3 (1.0–1.8)	1.6 (1.1–2.4)	0.9 (0.6–1.5)
Violent crime	14/61	3.6 (2.1–6.1)	1.4 (1.1–1.8)	2.7 (1.5–4.9)	1.5 (0.8–3.0)	N/A	N/A

Notes:
*Adjusted for psychiatric morbidity prior to baseline and immigrant status.
‡Hospitalisations for gender identity disorder were excluded.
N/A Not applicable due to sparse data.
doi:10.1371/journal.pone.0016885.t002

separately lists the outcomes depending on when sex reassignment was performed: during the period 1973-1988 or 1989–2003. Even though the overall mortality was increased across both time periods, it did not reach statistical significance for the period 1989–2003. The Kaplan-Meier curve (Figure 1) suggests that survival of transsexual persons started to diverge from that of matched controls after about 10 years of follow-up. The cause-specific mortality from suicide was much higher in sex-reassigned persons, compared to matched controls. Mortality due to cardiovascular disease was moderately increased among the sex-reassigned, whereas the numerically increased risk for malignancies was borderline statistically significant. The malignancies were lung cancer (N = 3), tongue cancer (N = 1), pharyngeal cancer (N = 1), pancreas cancer (N = 1), liver cancer (N = 1), and unknown origin (N = 1).

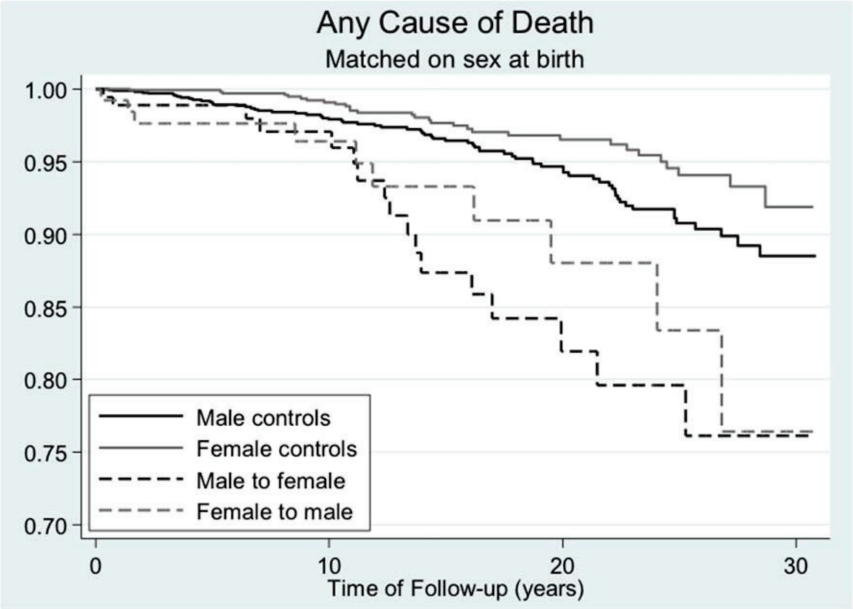

Figure 1. Death from any cause as a function of time after sex reassignment among 324 transsexual persons in Sweden (male-to-female: N = 191, female-to-male: N = 133), and population controls matched on birth year.
doi:10.1371/journal.pone.0016885.g001

Psychiatric morbidity, substance misuse, and accidents

Sex-reassigned persons had a higher risk of inpatient care for a psychiatric disorder other than gender identity disorder than controls matched on birth year and birth sex (Table 2). This held after adjustment for prior psychiatric morbidity, and was true regardless of whether sex reassignment occurred before or after 1989. In line with the increased mortality from suicide, sex-reassigned individuals were also at a higher risk for suicide attempts, though this was not statistically significant for the time period 1989–2003. The risks of being hospitalised for substance misuse or accidents were not significantly increased after adjusting for covariates (Table 2).

Crime rate

Transsexual individuals were at increased risk of being convicted for any crime or violent crime after sex reassignment (Table 2); this was, however, only significant in the group who underwent sex reassignment before 1989.

Gender differences

Comparisons of female-to-males and male-to-females, although hampered by low statistical power and associated wide confidence intervals, suggested mostly similar risks for adverse outcomes (Tables S1 and S2). However, violence against self (suicidal behaviour) and others ([violent] crime) constituted important exceptions. First, male-to-females had significantly increased risks for suicide attempts compared to both female (aHR 9.3; 95% CI 4.4–19.9) and male (aHR 10.4; 95% CI 4.9–22.1) controls. By contrast, female-to-males had significantly increased risk of suicide attempts only compared to male controls (aHR 6.8; 95% CI 2.1–21.6) but not compared to female controls (aHR 1.9; 95% CI 0.7–4.8). This suggests that male-to-females are at higher risk for suicide attempts after sex reassignment, whereas female-to-males maintain a female pattern of suicide attempts after sex reassignment (Tables S1 and S2).

Second, regarding any crime, male-to-females had a significantly increased risk for crime compared to female controls (aHR 6.6; 95% CI 4.1–10.8) but not compared to males (aHR 0.8; 95% CI 0.5–1.2). This indicates that they retained a male pattern regarding criminality. The same was true regarding violent crime. By contrast, female-to-males had higher crime rates than female controls (aHR 4.1; 95% CI 2.5–6.9) but did not differ from male controls. This indicates a shift to a male pattern regarding criminality and that sex reassignment is coupled to increased crime rate in female-to-males. The same was true regarding violent crime.

Discussion

Principal findings and comparison with previous research

We report on the first nationwide population-based, long-term follow-up of sex-reassigned transsexual persons. We compared our cohort with randomly selected population controls matched for age and gender. The most striking result was the high mortality rate in both male-to-females and female-to males, compared to the general population. This contrasts with previous reports (with one exception[8]) that did not find an increased mortality rate after sex reassignment, or only noted an increased risk in certain subgroups.[7,9,10,11] Previous clinical studies might have been biased since people who regard their sex reassignment as a failure are more likely to be lost to follow-up. Likewise, it is cumbersome to track deceased persons in clinical follow-up studies. Hence, population-based register studies like the present are needed to improve representativity.[19,34]

The poorer outcome in the present study might also be explained by longer follow-up period (median >10 years) compared to previous studies. In support of this notion, the survival curve (Figure 1) suggests increased mortality from ten years after sex reassignment and onwards. In accordance, the overall mortality rate was only significantly increased for the group operated before 1989. However, the latter might also be explained by improved health care for transsexual persons during 1990s, along with altered societal attitudes towards persons with different gender expressions.[35]

Mortality due to cardiovascular disease was significantly increased among sex reassigned individuals, albeit these results should be interpreted with caution due to the low number of events. This contrasts, however, a Dutch follow-up study that reported no increased risk for cardiovascular events.[10,11] A recent meta-analysis concluded, however, that data on cardiovascular outcome after cross-sex steroid use are sparse, inconclusive, and of very low quality.[34]

With respect to neoplasms, prolonged hormonal treatment might increase the risk for malignancies,[36] but no previous study has tested this possibility. Our data suggested that the cause-specific risk of death from neoplasms was increased about twice (borderline statistical significance). These malignancies (see Results), however, are unlikely to be related to cross-hormonal treatment.

There might be other explanations to increased cardiovascular death and malignancies. Smoking was in one study reported in almost 50% by the male-to females and almost 20% by female-to-males.[9] It is also possible that transsexual persons avoid the health care system due to a presumed risk of being discriminated.

Mortality from suicide was strikingly high among sex-reassigned persons, also after adjustment for prior psychiatric morbidity. In line with this, sex-reassigned persons were at increased risk for suicide attempts. Previous reports [6,8,10,11] suggest that transsexualism is a strong risk factor for suicide, also after sex reassignment, and our long-term findings support the need for continued psychiatric follow-up for persons at risk to prevent this.

Inpatient care for psychiatric disorders was significantly more common among sex-reassigned persons than among matched controls, both before and after sex reassignment. It is generally accepted that transsexuals have more psychiatric ill-health than the general population prior to the sex reassignment.[18,21,22,33] It should therefore come as no surprise that studies have found high rates of depression,[9] and low quality of life[16,25] also after sex reassignment. Notably, however, in this study the increased risk for psychiatric hospitalisation persisted even after adjusting for psychiatric hospitalisation prior to sex reassignment. This suggests that even though sex reassignment alleviates gender dysphoria, there is a need to identify and treat co-occurring psychiatric morbidity in transsexual persons not only before but also after sex reassignment.

Criminal activity, particularly violent crime, is much more common among men than women in the general population. A previous study of all applications for sex reassignment in Sweden up to 1992 found that 9.7% of male-to-female and 6.1% of female-to-male applicants had been prosecuted for a crime.[33] Crime after sex reassignment, however, has not previously been studied. In this study, male-to-female individuals had a higher risk for criminal convictions compared to female controls but not compared to male controls. This suggests that the sex reassignment procedure neither increased nor decreased the risk for criminal offending in male-to-females. By contrast, female-to-males were at a higher risk for criminal convictions compared to female controls and did not differ from male controls, which suggests increased crime proneness in female-to-males after sex reassignment.

Strengths and limitations of the study

Strengths of this study include nationwide representativity over more than 30 years, extensive follow-up time, and minimal loss to follow-up. Many previous studies suffer from low outcome ascertainment,[6,9,21,29] whereas this study has captured almost the entire population of sex-reassigned transsexual individuals in Sweden from 1973–2003. Moreover, previous outcome studies have mixed pre-operative and post-operative transsexual persons,[22,37] while we included only post-operative transsexual persons that also legally changed sex. Finally, whereas previous studies either lack a control group or use standardised mortality rates or standardised incidence rates as comparisons,[9,10,11] we selected random population controls matched by birth year, and either birth or final sex.

Given the nature of sex reassignment, a double blind randomized controlled study of the result after sex reassignment is not feasible. We therefore have to rely on other study designs. For the purpose of evaluating whether sex reassignment is an effective treatment for gender dysphoria, it is reasonable to compare reported gender dysphoria pre and post treatment. Such studies have been conducted either prospectively[7,12] or retrospectively,[5,6,9,22,25,26,29,38] and suggest that sex reassignment of transsexual persons improves quality of life and gender dysphoria. The limitation is of course that the treatment has not been assigned randomly and has not been carried out blindly.

For the purpose of evaluating the safety of sex reassignment in terms of morbidity and mortality, however, it is reasonable to compare sex reassigned persons with matched population controls. The caveat with this design is that transsexual persons before sex reassignment might differ from healthy controls (although this bias can be statistically corrected for by adjusting for baseline differences). It is therefore important to note that the current study is only informative with respect to transsexuals persons health after sex reassignment; no inferences can be drawn as to the effectiveness of sex reassignment as a treatment for transsexualism. In other words, the results should not be interpreted such as sex reassignment *per se* increases morbidity and mortality. Things might have been even worse without sex reassignment. As an analogy, similar studies have found increased somatic morbidity, suicide rate, and overall mortality for patients treated for bipolar disorder and schizophrenia.[39,40] This is important information, but it does not follow that mood stabilizing treatment or antipsychotic treatment is the culprit.

Other facets to consider are first that this study reflects the outcome of psychiatric and somatic treatment for transsexualism provided in Sweden during the 1970s and 1980s. Since then, treatment has evolved with improved sex reassignment surgery, refined hormonal treatment,[11,41] and more attention to psychosocial care that might have improved the outcome. Second, transsexualism is a rare condition and Sweden is a small country (9.2 million inhabitants in 2008). Hence, despite being based on a comparatively large national cohort and long-term follow-up, the statistical power was limited. Third, regarding psychiatric morbidity after sex reassignment, we assessed inpatient psychiatric care. Since most psychiatric care is provided in outpatient settings (for which no reliable data were available), underestimation of the *absolute* prevalences was inevitable. However, there is no reason to believe that this would change the *relative risks* for psychiatric morbidity unless sex-reassigned transsexual individuals were more likely than matched controls to be admitted to hospital for any given psychiatric condition.

Finally, to estimate start of follow-up, we prioritized using the date of a gender identity disorder diagnosis *after* changed sex status over *before* changed sex status, in order to avoid overestimating person-years at risk after sex-reassignment. This means that adverse outcomes might have been underestimated. However, given that the median time lag between the hospitalization before and after change of sex status was less than a year (see Methods), this maneuver is unlikely to have influenced the results significantly. Moreover, all deaths will be recorded regardless of this exercise and mortality hence correctly estimated.

Conclusion

This study found substantially higher rates of overall mortality, death from cardiovascular disease and suicide, suicide attempts, and psychiatric hospitalisations in sex-reassigned transsexual individuals compared to a healthy control population. This highlights that post surgical transsexuals are a risk group that need long-term psychiatric and somatic follow-up. Even though surgery and hormonal therapy alleviates gender dysphoria, it is apparently not sufficient to remedy the high rates of morbidity and mortality found among transsexual persons. Improved care for the transsexual group after the sex reassignment should therefore be considered.

Supporting Information

Table S1 Risk of various outcomes in sex-reassigned persons in Sweden compared to population controls matched for birth year and *birth sex*.
(DOCX)

Table S2 Risk of various outcomes in sex-reassigned persons in Sweden compared to controls matched for birth year and *final sex*.
(DOCX)

Author Contributions

Conceived and designed the experiments: CD PL AJ NL ML. Performed the experiments: MB AJ. Analyzed the data: CD PL MB AJ NL ML. Contributed reagents/materials/analysis tools: PL NL AJ. Wrote the paper: CD PL MB AJ NL ML.

References

1. World Health Organization (1993) The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic criteria for research. Geneva: WHO.
2. American Psychiatric Association, ed (1994) Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: APA.
3. Meyer W, Bockting W, Cohen-Kettenis P, Coleman E, DiCeglie D, et al. (2002) The Harry Benjamin International Gender Dysphoria Association's Standards of Care for Gender Identity Disorders, Sixth Version. Journal of Psychology & Human Sexuality 13: 1–30.
4. Cohen-Kettenis PT, Gooren LJG (1999) Transsexualism: A review of etiology, diagnosis and treatment. J Psychosom Res 46: 315–333.
5. Wålinder J, Thuwe I (1975) A social-psychiatric follow-up study of 24 sex-reassigned transsexuals. Göteborg, Sweden: Scandinavian University Books.
6. Eldh J, Berg A, Gustafsson M (1997) Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg 31: 39–45.
7. Johansson A, Sundbom E, Höjerback T, Bodlund O (2010) A five-year follow-up study of Swedish adults with gender identity disorder. Arch Sex Behav 39: 1429–1437.
8. Sørensen T, Hertoft P (1982) Male and female transsexualism: the Danish experience with 37 patients. ArchSex Behav 11: 133–155.
9. De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, et al. (2005) Sexual and physical health after sex reassignment surgery. Arch Sex Behav 34: 679–690.
10. van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ (1997) Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol Oxf 47: 337–342.

11. Gooren LJ, Giltay EJ, Bunck MC (2008) Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. J Clin Endocrinol Metab 93: 19–25.
12. Smith YL, van Goozen SH, Cohen-Kettenis PT (2001) Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. J Am Acad Child Adolesc Psychiatry 40: 472–481.
13. Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT (2005) Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. Psychol Med 35: 89–99.
14. Leavitt F, Berger JC, Hoeppner JA, Northrop G (1980) Presurgical adjustment in male transsexuals with and without hormonal treatment. J Nerv Ment Dis 168: 693–697.
15. Cohen Kettenis PT, van Goozen SH (1997) Sex reassignment of adolescent transsexuals: a follow-up study. J Am Acad Child Adolesc Psychiatry 36: 263–271.
16. Newfield E, Hart S, Dibble S, Kohler L (2006) Female-to-male transgender quality of life. Qual Life Res 15: 1447–1457.
17. Landén M, Wålinder J, Hambert G, Lundström B (1998) Factors predictive of regret in sex reassignment. Acta Psychiatrica Scandinavica 97: 284–289.
18. Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A (2005) Psychiatric comorbidity in gender identity disorder. J Psychosom Res 58: 259–261.
19. Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, et al. (2010) Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol (Oxf) 72: 214–231.
20. Landén M, Wålinder J, Lundström B (1996) Incidence and sex ratio of transsexualism in Sweden. Acta Psychiatrica Scandinavica 93: 261–263.
21. Lobato MI, Koff WJ, Manenti C, da Fonseca Seger D, Salvador J, et al. (2006) Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. Arch Sex Behav 35: 711–715.
22. Bodlund O, Kullgren G (1996) Transsexualism-General outcome and prognostic factors. A five year follow-up study of 19 transsexuals in the process of changing sex. Arch Sex Behav 25: 303–316.
23. Lindemalm G, Körlin D, Uddenberg N (1986) Long-term follow-up of "sex change" in 13 male-to-female transsexuals. Arch Sex Behav 15: 187–210.
24. Rauchfleisch U, Barth D, Battegay R (1998) [Results of long-term follow-up of transsexual patients]. Nervenarzt 69: 799–805.
25. Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller MD, et al. (2009) Quality of life 15 years after sex reassignment surgery for transsexualism. Fertil Steril 92: 1685–1689 e1683.
26. Zimmermann A, Zimmer R, Kovacs L, Einodshofer S, Herschbach P, et al. (2006) [Transsexuals' life satisfaction after gender transformation operations]. Chirurg 77: 432–438.
27. Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A (1999) The reported sex and surgery satisfactions of 28 postoperative male-to- female transsexual patients. Arch Sex Behav 28: 71–89.
28. Hepp U, Klaghofer R, Burkhard-Kubler R, Buddeberg C (2002) [Treatment follow-up of transsexual patients. A catamnestic study]. Nervenarzt 73: 283–288.
29. Lawrence AA (2003) Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. Arch Sex Behav 32: 299–315.
30. Kaube H, Biemer E (1991) [Results of sex change operations in 30 transsexual patients: psychosocial and sexual adaptation–surgical complications]. Handchir Mikrochir Plast Chir 23: 276–278.
31. Dolmén L (2001) Brottsligheten i olika länder (Criminality in different countries). Stockholm: Brottsförebyggande rådet (the Swedish National Council for Crime Prevention).
32. Fazel S, Grann M (2006) The population impact of severe mental illness on violent crime. Am J Psychiatry 163: 1397–1403.
33. Landén M, Wålinder J, Lundström B (1998) Clinical characteristics of a total cohort of female and male applicants for sex reassignment: a descriptive study. Acta Psychiatrica Scandinavica 97: 189–194.
34. Elamin MB, Garcia MZ, Murad MH, Erwin PJ, Montori VM (2010) Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. Clin Endocrinol (Oxf) 72: 1–10.
35. Landén M, Innala S (2000) Attitudes toward transsexualism in a Swedish national survey. Archives of Sexual Behavior 29: 375–388.
36. Mueller A, Gooren L (2008) Hormone-related tumors in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol 159: 197–202.
37. Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L (2009) Transsexualism in Serbia: a twenty-year follow-up study. J Sex Med 6: 1018–1023.
38. Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A (1999) The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. Arch Sex Behav 28: 71–89.
39. Ösby U, Brandt L, Correia N, Ekbom A, Sparén P (2001) Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 58: 844–850.
40. Tidemalm D, Langstrom N, Lichtenstein P, Runeson B (2008) Risk of suicide after suicide attempt according to coexisting psychiatric disorder: Swedish cohort study with long term follow-up. Bmj 337: a2205.
41. Toorians AW, Thomassen MC, Zweegman S, Magdeleyns EJ, Tans G, et al. (2003) Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. J Clin Endocrinol Metab 88: 5723–5729.

Mental Health of Transgender and Gender Nonconforming Youth Compared With Their Peers

Tracy A. Becerra-Culqui, PhD, MPH, OT/L,[a] Yuan Liu, PhD,[b] Rebecca Nash, MPH,[c] Lee Cromwell, MS,[d] W. Dana Flanders, MD, DSc,[c] Darios Getahun, MD, PhD, MPH,[a] Shawn V. Giammattei, PhD,[e] Enid M. Hunkeler, MA,[f] Timothy L. Lash, DSc,[c] Andrea Millman, MA,[f] Virginia P. Quinn, PhD, MPH,[a] Brandi Robinson, MPH,[d] Douglas Roblin, PhD,[g] David E. Sandberg, PhD,[h] Michael J. Silverberg, PhD, MPH,[f] Vin Tangpricha, MD, PhD,[i,j] Michael Goodman, MD, MPH[c]

abstract

BACKGROUND: Understanding the magnitude of mental health problems, particularly life-threatening ones, experienced by transgender and/or gender nonconforming (TGNC) youth can lead to improved management of these conditions.

METHODS: Electronic medical records were used to identify a cohort of 588 transfeminine and 745 transmasculine children (3–9 years old) and adolescents (10–17 years old) enrolled in integrated health care systems in California and Georgia. Ten male and 10 female referent cisgender enrollees were matched to each TGNC individual on year of birth, race and/or ethnicity, study site, and membership year of the index date (first evidence of gender nonconforming status). Prevalence ratios were calculated by dividing the proportion of TGNC individuals with a specific mental health diagnosis or diagnostic category by the corresponding proportion in each reference group by transfeminine and/or transmasculine status, age group, and time period before the index date.

RESULTS: Common diagnoses for children and adolescents were attention deficit disorders (transfeminine 15%; transmasculine 16%) and depressive disorders (transfeminine 49%; transmasculine 62%), respectively. For all diagnostic categories, prevalence was severalfold higher among TGNC youth than in matched reference groups. Prevalence ratios (95% confidence intervals [CIs]) for history of self-inflicted injury in adolescents 6 months before the index date ranged from 18 (95% CI 4.4–82) to 144 (95% CI 36–1248). The corresponding range for suicidal ideation was 25 (95% CI 14–45) to 54 (95% CI 18–218).

CONCLUSIONS: TGNC youth may present with mental health conditions requiring immediate evaluation and implementation of clinical, social, and educational gender identity support measures.

[a]*Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California; Departments of* [b]*Biostatistics and Bioinformatics and* [c]*Epidemiology, Rollins School of Public Health, and* [i]*Emory School of Medicine, Emory University, Atlanta, Georgia;* [d]*Center for Clinical and Outcomes Research, Kaiser Permanente Georgia, Atlanta, Georgia;* [e]*Rockway Institute, Alliant International University, San Francisco, California;* [f]*Division of Research, Kaiser Permanente, Northern California, Oakland, California;* [g]*Mid-Atlantic Permanente Research Institute, Kaiser Permanente Mid-Atlantic States, Rockville, Maryland;* [h]*Department of Pediatrics, Medical School, University of Michigan, Ann Arbor, Michigan; and* [j]*Atlanta Veterans Affairs Medical Center, Atlanta, Georgia*

Drs Becerra-Culqui and Goodman conceptualized and designed the study, contributed to the acquisition of data, conceptualized the analysis plan, coordinated the interpretation of results (including contributing expertise in epidemiologic methods and childhood developmental and/or psychological outcomes), and drafted and finalized the manuscript; Drs Getahun, Nash, Quinn, Roblin, and Silverberg and Ms Hunkeler conceptualized and designed the study, contributed to the acquisition of data, critically reviewed the manuscript for important intellectual content

WHAT'S KNOWN ON THIS SUBJECT: Small, specialized, clinic-based studies reveal a high prevalence of mental health diagnoses and self-reported emotional and behavioral problems among transgender and/or gender nonconforming youth.

WHAT THIS STUDY ADDS: In this large cohort study of an unselected transgender and/or gender nonconforming group, youth experienced a high relative prevalence of mental health conditions such as anxiety, depression, and attention deficit disorders compared with their cisgender counterparts.

To cite: Becerra-Culqui TA, Liu Y, Nash R, et al. Mental Health of Transgender and Gender Nonconforming Youth Compared With Their Peers. *Pediatrics.* 2018;141(5):e20173845

As gender identity develops, it may not match the gender of rearing or gender assigned at birth, which are typically based on the appearance of external genitalia.[1–3] When gender identity differs from the one assigned at birth, the terms gender diverse or gender nonconforming may apply.[4,5] Although the natural history of gender nonconformity presented in early childhood remains an area of ongoing research, some gender nonconforming children may go on to adopt an identity that is different from their assigned gender (10%–30%, according to reported estimates).[6,7] Researchers in studies of gender development in the general population support that gender-typed behavior is noticeable and stable between 3 and 8 years of age, especially in children with relatively high or low gender-typical behavior.[8,9] Individuals may identify as transgender, a term that refers more narrowly to those whose identity is "opposite" of their assigned gender.[10] Conversely, individuals who identify with the gender assigned to them at birth are sometimes referred to as cisgender.[10]

An important priority for the health of transgender and/or gender nonconforming (TGNC) children and adolescents is the identification and management of mental health conditions.[11–13] These conditions may be related to gender dysphoria, which is defined as a feeling of distress when one's assigned gender does not match their identity.[14] In addition, children with gender nonconforming behavior may experience stress from prejudice and discrimination because of being part of a minority group, which can create or exacerbate emotional and behavioral problems.[15]

The literature on TGNC youth consistently reveals a high prevalence of self-reported emotional and behavioral problems and mental health diagnoses.[16–23] Most of the available data used to address the mental health status of TGNC youth come from specialized clinics providing care to this population.[24] Although researchers in clinic-based studies offer detailed and high-quality data,[25,26] they often lack information on individuals who have not sought or had no access to specialized care. Moreover, a reliance on specialized clinics to identify study participants may yield relatively small sample sizes, making it difficult to select comparable reference groups from the same underlying population.[27]

These issues motivated the researchers in the Study of Transition, Outcomes, and Gender (STRONG), which was designed to assess morbidity among TGNC people overall and in the transfeminine and transmasculine subgroups of different ages, and captured in any care setting. However, this study communication is focused on cohort members who first presented as TGNC before their 18th birthday. Our objectives in this study were to estimate the prevalence of mental health diagnoses among transfeminine and transmasculine children and adolescents at the time of their initial presentation (index date) and compare their mental health status to that of their cisgender counterparts.

METHODS

The STRONG was designed as an electronic medical record (EMR)–based retrospective and prospective cohort study of members at 3 Kaiser Permanente (KP) sites (Georgia, Northern California, and Southern California) in partnership with the coordinating center at the Emory University Rollins School of Public Health. These KP sites provide comprehensive health services to >8.8 million members who are sociodemographically diverse and representative of their respective communities.[28,29] In the clinical setting, the identification of TGNC youth may begin at age 13 years during physical examinations as part of the psychosocial and/or behavioral assessment recommended by the American Academy of Pediatrics[30]; however, some TGNC children may be identified earlier or later in life. All activities were reviewed and approved by the institutional review boards of the 4 participating institutions.

As described previously,[31,32] persons with first evidence of TGNC status between January 1, 2006, and December 31, 2014, were identified on the basis of *International Classification of Diseases, Ninth Edition* (ICD-9) codes and the presence of specific keywords in free-text clinical notes (Supplemental Table 5). TGNC status was then verified (Supplemental Fig 1). A second free-text program was developed with additional anatomy-related or gender-affirmation keywords, which were reviewed and adjudicated for transfeminine or transmasculine status (Supplemental Table 6). Transfeminine and/or transmasculine status was assigned by using demographic information from the EMRs of 220 children whose gender assignment could not be determined from text strings because a validation revealed that the demographic variable accurately reflected assigned gender in 96% of youth. Subjects with evidence of disorders of sex development (eg, variation of chromosomal, gonadal, and/or anatomic sex development) were excluded because they may have distinct medical histories and gender identity trajectories.[33]

Ten male and 10 female cisgender KP enrollees were matched to each member of the final validated TGNC cohort on the basis of year of birth, race and/or ethnicity, site, and membership year of the index date. Because reference group enrollees had not been identified as TGNC by the methods described above, they

TABLE 1 Characteristics of the TGNC Children and Adolescents Enrolled in the STRONG

Child and Adolescent Characteristics	Transfeminine Cohort			Transmasculine Cohort		
	Transfeminine Cohort, *n* (%)	Reference Males, *n* (%)	Reference Females, *n* (%)	Transmasculine Cohort, *n* (%)	Reference Males, *n* (%)	Reference Females, *n* (%)
Age,[a] y						
3–9	161 (27)	1605 (28)	1598 (28)	90 (12)	892 (12)	888 (12)
10–17	427 (73)	4206 (72)	4204 (72)	655 (88)	6448 (88)	6459 (88)
Health plan site						
KPNC	344 (59)	3392 (58)	3378 (58)	431 (58)	4238 (58)	4245 (58)
KPSC	227 (39)	2249 (39)	2254 (39)	295 (40)	2915 (40)	2912 (40)
KPGA	17 (2.9)	170 (2.9)	170 (2.9)	19 (2.6)	187 (2.6)	190 (2.6)
Race and/or ethnicity						
Non-Hispanic white	268 (46)	2633 (45)	2629 (45)	374 (50)	3663 (50)	3671 (50)
Non-Hispanic African American	53 (9.0)	523 (9.0)	521 (9.0)	57 (7.7)	564 (7.7)	564 (7.7)
Asian American and/or Pacific Islander	37 (6.3)	367 (6.3)	370 (6.4)	60 (8.1)	596 (8.1)	594 (8.1)
Hispanic	179 (30)	1779 (31)	1772 (31)	204 (27)	2018 (27)	2020 (27)
Other and/or unknown	51 (8.7)	509 (8.8)	510 (8.8)	50 (6.7)	499 (6.8)	498 (6.8)
Use ever before index date (average visits per y)						
0	22 (3.7)	325 (5.6)	321 (5.5)	23 (3.1)	367 (5.0)	350 (4.8)
<1	15 (2.6)	568 (9.8)	530 (9.1)	25 (3.4)	763 (10)	746 (10)
1–3	127 (22)	1815 (31)	1879 (32)	154 (21)	2583 (35)	2562 (35)
>3–6	171 (29)	1712 (29)	1781 (31)	240 (32)	2200 (30)	2235 (30)
>6–9	115 (20)	757 (13)	763 (13)	107 (14)	795 (11)	777 (11)
>9	137 (23)	631 (11)	528 (9.1)	196 (26)	630 (8.6)	675 (9.2)
Unknown	1 (0.2)	3 (0.1)	0 (0.0)	0 (0.0)	2 (0.0)	2 (0.0)
Use 6 mo before index date (average visits per mo)						
0	101 (17)	2225 (38)	2062 (36)	111 (15)	2825 (39)	2502 (34)
<1	258 (44)	2846 (49)	2903 (50)	277 (37)	3531 (48)	3640 (50)
1–2	141 (24)	552 (9.5)	625 (11)	195 (26)	757 (10)	901 (12)
>2	87 (15)	186 (3.2)	212 (3.7)	162 (22)	225 (3.1)	302 (4.1)
Unknown	1 (0.2)	2 (0.0)	0 (0.0)	0 (0.0)	2 (0.0)	2 (0.0)
Total	588 (2.1)	5811 (21)	5802 (21)	745 (2.7)	7340 (27)	7347 (27)

KPGA, Kaiser Permanente Georgia; KPNC, Kaiser Permanente Northern California; KPSC, Kaiser Permanente Southern California.

[a] Assessed at index date (date of first evidence of transgender status in EMRs).

were assumed to be cisgender (ie, no evidence that gender identity does not correspond to assigned gender at birth). The race and/or ethnicity categories used were non-Hispanic white, non-Hispanic African American, Asian American and/or Pacific Islander, Hispanic, and other races. Index date was defined on the basis of the first recorded evidence of TGNC status. For some TGNC cohort members, <10 matched reference cisgender males or females were available; no TGNC individual was matched to <7 referents of either sex.

Subjects 3 through 17 years old at the index date were included in this study. Children <3 years old were excluded to reduce possible instability in gender identification and mental health diagnoses among the cohort.[8] The ICD-9 codes for mental health diagnoses were grouped into categories of conditions according to recommendations from the Mental Health Research Network[34]: anxiety disorders, attention deficit disorders, autism spectrum disorders, bipolar disorders, conduct and/or disruptive disorders, depressive disorders, eating disorders, other psychoses, personality disorders, schizophrenia spectrum disorders, self-inflicted injuries (including poisonings), substance use disorders, and suicidal ideation (Supplemental Table 7). People could be represented more than once if they had multiple diagnoses and were thus counted in each category for which they had a diagnosis.

The prevalence of mental health conditions in each of these categories was calculated for 2 time windows: any time (ever) and within 6 months before the index date. These 2 time windows were selected to examine mental health status just proximal to TGNC identification and to capture longer-standing conditions diagnosed at earlier ages (eg, autism spectrum disorders). In these calculations, the numerator for each disorder or group of disorders included persons with at least 1 relevant diagnostic code recorded during the time interval of interest. All prevalence estimates were calculated separately for transfeminine and transmasculine subjects within 2 age groups: 3 to 9 years (children) and 10 to 17 years (adolescents). Age categorization was selected to separately represent young school-aged children and adolescents by using the adolescent starting age of 10 years, corresponding to the World Health Organization's definition.[35] To assess differences in the severity of the conditions of interest, additional

TABLE 2 Prevalence of Mental Health Diagnoses in TGNC Children Ages 3–9 Years Relative to Those in Referent Groups

Categories of Mental Health Disorders	Prevalence in Transfeminine Subjects, *N* (%)	PR (95% CI)[a] in Transfeminine Subjects		Prevalence in Transmasculine Subjects, *N* (%)	PR (95% CI)[a] in Transmasculine Subjects	
		Versus Reference Males	Versus Reference Females		Versus Reference Males	Versus Reference Females
All diagnoses of interest						
Ever before index date	51 (31.7)	3.0 (2.3–3.9)	5.7 (4.2–7.7)	31 (34.4)	3.3 (2.3–4.6)	5.4 (3.7–7.8)
6 mo before index date	46 (28.6)	6.0 (4.3–8.4)	13.0 (8.7–19.6)	26 (28.9)	5.9 (3.8–9.0)	10.7 (6.4–17.8)
Anxiety disorders						
Ever before index date	19 (11.8)	4.4 (2.6–7.4)	6.3 (3.6–10.9)	14 (15.6)	6.3 (3.3–11.9)	6.0 (3.2–11.3)
6 mo before index date	15 (9.3)	16.3 (6.7–41.4)	23.3 (8.8–68.5)	9 (10.0)	9.8 (3.4–27.6)	12.2 (4.0–37.3)
Attention deficit disorders						
Ever before index date	24 (14.9)	3.3 (2.1–5.0)	6.1 (3.8–9.9)	14 (15.6)	2.8 (1.6–4.9)	6.9 (3.6–13.2)
6 mo before index date	22 (13.7)	5.0 (3.1–8.1)	10.9 (6.1–19.6)	14 (15.6)	4.2 (2.3–7.6)	12.6 (5.9–26.8)
Autism spectrum disorders						
Ever before index date	8 (5.0)	2.2 (0.9–4.9)	11.8 (3.7–38.9)	0	NC	NC
6 mo before index date	8 (5.0)	3.9 (1.5–9.5)	20.8 (5.5–95.3)	0	NC	NC
Conduct and/or disruptive disorders						
Ever before index date	12 (7.5)	3.3 (1.5–6.7)	14.2 (5.4–38.8)	7 (7.8)	6.2 (2.0–17.5)	12.3 (3.5–45.5)
6 mo before index date	8 (5.0)	8.3 (2.8–23.8)	83.0 (11.0–3707.3)	[b]	13.7 (2.3–95.1)	20.5 (2.9–229.2)
Depressive disorders						
Ever before index date	9 (5.6)	6.7 (2.5–17.0)	7.8 (2.9–20.6)	10 (11.1)	27.5 (7.7–123.0)	12.3 (5.0–30.5)
6 mo before index date	6 (3.7)	8.8 (2.4–31.1)	12.3 (3.1–51.5)	8 (8.9)	43.0 (8.4–422.3)	28.5 (6.7–170.2)
Eating disorders						
Ever before index date	[b]	3.7 (0.8–12.6)	6.7 (1.4–28.8)	0	NC	NC
6 mo before index date	[b]	10.0 (0.1–787.4)	10.0 (0.1–784.0)	0	NC	NC

NC, not calculated because there were 0 cases among transgender subjects.

[a] Logistic regression with exact 95% CIs for rare events (prevalence ≤10% in both the transgender and referent cohorts) or logistic regression with log link and approximate 95% CIs for not-rare events (>10% prevalence in either the transgender or referent cohorts).

[b] Fewer than 5 cases were not reported.

analyses were conducted for admittance or most serious diagnoses associated with hospitalizations.

Each prevalence estimate in the TGNC cohort was compared with corresponding estimates among matched cisgender male and female referents. For ease in presenting results, cisgender males and females will be referred to as male or female referents. Referents were assigned the same index date as the matched TGNC cohort member. For rare events (prevalence ≤10% in both the TGNC and referent cohorts), the prevalence ratios (PRs) were approximated by calculating the odds ratios with exact 95% confidence intervals (CIs). For events with >10% prevalence in either group, PRs and CIs were calculated by using logistic regression with the log link option.

In addition to the primary analysis that captures the true prevalence of mental health conditions, we conducted sensitivity analyses to address possible differences in the prevalence of mental health conditions because of differences in health care visit frequency (use) between TGNC cohort members and those in the referent groups. We excluded the index date from the time window, and when the sample size was sufficient (>5 cases in each group), the PR estimates were adjusted for use of care. Average health care use was calculated for each individual by dividing the total number of visits by the cumulative duration of enrollment; this was expressed as the number of visits per year of enrollment in the analyses of "ever" prevalence and as the number of visits per month of enrollment in the analyses within 6 months before the index date. In adjusted analyses, average use was dichotomized for each time interval as above (high) or below (low) the median by using cutoffs for the overall population.

Analyses were conducted by using SAS version 9.4 (SAS Institute, Inc, Cary, NC) with custom macros developed at the Biostatistics and Bioinformatics Shared Resource at the Winship Cancer Institute of Emory University.[36]

RESULTS

A total of 2164 cohort candidates 3 to 17 years of age at the index date were initially identified in the EMR. After validation, 1347 (62%) were confirmed as TGNC. People excluded from the TGNC cohort were most often those with keywords referring to family or partners, standard disclaimers not related to care (eg, listing indications for hormone use), or evidence of disorders of sex development. After excluding subjects with unknown gender assigned at birth ($N = 14$), the final analysis data set was based on a cohort of 1333 subjects matched with

TABLE 3 Prevalence of Mental Health Diagnoses in TGNC Adolescents Ages 10–17 Years Relative to Those in Referent Groups

Categories of Mental Health Disorders	Prevalence in Transfeminine Subjects, *N* (%)	PR (95% CI)[a] in Transfeminine Subjects		Prevalence in Transmasculine Subjects, *N* (%)	PR (95% CI)[a] in Transmasculine Subjects	
		Versus Reference Males	Versus Reference Females		Versus Reference Males	Versus Reference Females
All diagnoses of interest						
Ever before index date	303 (71.0)	3.0 (2.8–3.3)	3.6 (3.3–3.9)	488 (74.5)	3.0 (2.8–3.2)	3.7 (3.4–3.9)
6 mo before index date	253 (59.3)	7.8 (6.8–8.9)	8.6 (7.5–9.8)	429 (65.5)	7.8 (7.1–8.7)	8.7 (7.8–9.6)
Anxiety disorders						
Ever before index date	159 (37.2)	5.0 (4.2–5.8)	4.2 (3.6–4.9)	255 (38.9)	4.9 (4.3–5.6)	4.0 (3.5–4.5)
6 mo before index date	106 (24.8)	18.0 (13.3–24.4)	9.2 (7.2–11.8)	175 (26.7)	15.7 (12.5–19.6)	8.7 (7.2–10.5)
Attention deficit disorders						
Ever before index date	107 (25.1)	2.0 (1.7–2.4)	5.3 (4.3–6.5)	106 (16.2)	1.3 (1.0–1.5)	3.3 (2.7–4.1)
6 mo before index date	68 (15.9)	3.8 (2.9–4.9)	9.0 (6.6–12.4)	69 (10.5)	2.5 (1.9–3.3)	6.4 (4.6–8.8)
Autism spectrum disorders						
Ever before index date	31 (7.3)	4.1 (2.6–6.4)	25.2 (12.7–52.9)	24 (3.7)	1.8 (1.1–2.8)	7.6 (4.3–13.5)
6 mo before index date	25 (5.9)	8.1 (4.6–14.3)	260.8 (42.5–10 733.9)	17 (2.6)	3.4 (1.8–6.1)	17.2 (7.4–42.1)
Bipolar disorders						
Ever before index date	23 (5.4)	9.9 (5.3–18.5)	10.3 (5.5–19.5)	34 (5.2)	8.6 (5.2–13.9)	8.0 (4.9–12.9)
6 mo before index date	16 (3.8)	18.1 (7.5–46.9)	14.8 (6.4–35.6)	19 (2.9)	11.3 (5.5–23.3)	14.8 (6.9–32.8)
Conduct and/or disruptive disorders						
Ever before index date	60 (14.1)	2.8 (2.1–3.7)	6.6 (4.8–9.0)	59 (9.0)	1.7 (1.3–2.3)	4.5 (3.2–6.2)
6 mo before index date	22 (5.2)	5.3 (3.0–9.1)	12.6 (6.4–25.2)	27 (4.1)	5.5 (3.3–9.0)	10.6 (5.9–19.1)
Depressive disorders						
Ever before index date	207 (48.5)	5.8 (5.1–6.7)	4.4 (3.9–5.0)	403 (61.5)	7.0 (6.4–7.8)	5.7 (5.2–6.2)
6 mo before index date	172 (40.3)	23.5 (18.2–30.4)	10.1 (8.4–12.2)	326 (49.8)	22.8 (19.0–27.3)	13.3 (11.5–15.4)
Eating disorders						
Ever before index date	18 (4.2)	7.7 (3.9–14.9)	3.3 (1.8–5.7)	28 (4.3)	6.0 (3.6–9.8)	3.2 (2.0–5.0)
6 mo before index date	11 (2.6)	18.5 (6.2–61.2)	6.1 (2.6–13.8)	19 (2.9)	27.5 (11.0–77.6)	8.7 (4.4–17.0)
Psychoses						
Ever before index date	19 (4.5)	19.5 (8.6–47.3)	12.2 (5.9–25.5)	32 (4.9)	12.2 (7.0–21.3)	14.4 (8.1–25.9)
6 mo before index date	10 (2.3)	20.1 (6.2–75.4)	100.6 (14.2–4375.0)	18 (2.8)	22.7 (9.4–60.6)	30.4 (11.5–93.8)
Personality disorders						
Ever before index date	10 (2.3)	14.4 (4.9–44.7)	11.2 (4.1–31.2)	15 (2.3)	11.6 (5.1–26.6)	7.9 (3.7–16.6)
6 mo before index date	[b]	19.8 (2.8–220.0)	19.8 (2.8–219.9)	9 (1.4)	29.9 (7.4–172.1)	29.9 (7.4–172.4)
Schizophrenia spectrum disorders						
Ever before index date	5 (1.2)	49.7 (5.5–2357.0)	24.9 (4.1–261.7)	13 (2.0)	21.7 (7.7–69.9)	32.6 (10.0–137.8)
6 mo before index date	[b]	[c]	14.8 (1.7–178.2)	10 (1.5)	99.8 (14.2–4338.3)	50.0 (10.6–470.2)
Self-inflicted injuries						
Ever before index date	11 (2.6)	3.9 (1.8–8.2)	4.1 (1.8–8.6)	54 (8.2)	14.0 (9.1–21.8)	8.7 (5.9–12.8)
6 mo before index date	7 (1.6)	69.9 (9.0–3159.2)	17.5 (4.4–81.7)	28 (4.3)	143.7 (36.1–1247.8)	20.5 (10.4–42.4)
Substance use disorders						
Ever before index date	33 (7.7)	3.0 (1.9–4.5)	3.7 (2.4–5.6)	46 (7.0)	2.4 (1.7–3.4)	3.3 (2.3–4.7)
6 mo before index date	24 (5.6)	5.8 (3.3–9.8)	8.9 (4.9–16.0)	34 (5.2)	4.5 (2.9–6.9)	8.2 (5.0–13.2)
Suicidal ideation						
Ever before index date	32 (7.5)	17.8 (9.7–33.6)	11.3 (6.5–19.4)	68 (10.4)	21.2 (13.8–33.2)	11.0 (7.7–15.9)
6 mo before index date	21 (4.9)	54.2 (18.2–218.3)	31.0 (12.6–86.7)	47 (7.2)	45.2 (22.9–97.1)	24.9 (14.3–44.6)

[a] Logistic regression with exact 95% CIs for rare events (prevalence ≤10% in both the transgender and referent cohorts) or logistic regression with log link and approximate 95% CIs for not-rare events (>10% prevalence in either the transgender or referent cohorts).

[b] Fewer than 5 cases were not reported.

[c] Not calculated because there were 0 cases among referents.

TABLE 4 Prevalence of Hospitalization for Mental Health Diagnoses in TGNC Children Ages 10–17 Years Relative to Those in Referent Groups

Categories of Mental Health Disorders	Prevalence in Transfeminine Subjects, *N* (%)	PR (95% CI)[a] in Transfeminine Subjects		Prevalence in Transmasculine Subjects, *N* (%)	PR (95% CI)[a] in Transmasculine Subjects	
		Versus Reference Males	Versus Reference Females		Versus Reference Males	Versus Reference Females
All diagnoses of interest						
Ever before index date	58 (13.6)	9.9 (6.9–14.0)	8.9 (6.3–12.5)	99 (15.1)	10.2 (7.8–13.3)	7.8 (6.1–10.0)
6 mo before index date	33 (7.7)	43.9 (19.7–110.7)	35.1 (16.7–80.4)	59 (9.0)	35.3 (20.4–64.1)	21.9 (13.7–35.8)
Anxiety disorders						
Ever before index date	9 (2.1)	9.0 (3.2–24.9)	6.0 (2.3–14.8)	25 (3.8)	15.0 (7.7–29.8)	13.4 (7.1–26.0)
6 mo before index date	6 (1.4)	59.8 (7.2–2757.2)	29.9 (5.3–303.7)	13 (2.0)	43.4 (11.9–238.3)	32.6 (10.0–137.8)
Attention deficit disorders						
Ever before index date	20 (4.7)	9.8 (5.0–19.1)	14.7 (7.0–31.7)	14 (2.1)	4.0 (2.0–7.7)	9.4 (4.2–20.9)
6 mo before index date	6 (1.4)	19.9 (4.2–123.6)	59.8 (7.2–2755.8)	[b]	[c]	9.9 (1.3–74.0)
Autism spectrum disorders						
Ever before index date	[b]	6.6 (1.4–28.0)	39.7 (3.9–1957.7)	5 (0.8)	5.0 (1.3–16.0)	8.3 (2.0–32.6)
6 mo before index date	[b]	[c]	[c]	[b]	3.3 (0.1–41.0)	[c]
Bipolar disorders						
Ever before index date	12 (2.8)	30.3 (9.1–129.6)	13.5 (5.2–36.4)	18 (2.8)	10.1 (4.9–20.7)	9.1 (4.5–18.2)
6 mo before index date	[b]	39.7 (3.9–1958.7)	19.8 (2.8–219.9)	8 (1.2)	15.9 (4.6–62.0)	19.9 (5.3–90.7)
Conduct and/or disruptive disorders						
Ever before index date	10 (2.3)	16.8 (5.5–56.4)	16.8 (5.5–56.4)	10 (1.5)	5.9 (2.4–13.6)	6.7 (2.7–15.9)
6 mo before index date	5 (1.2)	49.7 (5.5–2357.0)	[c]	[b]	39.6 (3.9–1951.1)	39.6 (3.9–1954.4)
Depressive disorders						
Ever before index date	41 (9.6)	21.1 (12.1–38.1)	10.3 (6.4–16.4)	83 (12.7)	17.8 (12.5–25.2)	9.1 (6.8–12.1)
6 mo before index date	26 (6.1)	68.0 (23.4–269.3)	54.3 (20.4–182.2)	49 (7.5)	104.0 (41.5–335.9)	21.7 (12.9–37.2)
Eating disorders						
Ever before index date	[b]	6.6 (0.5–57.7)	2.8 (0.3–14.9)	6 (0.9)	29.8 (5.3–302.1)	4.0 (1.3–10.9)
6 mo before index date	[b]	[c]	3.3 (0.1–41.0)	[b]	29.8 (5.3–302.1)	4.0 (1.3–10.9)
Psychoses						
Ever before index date	8 (1.9)	26.7 (6.4–156.9)	11.4 (3.6–37.2)	10 (1.5)	20.0 (6.2–74.7)	12.5 (4.4–36.6)
6 mo before index date	5 (1.2)	49.7 (5.5–2357.0)	49.7 (5.5–2355.8)	[b]	19.8 (2.8–219.1)	9.9 (1.8–53.3)
Personality disorders						
Ever before index date	[b]	39.7 (3.9–1958.7)	19.8 (2.8–219.9)	8 (1.2)	26.5 (6.3–155.7)	8.9 (3.0–26.0)
6 mo before index date	0 (0)	NC	NC	7 (1.1)	[c]	69.7 (8.9–3144.6)
Schizophrenia spectrum disorders						
Ever before index date	[b]	[c]	14.8 (1.7–178.2)	[b]	9.9 (1.8–53.2)	13.2 (2.2–90.4)
6 mo before index date	0 (0)	NC	NC	[b]	9.9 (0.1–773.9)	9.9 (0.1–775.2)
Self-inflicted injuries						
Ever before index date	[b]	6.6 (0.5–57.7)	4.9 (0.4–34.6)	13 (2.0)	65.2 (14.7–596.2)	13.0 (5.3–33.4)
6 mo before index date	[b]	[c]	[c]	7 (1.1)	[c]	34.8 (6.6–344.4)
Substance use disorders						
Ever before index date	8 (1.9)	5.7 (2.1–14.7)	4.2 (1.6–10.1)	16 (2.4)	6.2 (3.1–12.0)	6.2 (3.1–12.1)
6 mo before index date	6 (1.4)	29.9 (5.3–303.9)	12.0 (3.0–49.7)	9 (1.4)	11.2 (3.8–33.5)	11.2 (3.8–33.6)
Suicidal ideation						
Ever before index date	9 (2.1)	15.1 (4.8–51.7)	5.6 (2.2–13.6)	29 (4.4)	19.8 (10.2–40.1)	11.5 (6.5–20.4)
6 mo before index date	7 (1.6)	[c]	23.3 (5.3–140.2)	17 (2.6)	24.5 (9.6–70.1)	21.5 (8.7–57.7)

NC, not calculated because there were 0 cases among transgender subjects.

[a] Logistic regression with exact 95% CIs for rare events (prevalence ≤10% in both the transgender and referent cohorts) or logistic regression with log link and approximate 95% CIs for not-rare events (>10% prevalence in either the transgender or referent cohorts).

[b] Fewer than 5 cases were not reported.

[c] Not calculated because there were 0 cases among referents.

13 151 reference males and 13 149 reference females.

The cohort included 588 (44%) transfeminine and 745 (56%) transmasculine children and adolescents (Table 1). Children <10 years old represented 27% of the transfeminine cohort and 12% of the transmasculine cohort. Compared with TGNC children (*n* = 251), in which 36% (*n* = 90) were transfeminine, 61% (*n* = 655) of adolescents (*n* = 1082) were transmasculine. More than 45% of subjects in both groups were white; Hispanics represented 30% of transfeminine and 27% of transmasculine subjects, whereas the remainder of the study population was approximately equally distributed among African Americans, Asian Americans and/or Pacific Islanders, and persons whose race and/or ethnicity was characterized as other or unknown. Health care use levels were much higher in both transfeminine and transmasculine subjects than in those in the corresponding reference groups.

The most common diagnostic categories among TGNC children 3 to 9 years of age were attention deficit disorders (15% transfeminine; 16% transmasculine) and anxiety disorders (12% transfeminine; 16% transmasculine; Table 2). The PR (95% CI) estimates for attention deficit disorders ranged from 2.8 (95% CI 1.6–4.9) to 13 (95% CI 5.9–27). The PR (95% CI) estimates for anxiety disorders ranged from 4.4 (95% CI 2.6–7.4) to 23 (95% CI 8.8–69) depending on the time window before the index date and the reference group. Among transfeminine children, 5% had an autism spectrum disorder diagnosis; however, no cases were observed in transmasculine children. For all the diagnostic categories, the most pronounced PR estimates were observed within the 6-month period before the index date. Among transfeminine children, the highest PR (95% CI) estimate was for conduct and/or disruptive disorders relative to reference females (83 [95% CI 11–3707]). Among transmasculine children, the highest PR (95% CI) estimate was for depressive disorders relative to reference males (43 [95% CI 8.4–422]). Additional analyses of the prevalence of hospitalizations by mental health diagnostic category were not possible in this age group because of small sample sizes.

In the adolescent group (age 10–17 years), like in the younger age group, attention deficit disorders and anxiety disorders remained common ("ever" prevalence: 25% transfeminine and 16% transmasculine; 40% both transfeminine and transmasculine, respectively; Table 3). The diagnostic category with the highest prevalence in this age group was depressive disorders, which were found in 49% of transfeminine and 62% of transmasculine subjects. For all diagnostic categories, PR estimates used to compare STRONG adolescents to matched reference groups were highest within 6 months before the index date. Compared with reference females, transfeminine and transmasculine adolescents experienced particularly pronounced increased prevalence in psychoses (PR 101 and 95% CI 14–4375; PR 30 and 95% CI 12–94, respectively). Additionally, the PR estimates among transfeminine subjects were particularly elevated for autism spectrum disorders (PR 261; 95% CI 43–10 734) and among transmasculine subjects for schizophrenia spectrum disorders (PR 50; 95% CI 11–470) compared with reference females. Compared with reference males, PR estimates for suicidal ideation and self-inflicted injuries for transfeminine subjects were 54 (95% CI 18–218) and 70 (95% CI 9.0–159), respectively, which were also high among transmasculine subjects, (45 [95% CI 23–97] and 144 [95% CI 14–4338], respectively).

When prevalence estimates were limited to mental health conditions recorded during hospitalizations, the patterns among adolescents generally remained the same. In several instances, however, the PR estimates could not be calculated because of the absence of cases in the reference groups (Table 4).

The median cutoff values used for adjusted analyses were 3.2 average visits per year for the "ever" analyses and 0.2 average visits per month for the 6-month analyses. The prevalence estimates were slightly attenuated or remained approximately the same for most diagnostic categories. However, some estimates changed appreciably. For children 3 to 9 years, adjusting for use 6 months before and excluding the index date produced the largest decrease in the PR (95% CI) for anxiety disorders, from 23 (95% CI 8.8–69) to 9.0 (95% CI 2.9–29) when transfeminine children were compared with reference males (Supplemental Table 8). The PR (95% CI) for suicidal ideation among transfeminine adolescents compared with reference males within 6 months of the index date decreased from 54 (95% CI 18–218) to 38 (95% CI 12–159; Supplemental Table 9).

DISCUSSION

The results of this study reveal that among TGNC youth, mental health conditions, specifically anxiety and depression, are common and often severe among adolescents, as evidenced by diagnoses associated with hospitalizations. Gender nonconforming children (3–9 years of age) have a higher prevalence of anxiety and attention deficit disorders compared with their cisgender counterparts. In nearly all instances, mental health diagnoses were more common in the TGNC youth than in referent children and adolescents.

These results support findings from previous research in which the sample sizes were much smaller.[17,19–22,37–42] Researchers in a survey of 101 transfeminine and transmasculine patients ages 12 to 24 years in a transgender youth clinic in Los Angeles found that 35% had symptoms of depression and >50% had suicidal thoughts.[19] In comparison, we found that adolescents had a higher prevalence (40%–60%) of depression but a lower prevalence of suicidal ideation (5%–10%). In a medical record abstraction study of 97 transfeminine and transmasculine patients ages 4 to 20 years presenting to the Gender Management Service Clinic at Boston Children's Hospital, 44% presented with a significant psychiatric history, 21% had a history of self-mutilation, and 9% had documentation of suicide attempts.[22] In a UK study, a baseline chart review of children 5 to 11 years old referred to a national specialty clinic revealed that 17% had symptoms of anxiety, and 15% had a history of suicidal ideation, self-harm, and/or a diagnosis of attention-deficit/hyperactivity disorder recorded before entering services.[39] Our results for children were similar for demonstrated anxiety (9%–16%) and attention deficit disorders (14%–16%). Direct comparisons to the current study are challenging because there are methodological differences. Two important differences are the way in which mental health conditions were ascertained and presentations of age. In addition, we included a broader population of children and adolescents who were not necessarily seeking treatment for gender-related issues.

In recent years, researchers in several studies have suggested that gender dysphoria may be associated with autism spectrum disorders.[43–45] The most widely cited evidence supporting this hypothesis comes from a study of 204 children and/or adolescents referred to the Gender Identity Clinic in Amsterdam.[46] The presence of an autism spectrum disorder was established via a standardized diagnostic interview,[47] yielding a prevalence of 10% among transfeminine patients and 4% among transmasculine patients, which was reported by the authors to be higher than the 1% estimate reported in the general population. The prevalence of autism spectrum disorders in our study was somewhat lower (7% in transfeminine and 3% in transmasculine subjects across both age groups), but our case ascertainment was based on documented diagnostic codes, and the denominator in our calculations was not limited to children with established gender dysphoria. With these differences in mind, our results are generally comparable to those reported in the Dutch study.

The gender ratio in this TGNC cohort reveals that transfeminine youth may present earlier in age than transmasculine individuals, which may pose a unique challenge to the early identification of mental health needs in transmasculine children and adolescents. Historically, researchers in studies of TGNC adolescents have reported a greater proportion of transfeminine than transmasculine subjects, but in recent years, the direction of the transmasculine: transfeminine ratio appears to have changed.[48] For example, researchers in 1 recent study observed that transmasculine youth with gender dysphoria (aged 12–24 years) presented in significantly higher numbers than their transfeminine counterparts.[19] Our data, which were based on EMRs, were used to confirm this observation. Therefore, providers should also be aware of the growing transmasculine population needing timely and appropriate medical and psychosocial services.

An important contribution of the STRONG to the extant literature is its relatively large cohort, which allowed for focusing on previously understudied groups (such as young children), and an evaluation of relatively rare events (such as hospitalizations). In addition, the current study was based on children and adolescents who were not necessarily in specialized care and enrolled in a large health care system; and we did not require participant opt-in. The availability of a well-defined source population allowed for matching transfeminine and transmasculine study subjects to male and female referents of the same age, race and/or ethnicity, and geographic region. This design feature permitted direct comparisons of prevalence estimates among transfeminine, transmasculine, and cisgender referent groups.

A limitation of this study is its cross-sectional design. Although we were able to retrospectively ascertain mental health conditions before the index date and we matched on the basis of membership year, a differential ascertainment of diagnoses could have occurred. The identification of the TGNC cohort was based on health care use, which is different from the matched referent groups. Results from sensitivity analyses adjusting for use and excluding the index date revealed a similar or slight attenuation of the PR results for most diagnostic categories. However, when adjusting for use 6 months before the index date, a more notable attenuation of PRs was seen in anxiety disorders in transfeminine children and suicidal ideation in transfeminine adolescents compared with reference males, indicating possible higher surveillance of mental health conditions in the several months before cohort identification. Nevertheless, this baseline study reveals that TGNC youth experience a multitude of mental health problems before initial presentation. However, there is indication that TGNC children who receive meaningful gender identity support do not necessarily experience elevated rates of depression and anxiety.[49] As the STRONG cohort follow-up extends, it will be possible to examine temporal changes in the frequency and severity of mental health problems, particularly in relation to the age of gender affirmation, which is an area of considerable uncertainty, and the impact of interventions to treat gender dypshoria.[50–53]

CONCLUSIONS

The most important finding is the high frequency of mental health conditions that TGNC children and adolescents experience. Especially worrisome are the results for suicidal ideation and self-inflicted injuries with prevalence estimates orders of a magnitude that is higher in TGNC children and adolescents than in matched cisgender reference groups. For nearly all mental health disorders, the PRs increased during the time window closest to the index date. Overall, these data reveal that children and adolescents presenting as TGNC to health care providers may require not only thorough and immediate evaluation of mental health needs but also urgent implementation of social and educational measures of gender identity support.

ABBREVIATIONS

CI: confidence interval
EMR: electronic medical record
ICD-9: *International Classification of Diseases, Ninth Edition*
KP: Kaiser Permanente
PR: prevalence ratio
STRONG: Study of Transition, Outcomes, and Gender
TGNC: transgender and/or gender nonconforming

---

within their areas of expertise (such as epidemiologic methods, bias, health care access and health service use interpretation, and the broad messaging of the manuscript), and revised the manuscript; Drs Liu, Flanders, and Nash provided substantial statistical analysis consultation, conducted the analyses, and critically reviewed and revised the manuscript for important statistical interpretation of the data; Ms Cromwell substantially contributed to the design of multisite data collection, critically reviewed the manuscript for appropriate interpretation of the data variables with respect to the results, and revised the manuscript; Ms Millman and Ms Robinson conceptualized the study and substantially contributed to the acquisition of data by coordinating site data collection, critically reviewed and revised the manuscript by providing and ensuring the interpretation of results with respect to site-specific patient populations, and revised the manuscript; Drs Giammattei, Sandberg, and Tangpricha provided clinical consultation regarding the interpretation of results, revised the manuscript, and critically reviewed the manuscript for important intellectual content specific to transgender and/or gender nonconforming youth, gender transitioning, and the mental health outcomes discussed in the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2017-3845

Accepted for publication Feb 22, 2018

Address correspondence to Michael Goodman, MD, MPH, Department of Epidemiology, Emory University School of Public Health, 1518 Clifton Rd, NE, CNR 3021, Atlanta, GA 30322. E-mail: mgoodm2@emory.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Funded by contract AD-12-11-4532 from the Patient-Centered Outcomes Research Institute and grant R21HD076387 from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: Companions to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2017-3004 and www.pediatrics.org/cgi/doi/10.1542/peds.2018-0361.

REFERENCES

1. Lombardi E. Enhancing transgender health care. *Am J Public Health.* 2001;91(6):869–872
2. Wallien MS, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. *J Am Acad Child Adolesc Psychiatry.* 2008;47(12):1413–1423
3. Steensma TD, van der Ende J, Verhulst FC, Cohen-Kettenis PT. Gender variance in childhood and sexual orientation in adulthood: a prospective study. *J Sex Med.* 2013;10(11):2723–2733
4. Leibowitz SF, Spack NP. The development of a gender identity psychosocial clinic: treatment issues, logistical considerations, interdisciplinary cooperation, and future initiatives. *Child Adolesc Psychiatr Clin N Am.* 2011;20(4):701–724
5. Chen D, Hidalgo MA, Leibowitz S, et al. Multidisciplinary care for gender-diverse youth: a narrative review and unique model of gender-affirming care. *Transgend Health.* 2016;1(1):117–123
6. Costa R, Carmichael P, Colizzi M. To treat or not to treat: puberty

suppression in childhood-onset gender dysphoria. *Nat Rev Urol*. 2016;13(8):456–462

7. Fast AA, Olson KR. Gender development in transgender preschool children [published online ahead of print April 25, 2017]. *Child Dev*. doi:10.1111/cdev.12758
8. Golombok S, Rust J, Zervoulis K, Croudace T, Golding J, Hines M. Developmental trajectories of sex-typed behavior in boys and girls: a longitudinal general population study of children aged 2.5-8 years. *Child Dev*. 2008;79(5):1583–1593
9. Martin CL, Ruble DN. Patterns of gender development. *Annu Rev Psychol*. 2010;61:353–381
10. Rosenthal SM. Transgender youth: current concepts. *Ann Pediatr Endocrinol Metab*. 2016;21(4):185–192
11. Coleman E, Bockting WO, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int J Transgenderism*. 2012;13(4):165–232
12. Wilczynski C, Emanuele MA. Treating a transgender patient: overview of the guidelines. *Postgrad Med*. 2014;126(7):121–128
13. Levine DA; Committee on Adolescence. Office-based care for lesbian, gay, bisexual, transgender, and questioning youth. *Pediatrics*. 2013;132(1). Available at: www.pediatrics.org/cgi/content/full/132/1/e297
14. Schneider C, Cerwenka S, Nieder TO, et al. Measuring gender dysphoria: a multicenter examination and comparison of the Utrecht Gender Dysphoria Scale and the Gender Identity/Gender Dysphoria Questionnaire for adolescents and adults. *Arch Sex Behav*. 2016;45(3):551–558
15. Grossman AH, D'Augelli AR. Transgender youth and life-threatening behaviors. *Suicide Life Threat Behav*. 2007;37(5):527–537
16. Cohen-Kettenis PT, Steensma TD, de Vries AL. Treatment of adolescents with gender dysphoria in the Netherlands. *Child Adolesc Psychiatr Clin N Am*. 2011;20(4):689–700
17. de Vries AL, Doreleijers TA, Steensma TD, Cohen-Kettenis PT. Psychiatric comorbidity in gender dysphoric adolescents. *J Child Psychol Psychiatry*. 2011;52(11):1195–1202
18. Nahata L, Quinn GP, Caltabellotta NM, Tishelman AC. Mental health concerns and insurance denials among transgender adolescents. *LGBT Health*. 2017;4(3):188–193
19. Olson J, Schrager SM, Belzer M, Simons LK, Clark LF. Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender dysphoria. *J Adolesc Health*. 2015;57(4):374–380
20. Reisner SL, Biello KB, White Hughto JM, et al. Psychiatric diagnoses and comorbidities in a diverse, multicity cohort of young transgender women: baseline findings from project LifeSkills. *JAMA Pediatr*. 2016;170(5):481–486
21. Reisner SL, Vetters R, Leclerc M, et al. Mental health of transgender youth in care at an adolescent urban community health center: a matched retrospective cohort study. *J Adolesc Health*. 2015;56(3):274–279
22. Spack NP, Edwards-Leeper L, Feldman HA, et al. Children and adolescents with gender identity disorder referred to a pediatric medical center. *Pediatrics*. 2012;129(3):418–425
23. de Vries AL, Kreukels BP, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Comparing adult and adolescent transsexuals: an MMPI-2 and MMPI-A study. *Psychiatry Res*. 2011;186(2–3):414–418
24. Olson-Kennedy J, Cohen-Kettenis PT, Kreukels BP, et al. Research priorities for gender nonconforming/transgender youth: gender identity development and biopsychosocial outcomes. *Curr Opin Endocrinol Diabetes Obes*. 2016;23(2):172–179
25. Dekker MJ, Wierckx K, Van Caenegem E, et al. A European network for the investigation of gender incongruence: endocrine part. *J Sex Med*. 2016;13(6):994–999
26. Kreukels BP, Haraldsen IR, De Cuypere G, Richter-Appelt H, Gijs L, Cohen-Kettenis PT. A European network for the investigation of gender incongruence: the ENIGI initiative. *Eur Psychiatry*. 2012;27(6):445–450
27. Reisner SL, Deutsch MB, Bhasin S, et al. Advancing methods for US transgender health research. *Curr Opin Endocrinol Diabetes Obes*. 2016;23(2):198–207
28. Koebnick C, Langer-Gould AM, Gould MK, et al. Sociodemographic characteristics of members of a large, integrated health care system: comparison with US Census Bureau data. *Perm J*. 2012;16(3):37–41
29. Gordon NP. *How Does the Adult Kaiser Permanente Membership in Northern California Compare With the Larger Community?* Oakland, CA: Kaiser Permanente Division of Research; 2006
30. American Academy of Pediatrics. Periodicity schedule. 2017. Available at: https://www.aap.org/en-us/Documents/periodicity_schedule.pdf. Accessed July 12, 2017
31. Roblin D, Barzilay J, Tolsma D, et al. A novel method for estimating transgender status using electronic medical records. *Ann Epidemiol*. 2016;26(3):198–203
32. Quinn VP, Nash R, Hunkeler E, et al. Cohort profile: Study of Transition, Outcomes and Gender (STRONG) to assess health status of transgender people. *BMJ Open*. 2017;7(12):e018121
33. Lee PA, Houk CP, Ahmed SF, Hughes IA; International Consensus Conference on Intersex Organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. *Pediatrics*. 2006;118(2). Available at: www.pediatrics.org/cgi/content/full/118/2/e488
34. Coleman KJ, Stewart C, Waitzfelder BE, et al. Racial-ethnic differences in psychiatric diagnoses and treatment across 11 health care systems in the mental health research network. *Psychiatr Serv*. 2016;67(7):749–757
35. World Health Organization. Recognizing adolescence. 2014. Available at: http://apps.who.int/adolescent/second-decade/section2/page1/recognizing-adolescence.html. Accessed November 7, 2017
36. Nickleach D, Liu Y, Shrewsberry A, Ogan K, Kim S, Wang Z. SAS macros to conduct common biostatistical analyses and generate reports. In: SouthEast SAS User Group; October 20-23, 2013; St. Pete Beach, FL
37. Arcelus J, Claes L, Witcomb GL, Marshall E, Bouman WP. Risk factors for non-suicidal self-injury

among trans youth. *J Sex Med*. 2016;13(3):402–412

38. Kaltiala-Heino R, Sumia M, Työläjärvi M, Lindberg N. Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development. *Child Adolesc Psychiatry Ment Health*. 2015;9:9
39. Holt V, Skagerberg E, Dunsford M. Young people with features of gender dysphoria: demographics and associated difficulties. *Clin Child Psychol Psychiatry*. 2016;21(1):108–118
40. Shields JP, Cohen R, Glassman JR, Whitaker K, Franks H, Bertolini I. Estimating population size and demographic characteristics of lesbian, gay, bisexual, and transgender youth in middle school. *J Adolesc Health*. 2013;52(2):248–250
41. Diemer EW, Grant JD, Munn-Chernoff MA, Patterson DA, Duncan AE. Gender identity, sexual orientation, and eating-related pathology in a national sample of college students. *J Adolesc Health*. 2015;57(2):144–149
42. Chen M, Fuqua J, Eugster EA. Characteristics of referrals for gender dysphoria over a 13-year period. *J Adolesc Health*. 2016;58(3):369–371
43. Glidden D, Bouman WP, Jones BA, Arcelus J. Gender dysphoria and autism spectrum disorder: a systematic review of the literature. *Sex Med Rev*. 2016;4(1):3–14
44. Jacobs LA, Rachlin K, Erickson-Schroth L, Janssen A. Gender dysphoria and co-occurring autism spectrum disorders: review, case examples, and treatment considerations. *LGBT Health*. 2014;1(4):277–282
45. Van Der Miesen AI, Hurley H, De Vries AL. Gender dysphoria and autism spectrum disorder: a narrative review. *Int Rev Psychiatry*. 2016;28(1):70–80
46. de Vries AL, Noens IL, Cohen-Kettenis PT, van Berckelaer-Onnes IA, Doreleijers TA. Autism spectrum disorders in gender dysphoric children and adolescents. *J Autism Dev Disord*. 2010;40(8):930–936
47. Wing L, Leekam SR, Libby SJ, Gould J, Larcombe M. The diagnostic interview for social and communication disorders: background, inter-rater reliability and clinical use. *J Child Psychol Psychiatry*. 2002;43(3):307–325
48. Aitken M, Steensma TD, Blanchard R, et al. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. *J Sex Med*. 2015;12(3):756–763
49. Olson KR, Durwood L, DeMeules M, McLaughlin KA. Mental health of transgender children who are supported in their identities. *Pediatrics*. 2016;137(3):e20153223
50. Hembree WC. Guidelines for pubertal suspension and gender reassignment for transgender adolescents. *Child Adolesc Psychiatr Clin N Am*. 2011;20(4):725–732
51. Milrod C. How young is too young: ethical concerns in genital surgery of the transgender MTF adolescent. *J Sex Med*. 2014;11(2):338–346
52. Milrod C, Karasic DH. Age is just a number: WPATH-affiliated surgeons' experiences and attitudes toward vaginoplasty in transgender females under 18 years of age in the United States. *J Sex Med*. 2017;14(4):624–634
53. Shumer DE, Spack NP. Current management of gender identity disorder in childhood and adolescence: guidelines, barriers and areas of controversy. *Curr Opin Endocrinol Diabetes Obes*. 2013;20(1):69–73

Patient safety for children and young people with gender incongruence

Ukom

ukom.no

Patient safety for children and young people with gender incongruence

Published on March 9, 2023 Last updated on March 9, 2023

People with gender incongruence and gender dysphoria have different wishes and needs for health services. Many people live well with their gender incongruence and manage it without health care, while others want and need health care (see glossary in Chapter 13 for explanations of terms).

When Ukom addresses the topic of gender incongruence, we look at how patient safety is ensured in care and treatment services for gender incongruence and gender dysphoria. Our aim is to ensure safe help and treatment for children and young people with gender incongruence.

There is an ongoing public debate about treatment options for gender incongruence. This is demanding, and many people are reluctant to participate in the debate. It can be challenging and difficult to participate because there are major disagreements both between groups and within groups. We see that the choice of words and understanding of the complexity is important. The situation of insecurity and disagreement affects the development of health services.

In our report, we have tried to highlight different perspectives. At the same time, it is important for us to be clear about our findings. That is, what challenges patient safety. Many people have worked and are working to establish and build good health services for people with gender incongruence and gender dysphoria, both nationally and internationally. UCOM's report builds on this work. We point out that this field now needs a boost to improve patient safety, especially for the health care to be provided to children and young people in Norway.

Executive summary

Ukom has conducted an investigation into the treatment offered to children and young people with gender incongruence. The background was notifications directly to Ukom from relatives who questioned several aspects of patient safety. Several actors, both from the authorities, health personnel and patient and relatives' organizations, questioned the soundness and organization of the treatment services.

The report deals with children and young people in general. There has been a large increase in referrals to health services from people with gender incongruence in recent years. In particular, the number of teenage children and young people seeking or being referred for assessment and treatment in specialist health services has increased significantly. The largest increase is among adolescents and young adults who are registered as girls at birth but identify as boys. Our attention has therefore been particularly focused on teenagers and young people with gender incongruence and gender dysphoria seeking health care. Children and adolescents are not fully developed physically, mentally, sexually or socially. This requires particular vigilance in terms of patient safety. Our findings and recommendations will also be relevant to the provision of care for adults.

In this report, we have divided our findings into six main areas:

Insufficient knowledge

The evidence base, especially research-based knowledge for gender affirmative treatment (hormonal and surgical), is insufficient and the long-term effects are poorly known. This is particularly true for the adolescent population where the stability of their gender incongruence is also not known. There is a lack of research-based knowledge on the treatment of patients with non-binary gender incongruence. In order to ensure patient safety, Ukom considers it necessary that the knowledge base on gender incongruence and gender dysphoria is strengthened, and that health services are organized in line with the knowledge base.

Overall governance - a guideline with a different background

The Directorate of Health's national professional guideline on gender incongruence provides guidelines for the provision of health services. It concentrates on organization, equality and rights. This may have been important at the time the guideline was drawn up, because it was necessary to establish the health service provision for people who experience gender incongruence. At the same time, we consider that deviating from the requirement to develop evidence-based guidelines has created room for uncertainty and conflicting expectations. Health professionals have been given wide scope for interpretation within a relatively narrow field that lacks systematic knowledge synthesis in Norway. The guideline provides rights without clarifying issues related to prioritization and justifiability. This is demanding for the health personnel who administer the services on a daily basis.

Due diligence requirements - particularly in relation to children and young people

The national professional guideline for gender incongruence is not very prescriptive. It does not set specific requirements for assessment or requirements for medical indications for the initiation of treatment. The reference to children's capacity to consent and parents' right to information leaves room for interpretation. The guideline does not establish an adequate standard for the provision of health services, and we believe that for some patients it may pose a patient safety risk. This may go beyond the requirement of soundness, which is broadly based in health legislation, and may also be challenging for supervisory authorities.

Right to health care - a gap in expectations

Our survey suggests that there is a gap between what the guideline outlines and what is possible, given the current available services and knowledge base. The national guideline creates expectations among patients that the health service can hardly meet. This applies, among other things, to the right to specialist health services. It is difficult for the service to meet these expectations without a well-documented evidence base and without a good overview of any negative and harmful aspects of the various treatments. Requiring the use of principles for experimental treatment will provide a framework that ensures information, thorough follow-up and contributes to more knowledge.

Care and treatment provision - variation in practice and skills

There is great variation in the services and expertise offered in different parts of the country. There is a risk of under-, over- and incorrect treatment of children and young people with gender incongruence and gender dysphoria. In addition, we see that there are challenges in establishing a decentralized service in a narrow and complex field. In order to strengthen the service, Ukom believes that it is important to strengthen the health service provision in the primary health service, build increased interdisciplinary expertise in the specialist health service at regional level and ensure that the national treatment service has sufficient capacity for the current demand.

Performance climate and interaction

We see that in the field of gender incongruence, a challenging climate of expression has developed. The climate of expression in the public sphere affects the available information for children and young people with gender incongruence and gender dysphoria and their families. There is a significant impact on children and young people, also related to treatment and health services. We hear about fears and fears of getting it wrong from all sides. Different opinions about what is the right treatment can create difficult cross-pressures. Different emphasis and discussion of what necessary at group level can confuse and undermine patient-provider relationships and a personalized approach for the person concerned. There is a need to establish a constructive community for all those committed to good health care for people with gender incongruence.

Ukom recommends

We are concerned that children and young people with gender incongruence have safe and appropriate health services. We therefore make recommendations that can help to ensure that this group receives better and safer health services in the long term. Our recommendations relate to the revision of the guideline, a safe framework for treatment offered to children and adolescents and measures to strengthen the knowledge base. The recommendations will also contribute to systematic data collection and promote follow-up research. It is important that children and young people with gender incongruence and gender dysphoria, including non-binary people, are properly cared for while health services are being developed.

Ukom recommends:

1. that the Ministry of Health and Care Services commissions the Norwegian Directorate of Health to revise the national guideline on gender incongruence. The revision must, among other things, be based on a systematic review of the evidence. We point out several elements that should be included in the revision.
2. that puberty delaying treatment (puberty blockers) and hormonal and surgical gender affirmation treatment for children and adolescents be defined as investigational treatment. This is particularly important for teenagers with gender dysphoria.
3. that the Ministry of Health and Care Services consider whether a national medical quality register should be established for the treatment of children and young people with gender incongruence and gender dysphoria. Necessary measures must be taken to establish, operate and finance such a national quality registry to contribute to an overview, improve quality and reduce unwarranted variation in patient care.

2 Background

Published on March 9, 2023 Last updated on March 9, 2023

Why has Ukom launched an investigation

In 2022, Ukom received two reports of concern from relatives of persons who have undergone assessment and treatment for gender incongruence in the age range 16-21 years. In the reports of concern, the relatives refer to several different aspects of the current treatment services that may have an impact on patient safety.

- The relatives question the appropriateness of the treatment.
- The assessment was demanding and the follow-up was not sufficient in relation to the vulnerable and exposed situation the relatives perceived the young people to be in.
- There was insufficient follow-up for other diagnoses or issues that the young people also had, or questioned whether gender affirmative treatment was the right treatment for their child.
- Parents felt that the assessment and treatment process created a fear among young people that they would not receive treatment or would receive the wrong treatment.
- Information on treatment, efficacy and side effects was incomplete.
- Parents and family involvement was low. This put additional strain on both the young people and their families.
- Parents feel that there are cross-pressures from different quarters and communities that affect their children.

In recent years, much attention has been paid to the health service provision for people with gender incongruence both nationally and internationally. Over the past decade, there has been a large increase in the number of people who have been referred for treatment of gender incongruence. This has presented challenges for established treatment institutions. In Norway, many have called for improved health services for people with gender incongruence. The Norwegian Directorate of Health has drawn up national guidelines to expand and make treatment services available to the group. At the same time, several actors, both from the authorities, health personnel and patient and family organizations, are questioning the justification and organization of the treatment services.

It is also controversial whether the guidelines from the Norwegian Directorate of Health, and other guidelines from the authorities in this area, provide for a proper organization of treatment services for this group in Norway. There is an ongoing debate in the media, in social media and in work with the health service about the treatment and assistance offered to people with gender incongruence.

The public debate is characterized by different approaches to the treatment of gender incongruence. The debate also shows that gender incongruence is about more than medical treatment. Gender incongruence is about personal identity and the inclusion, acceptance and rights of a minority group. This is fundamental and applies to multiple patient groups, conditions and issues. The treatment of gender incongruence is also a policy issue. Reconciling medical and non-medical considerations has proven to be very challenging. This is reflected in the public debate.

In many areas, transgender people have poorer living conditions and quality of life than the general population. The government's new action plan for gender and sexuality diversity (2023-2026) states that the health services for people with gender incongruence have been inadequate over time.

Uncertainty about what constitutes appropriate treatment has led the authorities in some countries, such as England and Sweden, to tighten the treatment offered to people with gender incongruence. In Norway, on the other hand, guidelines have been laid down to expand and decentralize treatment services.

We started our investigation by conducting a survey of the treatment provision for people with gender incongruence. The mapping exercise revealed a number of unresolved issues with implications for patient safety that are particularly relevant for the treatment of children and young people who are developing psychologically, cognitively, physically and socially. Treatment options for gender incongruence may involve irreversible treatment with hormones and surgery that cause invasive changes. As a consequence, we concluded that it was particularly important to look at the patient safety of children and young people receiving treatment for gender incongruence.

In England, in 2022, the Healthcare Safety Investigation Branch (HSIB) published a report on the topic of gender incongruence. The starting point for their investigation was a report of concern about a young person who took his own life while waiting for assessment for gender incongruence. He was then under the care of local mental health services and there was a 24-month waiting time at the gender incongruence clinic. The survey looked specifically at the health service for young people (children and adolescents) with gender incongruence and found that there was a large increase in young people being referred to specialized units for gender incongruence. HSIB has shared experiences from its work with Ukom. The survey showed that the centralized health services lacked the capacity to accommodate the increased referral volume and had long waiting times. There was a lack of competence and capacity in
non-specialized care services to attend and assess young people with gender incongruence while they were awaiting assessment. The HSIB also communicated other findings from England (the Care Quality Commission) that health professionals at specialized gender incongruence treatment unit did not always feel respected, supported and valued and reported an absence of culture of transparency. Some of the health professionals experienced pressure due to conflicts and lack of consensus on the treatment of children and young people with gender incongruence and told of fear of voicing their opinions.

With this in mind, we have conducted a study of the health care and treatment services for children and adolescents with gender incongruence. We have looked at how health care and practices work today, and how the framework and guidelines for health care affect patient safety. Ukom does not go into the details of all help and treatment measures for gender incongruence and gender dysphoria, but we point out challenges in the current services to ensure that children and young people with gender incongruence and gender dysphoria receive help in a safe environment.

The report is based on services for children and young people, but many of our findings and recommendations will be relevant to services for all people with gender incongruence and gender dysphoria.

Our findings

Our survey shows several weaknesses in the provision of services for children and young people with gender incongruence and gender dysphoria. The findings show difficult dilemmas related to medical, legal and ethical issues. We have chosen to divide our findings into the following main themes:

- Overall governance - a guideline with a different background
- Care and treatment services - variation in practice and expertise
-

Insufficient knowledge

- Duty of care - particularly in relation to children and
- young people Right to healthcare - a gap in
- expectations Climate of communication and
  interaction

The next chapters deal with gender incongruence and patient and caregiver perspectives, before describing the findings in the following chapters.

PATIENT SAFETY FOR CHILDREN AND YOUNG PEOPLE WITH GENDER INCONGRUENCE

3 Briefly on gender incongruence

Published on March 9, 2023 Last updated on March 9, 2023

Table of contents

Gender incongruence can be defined as a mismatch between a person's gender identity and their registered sex at birth. Gender identity can be understood as a person's self-perceived gender, the internal sense of being a boy/man, girl/woman, not belonging to a gender (non-binary) or being a different type of gender. People with gender incongruence may also experience gender dysphoria in that the mismatch between gender identity and birth sex leads to discomfort and a strong desire to remove or change some or all primary or secondary sex characteristics.

In Norway, medical treatment for gender incongruence has been available since the end of the 1950s. The National Treatment Service at Oslo University Hospital has for over 40 years had a national function for the treatment of patients with gender incongruence.

Increased inflow - new patients

4 referrals per year — 1975-1990
50-70 / yr —2007-2010
400-600 / yr. —2018-2021

The health service has seen a marked increase in recent years in the number of patients seeking gender-affirming treatment. The number of people seeking or being referred to health care for gender incongruence and gender dysphoria is also increasing in several other Western countries. In particular, the number of children and adolescents seeking or being referred for such treatment in their teenage years has increased significantly. From 1975 to 1990, there were about four referrals per year for such treatment in Norway. In the last ten years, the National Treatment Service has reported an increase in referrals from approximately 50-70 per year in 2007-2010 to 400-600 referrals per year in 2018-2021. It is unknown why there is a large increase in the number of children and young people seeking or being referred for medical treatment. The largest increase is among adolescents and young adults who are registered as girls at birth but identify as boys.

Classification

Gender incongruence was previously classified under mental and behavioral disorders in the World Health Organization (WHO) diagnostic manual International Classification of Diseases (ICD). In the latest version ICD-11, gender incongruence has been moved from the section of diagnoses for mental disorders to a new chapter for sexual health, 'conditions related to sexual health'. This means that gender incongruence should no longer be considered a mental disorder. At the same time, it was decided that it is important to keep a diagnosis, partly because it triggers rights, such as healthcare and social security benefits.

The Directorate of eHealth has the main responsibility for the implementation of ICD-11 in Norway. The implementation work is in the preparation phase and has not yet started. The implementation may take several years because it will involve extensive changes to various systems and work processes. In 2020, temporary changes were made to the codes for gender incongruence in Norway pending the implementation of ICD-11. All codes under the chapter F64 Gender identity disorders were then taken out of use. The codes were replaced by new ones under the chapter Z76.8 Contact with health services under other specified circumstances. There are now three codes for gender incongruence; Z76.80 Gender incongruence in adolescence and adulthood, Z76.81 Gender incongruence in childhood and Z76.89 Unspecified gender incongruence. These are directly translated from the corresponding codes in ICD-11. This was done as a temporary solution in the Norwegian version of ICD-10 in anticipation of ICD-11. These codes are now used for medical coding of gender incongruence and are reported to the Norwegian Patient Registry. In addition, procedure codes are used for mapping and surgical procedures. There are no separate procedure codes for the initiation of hormone therapy. Diagnosis codes are used in combination with procedure codes.

Gender diversity and different gender expressions

For many people, exploring their gender identity is a natural part of their development from child to adult. Today, there is greater acceptance in society of different gender expressions. This acceptance is partly the result of increased knowledge, information and many years of advocacy efforts by various groups and individuals. It has also been argued that social media has made it easier to share, acknowledge and be open about feeling different. Despite the greater acceptance of gender diversity in society, many people with gender incongruence still experience stigma and discrimination. This is relevant knowledge for the health services and an important backdrop for the development of support and treatment services.

Treatments for gender incongruence

For people with gender incongruence and gender dysphoria, different interventions and treatments may be appropriate. Interventions and treatment for gender incongruence and gender dysphoria may vary from less invasive help to more invasive treatment, such as various hormonal treatments and surgical treatment. These may include counseling, psychosocial support sessions, coping skills training and speech therapy sessions with voice training. Assistive devices such as wigs, breast prostheses and penile prostheses may also be used. These aids are used in the assessment as 'real life experience'. That is, the person lives as the desired gender to assess whether it feels right. These are less invasive measures.

Puberty blockers and gender affirmative treatment involve hormonal treatment, and gender affirmative treatment may also involve surgical interventions. Gender affirmative treatment is known to be invasive and irreversible with different consequences and greater risk and potential for harm than less invasive treatment.

Puberty blockers

Children and young people who have reached puberty may be given hormonal treatment with puberty blockers (puberty inhibitors) to stop or delay puberty. Puberty blockers have traditionally been given to children who reach puberty too early, but can also be given as treatment for gender incongruence and gender dysphoria in children and adolescents. The reason for delaying puberty is that children and adolescents may experience increased discomfort, gender dysphoria, when puberty starts, and they experience physical development that is not in line with their own gender identity. The treatment prevents puberty from developing further and thus prevents a possible unwanted development.

Treatment with puberty blockers appears to be most effective in the early stages of puberty, both in terms of the development of sexual characteristics such as breasts, penis, facial and body hair and growth in length. The treatment has no age limit, but can start at the beginning of puberty at the earliest. Treatment can only be given for a few years. After that, a decision must be made whether to stop all hormone treatment or to switch to feminizing or masculinizing hormones. The treatment has known side effects such as weight gain, reduced height growth, hot flushes, lack of energy, depression and reduced bone mineralization. Little is known about the long-term effects.

Gender affirmative action

Gender-affirming treatments aim to affirm a person's gender identity. Unlike puberty blockers, which stop or delay unwanted physical development, gender affirming treatment involves giving the body a development or physical characteristics that are in line with one's gender identity. There are two types of gender-affirming treatment: gender-affirming hormone therapy and surgical treatment.

Gender-affirming hormone therapy can be offered from the age of 16, according to the guideline. Testosterone is given to persons whose registered sex is female and oestrogen and antiandrogen to persons whose registered sex is male. If the person has had puberty delayed with hormones, sex hormones are given in escalating treatment to simulate the development of puberty. Gender-affirming hormone therapy must be given for life to maintain the desired effect.

In individuals with registered female gender, physical changes can be expected in the form of deepening of the voice, enlargement of the clitoris to varying degrees, increased growth of facial and body hair, cessation of menstruation, decline of breast tissue, increased sex drive and decreased body fat to muscle mass ratio. In people with registered male gender, one can expect varying degrees of breast growth, decreased sex drive and erections, decreased testicular size and increased body fat in relation to muscle mass.

Surgical treatment can be given to people over 18 years of age. Current treatments include breast removal, removal of the ovaries and uterus and surgery of the external genitalia.

Many of the changes brought about by gender confirmation treatment are irreversible. The treatment has consequences for fertility that are permanently impaired. Possible side effects of the treatment may include liver disease and negative psychological reactions. For male-to-female treatment, there is an increased risk of blood clots, high blood pressure and liver disease. For female-to-male treatment, side effects may include excessive red blood cells, scarring acne and swelling of the body. This is not an exhaustive list of all possible known effects.

4 Input from patients and families

Published on March 9, 2023 Last updated on March 9, 2023

When discussing gender incongruence and the patient perspective, it is important to emphasize that people with gender incongruence have different wishes and needs for healthcare. Many people live well with their gender incongruence and manage it without health care, while others want and need health care.

Listening to the voices of patients, users and relatives is crucial for identifying areas of risk and improvement in health services. In conducting this study, it has been important to elicit multiple patient voices and perspectives. We have met several patients who are either undergoing treatment or have been in a treatment situation, and we have heard about a diversity of needs, preferences, opinions and experiences with the health service.

Message to health services

Here are some key messages that emerged from the conversations we had:

- Being in the process of exploring gender incongruence and gender dysphoria is demanding, and many people want support in their individual process.
- Gender-affirming treatment should be personalized. It is important that the treatment provider sees the individual with the resources and challenges they have.
- Many people with gender incongruence feel that there is a lack of expertise and comprehensive services.
- Many are concerned that respect and tolerance for gender diversity is being lost in the debate on binary gender affirmative action.
- All have highlighted the importance of thinking about the whole person and life course, including for transgender people.
- There is a fear of not being seen, not being heard and not getting the
- right help at the right time. Living with gender dysphoria over time and without help is very painful.
- Health services must offer support to both people with binary gender incongruence and non-binary gender incongruence.

> *"For many people, the most important thing is to be seen and heard. And when you have to wait nine months .... It's hard. We need to get rid of unnecessary waiting time"*

REPRESENTATIVE PATIENT ORGANIZATION/FORMER PATIENT
GENDER INCONGRUENCE

In addition, the people we have spoken to describe experiences such as powerlessness, frustration and exhaustion in their encounters with the health service. This is due to processes that are perceived as long and convoluted both in the encounter with the health service, in order to access help, and then in the assessment and treatment process. In addition, there is the burden of the time it takes to put in place a comprehensive health service for people with gender incongruence.

Need for help

Whether and to what extent gender incongruence affects health and social conditions will vary. There are many factors at play, for example, both social and biological factors influence the degree of dysphoria. High levels of gender dysphoria are very painful for the person living with it.
The burden of the disorder then greatly affects quality of life and daily functioning. For those living with dysphoria, it is very important that they receive health care.

Transgender people are a group that has been stigmatized, discriminated against and marginalized, also when dealing with health services. They have been met with attitudes where the challenges and problems caused by gender incongruence and gender dysphoria have not been recognized and understood. It is therefore important for the patient group to work for a dignified encounter with the health services at all stages of life, and to ensure that those who need treatment for gender dysphoria receive it.

One of the topics on which there are different opinions, also among patients and relatives, is who in the health service can start gender-affirming treatment and when. For example, several people tell us how important it is that a decision on gender-affirming treatment is given time and maturation. It is difficult to fully understand the consequences of the choice, and as many mention, there is "no quick fix".

"A lot of people have a breakdown after treatment. You have to work on a lot of things. Work on acceptance. For example, I always have to live with the fact that I was born in a girl's body."

REPRESENTATIVE PATIENT ORGANIZATION

At the same time, many people also talk about the importance of starting treatment early, because the changes brought about by puberty are also permanent.

"Gender affirmative treatment is life-saving treatment. Not providing treatment is also irreversible."

REPRESENTATIVE PATIENT ORGANIZATION

Everyone we spoke to emphasizes the importance of knowledge about gender incongruence at all levels of the health service, and that those who carry out assessment and treatment need specialist expertise.

"And then, of course, there's the fact that going through puberty is a trauma you don't want to go through, and we shouldn't take it lightly. And that balancing act, about when to start treatment and when it's not right, requires knowledge"

PREVIOUS PATIENT ON ASSESSMENT/TREATMENT FOR GENDER INCONGRUENCE

What is common in all our meetings with people with gender incongruence is a desire to put in place better health services. There is also a unanimous wish that everyone who experiences gender incongruence and gender dysphoria should be taken seriously and receive support and help.

Safe guarding

Relatives tell us how important it is that health care professionals meet young people with gender incongruence with openness and knowledge, and that relatives are involved as supporters throughout the process.
Relatives have information that can be important both in the assessment and in the further process. The need for relatives as supporters does not stop at the age of 16 or 18.

"Throughout the process, she has lacked follow-up. She tells of great loneliness. We have been left out all the way. Nowhere have they worked to include us as parents. But everyone, and especially young people, need supporters"

MOR

Many people tell us that assessment for gender-affirming treatment is a demanding process. On the one hand, it is perceived as very demanding if the process takes a long time. On the other hand, it is also demanding for many to experience time pressure, where the decision to start hormonal treatment must be made early before pubertal development gets too far along.