*Dr. Renzo Puccetti*

# Blocco puberale in minori affetti da disforia di genere

Audizione presso XII Commissione Permanente «Igiene e Sanità» Senato della Repubblica
Atto n.207
«Uso del medicinale Triptorelina»

# Pubertà

- Maturazione dei caratteri sessuali primari (gonadi)
- Maturazione dei caratteri sessuali secondari (genitali esterni, seno, pomo d'Adamo, peli)
- Scatto della crescita
- F: 8-13 anni; M: 9-14 anni

# Disforia di genere

- “La disforia di genere è una condizione caratterizzata da una intensa e persistente sofferenza causata dal sentire la propria identità di genere diversa dal proprio sesso”. (ISS)

# Disforia di genere

## DSM-5 GD criteria for Children

- A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months duration, as manifested by at least 6 of the following indicators:
- A strong desire to be of the other gender or an insistence that he or she is the other gender.
- In boys, a strong preference for cross-dressing or simulating female attire; in girls, a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
- A strong preference for cross-gender roles in make-believe or fantasy play.
- A strong preference for the toys, games, or activities typical of the other gender.
- A strong preference for playmates of the other gender.
- In boys, a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; in girls, a strong rejection of typically feminine toys, games, and activities.
- A strong dislike of one's sexual anatomy.
- A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

## DSM-5 GD criteria for Adolescents and adults

- A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months duration, as manifested by 2 or more of the following indicators:
- A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or, in young adolescents, the anticipated secondary sex characteristics).
- A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or, in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
- A strong desire for the primary and/or secondary sex characteristics of the other gender.
- A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
- A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender)
- A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender)

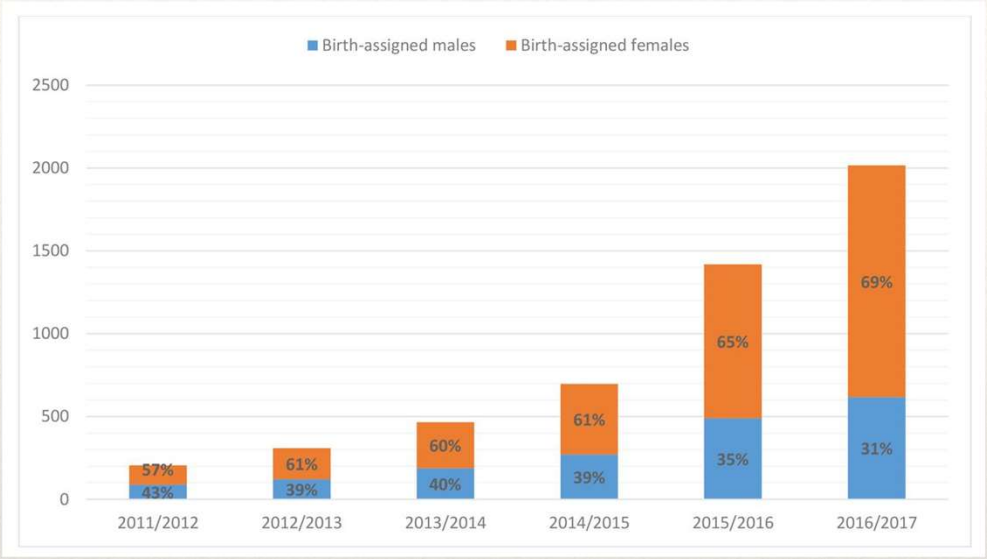
# Epidemiologia

- 2.730 minori randomizzati in San Francisco
- Età: 11-14 anni
- Domanda: “Qual’è il tuo genere?”
- Risposte possibili: maschio/femmina/transgender

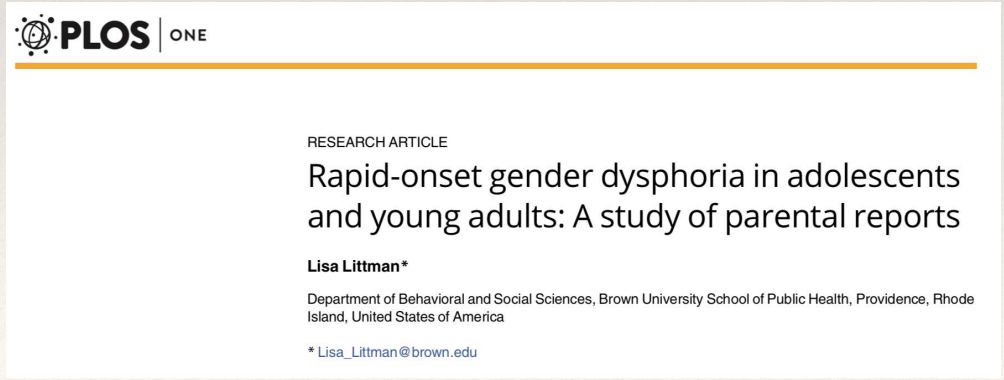
1,3%

Shields JP, et al. J Adolesc Health 2013; 52: 248–250.

# Il trend




Referrals to UK GID services: Assessment and support of children and adolescents with gender dysphoria. Arch Dis Child 2018; 103: 631–636.


PLOS ONE

RESEARCH ARTICLE

Rapid-onset gender dysphoria in adolescents and young adults: A study of parental reports

**Lisa Littman***

Department of Behavioral and Social Sciences, Brown University School of Public Health, Providence, Rhode Island, United States of America

* Lisa_Littman@brown.edu

Litmann L. PLoS ONE 13(8): e0202330.

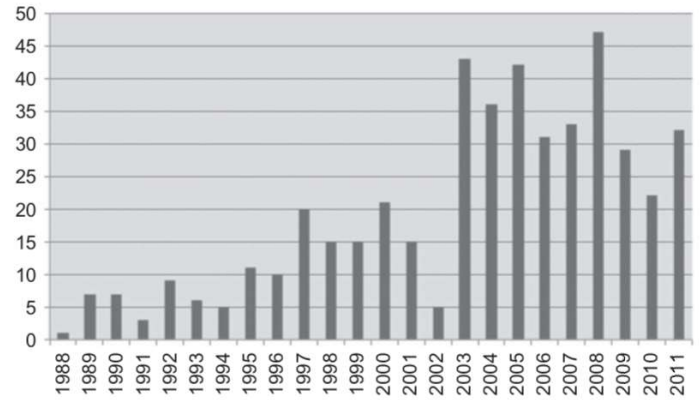



**FIGURE 1** Referred children, Dutch Gender Identity Clinic, 1987–2011.

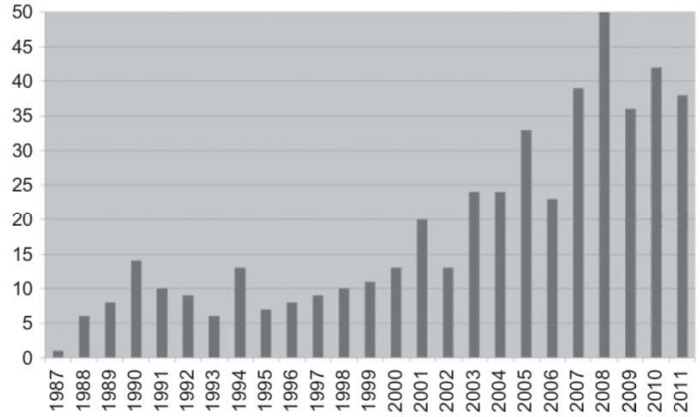
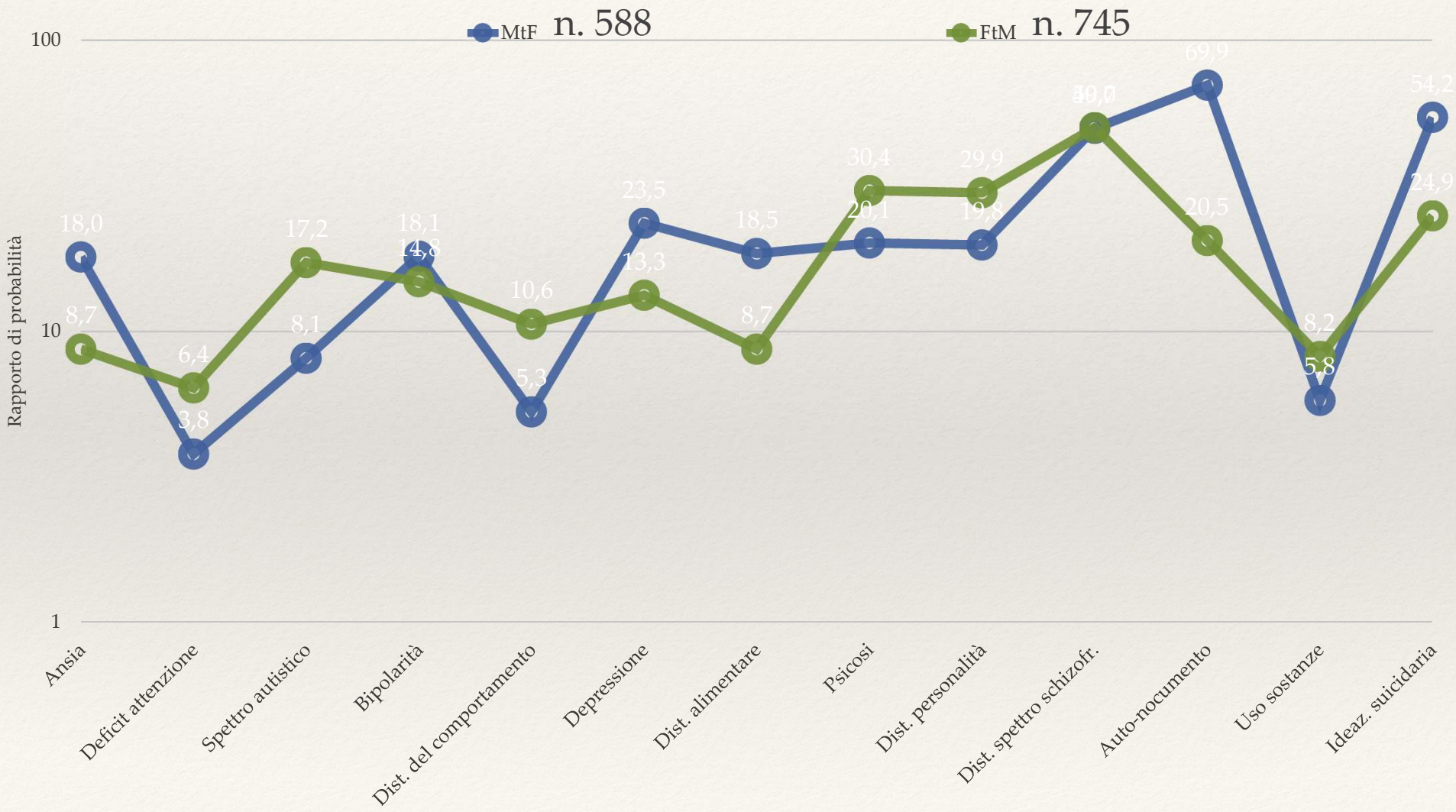



**FIGURE 2** Referred adolescents, Dutch Gender Identity Clinic, 1987–2011.

De Vries ALC, Cohen-Kettenis PT. Journal of Homosexuality 2012; 59: 301–320.

# Comorbidità psichiatrica




Mod. da Becerra-Culqui TA, et al. Pediatrics 2018; 141(5).

# Blocco puberale

European Child & Adolescent Psychiatry
7:246–248 (1998) © Steinkopff Verlag 1998

CASE REPORT

P.T. Cohen-Kettenis
S.H.M. van Goozen

## Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent

Accepted: 8 June 1998

P.T. Cohen-Kettenis (✉)
S.H.M. van Goozen
Department of Child and Adolescent Psychiatry of the Utrecht University Hospital, P.O. Box 85500
NL-3508 GA Utrecht
The Netherlands
e-mail: P.T. CohenKettenis@psych.azu.nl

**Abstract** Early cross-sex hormonal interventions (that is, between 16 and 18) as a treatment for young transsexuals are often considered to be risky. However, the delay of such treatment until after the development of secondary sex characteristics has obvious drawbacks for transsexual individuals. This paper reports a postoperative follow-up case-study of a female-to-male transsexual who was treated with a combination of an LHRH agonist (which delayed her secondary sex characteristics development) and psychotherapy at age 13, and subsequently underwent sex reassignment at 18.

**Key words** Gender identity disorder – transsexualism – adolescence – sex reassignment – hormone treatment

### Introduction

Sex reassignment for individuals with extreme gender identity disorder (GID) has long been restricted to adults. Prospective studies have shown that most GID children under 12 will not grow up to become transsexuals (5, 13, 14). Because of this, hormonal or any other medical intervention is never considered in prepubertal children. However, for some adolescents applying for sex reassignment, medical interventions may be a treatment option. Until recently, clinicians have been reluctant to start hormone treatment before the age of 18 or 21. It was felt that only in adulthood gender identity could be consolidated enough to allow for decisions regarding invasive interventions such as hormone and surgical therapy. Such a relatively late treatment start, however, has it drawbacks. Some individuals who have shown a pattern of extreme cross-sex identification from toddlerhood onwards may develop psychiatric disorders, e.g., depression, anorexia or social phobias, as a consequence of their hopelessness. Social and intellectual development may be adversely influenced. Also, the physical treatment outcome following interventions in adulthood is far less satisfactory than when treatment is started at an age at which secondary sex characteristics have not yet been fully developed. This is obviously an enormous and life-long disadvantage. Ross and Need (11) found that postoperative psychopathology was primarily associated with factors that made it difficult for postoperative transsexuals to pass successfully as their new gender or that continued to remind them of their transsexualism. Furthermore, follow-up studies show that unfavorable postoperative outcome seems to be related to a late rather than an early start of the sex reassignment surgery (SRS) procedure (for reviews, see 6, 10). Age at time of assessment also emerged as a factor differentiating two groups of male-to-female transsexuals with and without postoperative regrets (7).

In some gender identity clinics a selected group of transsexual adolescents are now being treated hormonally before they are legal adults (age 18), but still after the age of 16. A careful diagnostic procedure includes more rigorous eligibility criteria than used for adults and a prolonged diagnostic procedure. The first follow-up study of adolescent transsexuals showed that 1–5 years after surgery the now young adults functioned socially and psychologically


1. Blocco puberale
2. Transizione ormonale
3. Transizione chirurgica

# Gli obiettivi

1. Ridurre la disforia di genere
2. Prendere tempo
3. Facilitare il risultato chirurgo estetico

# Effetti psico-sociali

## PSYCHOSOCIAL EFFECTS

All relevant results are shown in Table 3.

### GnRHas

GnRHa treatment was associated with significant improvements in multiple psychological measures, including global functioning,[25–27] depression,[26,27] and overall behavioral and/or emotional problems.[26,27] The effects of GnRHas on anger and anxiety remain unclear with conflicting results.[26,27] Moreover, GnRHa treatment had no significant effect on symptoms of GD,[26,27] with researchers in 1 study observing a nonsignificant increase in GD and body image difficulties.[26]

**TABLE 3** Psychosocial Effects of Hormonal Treatments in Transgender Youth

| Study | Treatment | Outcome | | | | | |
|---|---|---|---|---|---|---|---|
| | | Global Functioning | Depression | Anger and Anxiety | Behavioral and Emotional Problems | | GD and Body Image |
| de Vries et al[27] (de Vries et al[26])[a] | GnRHa, GAH (not assessed) | Increase[b] (increase[c]) | Decrease[b] | Decrease[c] | CBCL: decrease[b] in total and internalizing scores, decrease[b] (decrease[c]) in externalizing scores | YSR: decrease[b] in total and internalizing scores, decrease[b] (decrease[c]) in externalizing scores | No significant effect[d] |
| Costa et al[25] | GnRHa | Increase[e] | — | — | — | — | — |

Although influential articles in this field, Cohen-Kettenis and Van Goozen[33] and Smith et al[34] were unable to be included in our study because of their focus on patients after sex reassignment surgery. CBCL, Child Behavior Checklist; YSR, Youth Self Report; —, not applicable.

[a] These 2 studies involved the same cohort and were therefore considered as 1 study. Parentheses are used to indicate the results of the earlier study[26] in which researchers examined a smaller subset of the cohort subsequently examined in the previous study.[27]

[b] Indicates significant change ($P < .05$).

[c] Indicates nonsignificant change ($P > .05$).

[d] It is important to note that the Utrecht Gender Dysphoria Scale that was used to measure GD in this study has various limitations, especially in relation to individuals who have already undergone social transition. Thus, the reported lack of improvement in GD here may reflect a lack of sensitivity in detecting psychological benefits. For example, it has been indicated in clinical experience that GnRHas help to satisfy the desire to prevent development of unwanted secondary sex characteristics (which is a criterion for GD under the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* in young adolescents), but the Utrecht Gender Dysphoria Scale does not have any items that address this issue.

[e] Indicates that a $P$ value was not calculated.


25. Costa R, Dunsford M, Skagerberg E, Holt V, Carmichael P, Colizzi M. Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. *J Sex Med.* 2015;12(11):2206–2214

26. de Vries AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics.* 2014;134(4):696–704

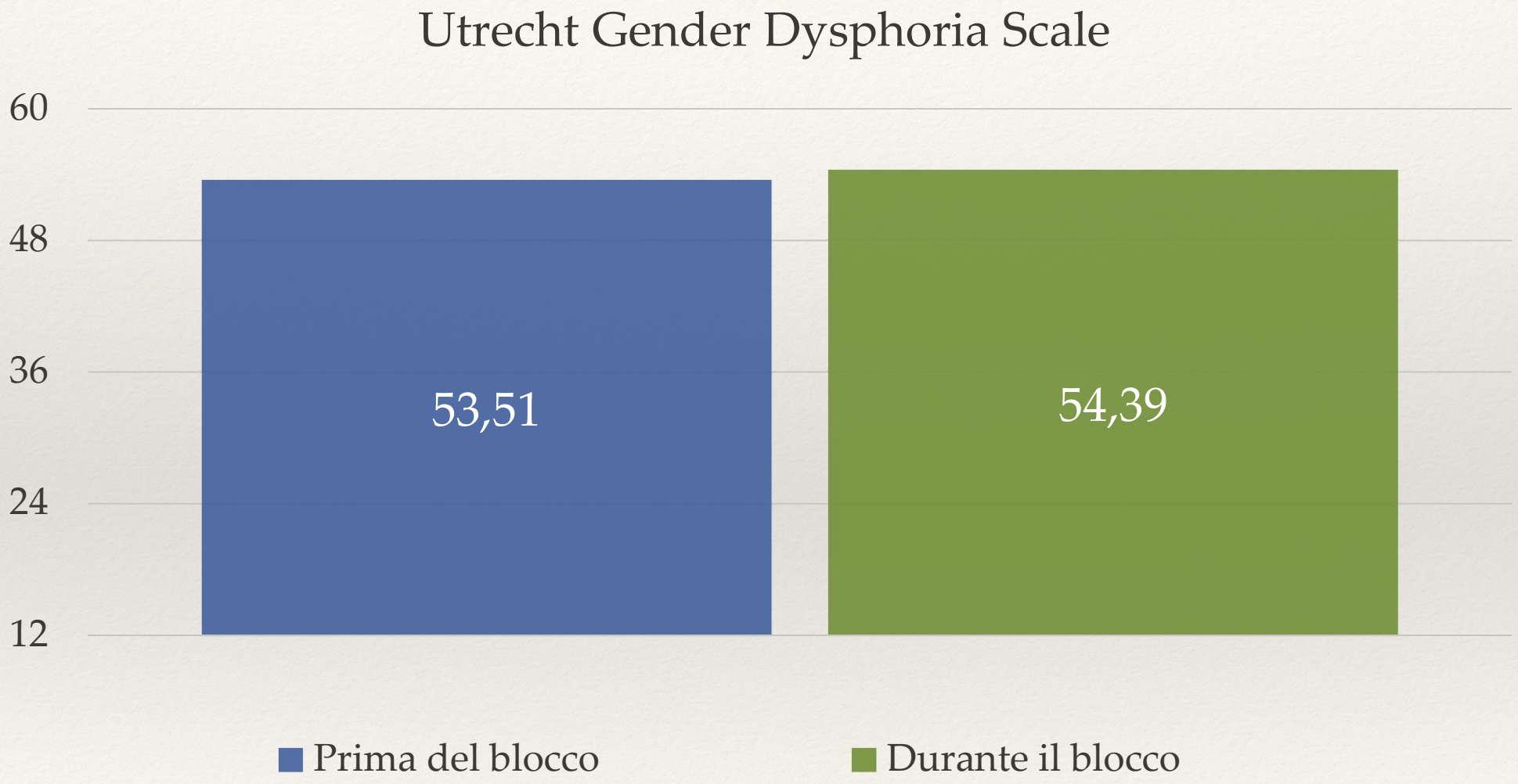
27. de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med.* 2011;8(8):2276–2283


GB

NL

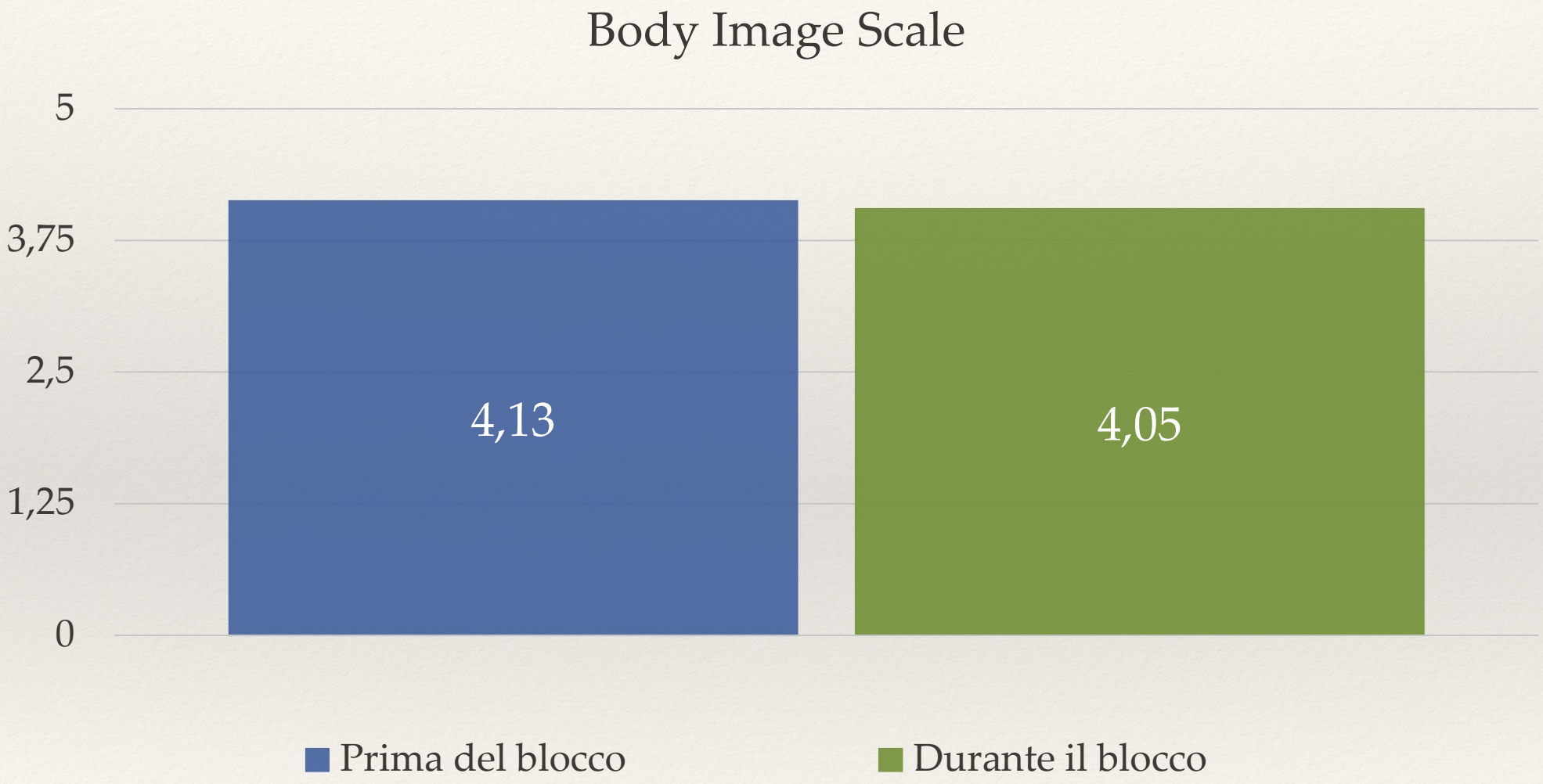
Chew D, et al. Pediatrics 2018; 141(4): pii: e20173742. doi: 10.1542/peds.2017-3742. Epub 2018 Mar 7

# Blocco puberale: effetto sulla disforia di genere



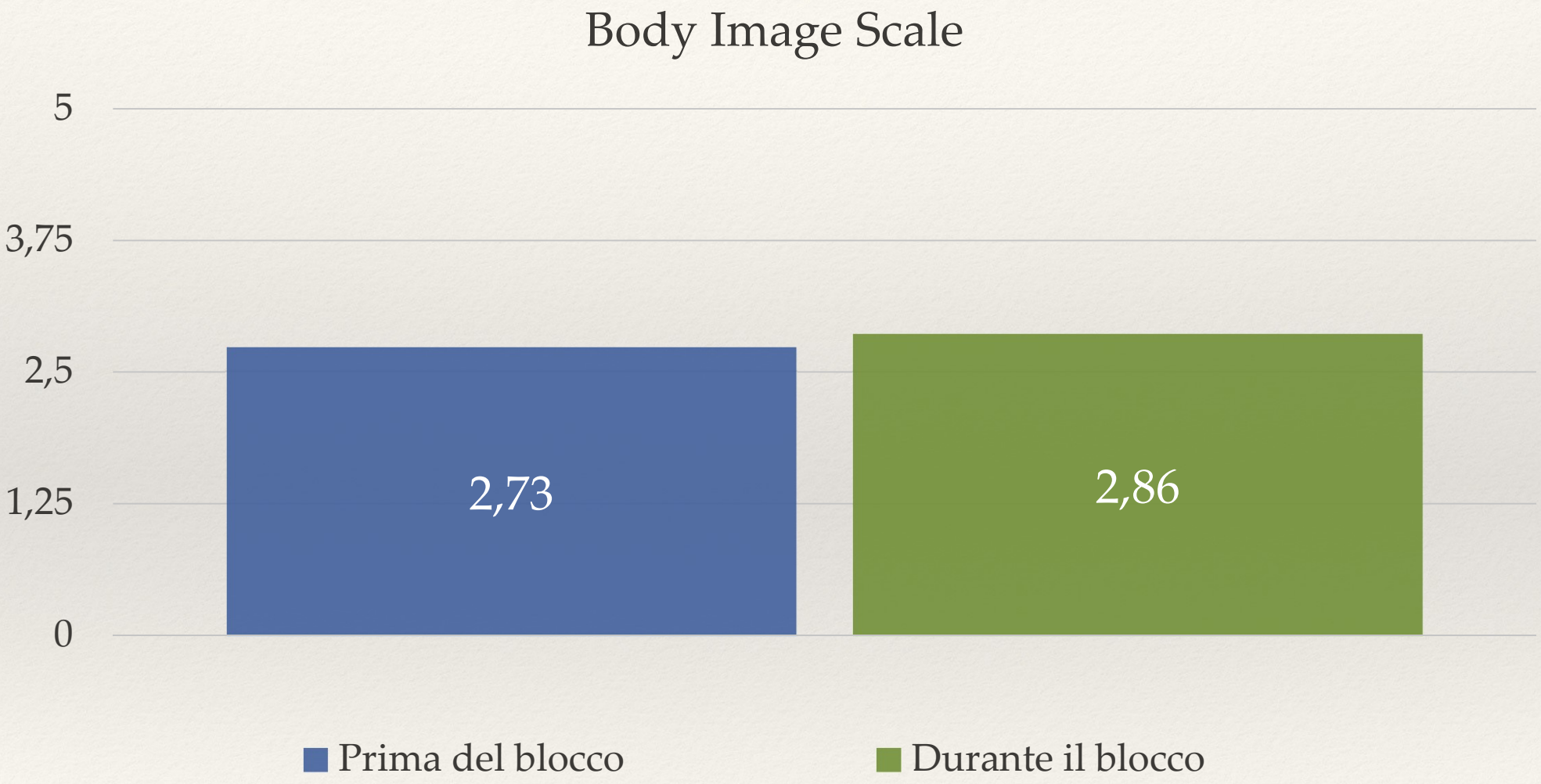

De Vries ALC, et al. Pediatrics 2014; 134(4): 696-704.

# Blocco puberale: effetto sull'insoddisfazione dei caratteri sessuali primari



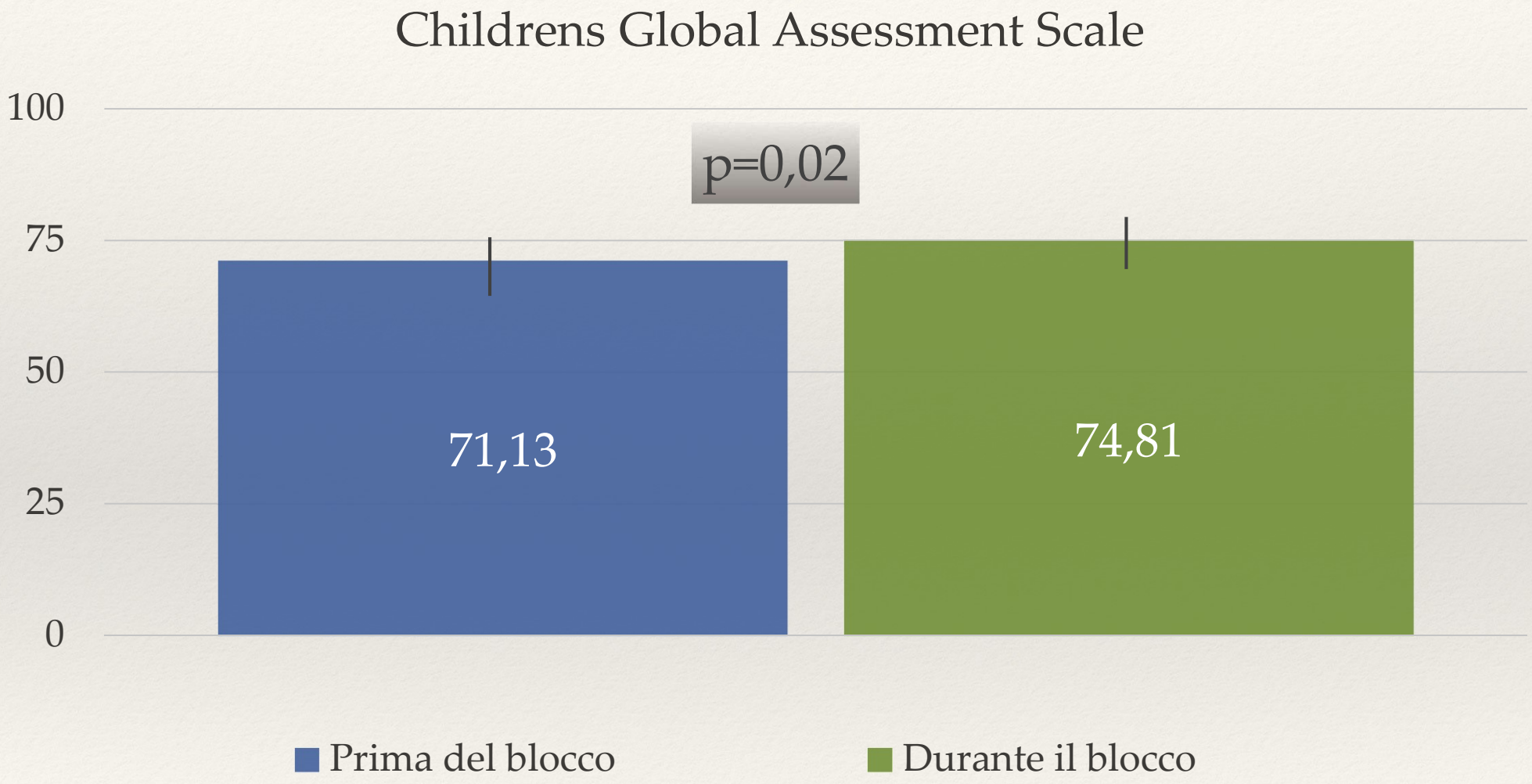

De Vries ALC, et al. Pediatrics 2014; 134(4): 696-704.

# Blocco puberale: effetto sull'insoddisfazione dei caratteri sessuali secondari



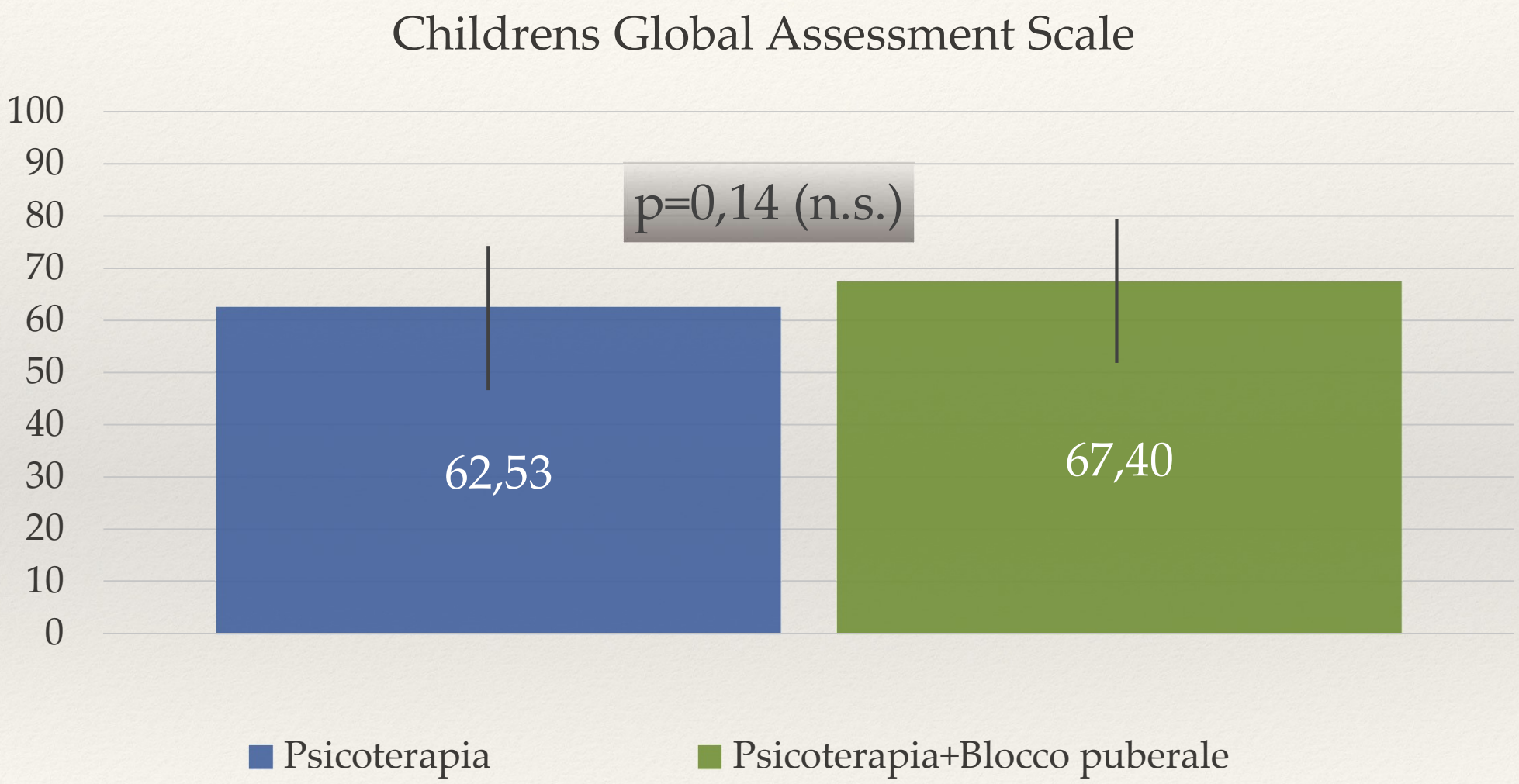

De Vries ALC, et al. Pediatrics 2014; 134(4): 696-704.

# Blocco puberale: effetto sul funzionamento globale




De Vries ALC, et al. Pediatrics 2014; 134(4): 696-704.

# Blocco puberale: effetto sul funzionamento globale




Costa R, et al. J Sex Med. 2015; 12(11): 2206-2214.

# CGAS: Una variazione clinicamente non significativa

| | |
|---|---|
| 100-91 | Superior functioning |
| 90-81 | Good functioning |
| 80-71 | No more than a slight impairment in functioning |
| 70-61 | Some difficulty in a single area, but generally functioning pretty well |
| 60-51 | Variable functioning with sporadic difficulties |
| 50-41 | Moderate degree of interference in functioning |
| 40-31 | Major impairment to functioning in several areas |
| 30-21 | Unable to function in almost all areas |
| 20-11 | Needs considerable supervision |
| 10-1 | Needs constant supervision |

# Che fine ha fatto la valutazione della disforia?



any type of physical intervention until they felt ready to make a decision in collaboration with their families and the clinicians. In those specific cases clinicians needed more time to make the decision of starting GnRHa because of possible comorbid psychiatric problems and/or psychological difficulties. If concomitant problems were observed (e.g., psychiatric problems, substantial problems with peers, or conflicts with parents or siblings), the young person was referred to a local mental health service. All possible medical and/or psychosocial interventions were well coordinated, integrated in a comprehensive management plan agreed with local services, and tended to be individualized in relation to the psychopathology/difficulty. The primary aim was for the child and the family to function better. After being assessed and, if necessary, treated for a psychiatric comorbidity, all delayed eligible GD individuals received puberty suppression. The interval from the start of the diagnostic procedure to the start of puberty suppression took about 1.5 years (1.5 ± 0.63 years from baseline). None of the delayed eligible individuals received puberty suppression at the time of this study.

**Main Outcome Measures**

*Socio-Demographic Information*

The data collected included: natal gender (male/female ratio), age (at assessment, at start of GnRHa), education level (yes/no), living arrangement (both parents, one parents, other), living in the chosen gender (partly, i.e., by wearing clothing and having a hairstyle that reflects gender identity/completely, i.e., by also using a name and pronouns congruent with gender identity/no), and change of name (yes/no).

*GD-Related Discomfort*

The Utrecht GD Scale (UGDS) was used to measure adolescents' GD-related discomfort. This is a 12-item questionnaire specifically developed to measure GD in a dimensional way. In particular, the UGDS focuses on core aspects of GD and gender identity. The adolescents are asked to rate their agreement on a 5-point scale. The total score ranges from 12 to 60. Higher UGDS total scores indicate high level of GD [13]. The scale has shown a high reliability (a Cronbach's alpha of 0.66–0.80 in one sample, and 0.78–0.92 in another); as reported by the authors, the lower alphas on the scale were only found among control subjects, which may be related to the lower variability of GD in these groups [13]. Cronbach's alpha for UGDS in our sample was 0.76–0.88. The UGDS has also shown a good discriminant validity, when adolescents and adults with and without a GD diagnosis were compared.

*Measure of Global Psychosocial Functioning*

The Children's Global Assessment Scale (CGAS) was used to assess adolescents' psychosocial functioning. The CGAS is one of the most widely used rating scales designed to measure how children and adolescents function psychosocially in daily life [14]. This clinical-rated instrument is divided into 10-point intervals and ranges from 1 to 100, with higher scores indicating better psychosocial functioning. The CGAS is useful to assess psychosocial/psychiatric outcomes, socio-cognitive competence and changes because of treatment [15]. In particular, it has been used in several longitudinal and epidemiological studies in clinical and non-clinical populations, naturalistic cohorts [16], and young GD individuals [9]. The inter-rater reliability was tested by Shaffer and his colleagues [14] before publication of CGAS, in order to minimize variation because of clinician background. Test–retest has been described in different studies with raters' consistence over time [16].

All CGAS were administered by qualified psychologists, psychotherapists, and psychiatrists who attended training and intra-class correlation assessment ($0.76 \leq$ Cronbach's $\alpha \leq 0.94$). Participants were assessed at baseline (Time 0) and every following 6 months, for a total of four evaluations over an 18-month period. Follow-up evaluations were performed 6 months from the baseline (Time 1: after 6 months of psychological support); 12 months from the baseline (Time 2: after 12 months of psychological support for delayed eligible GD adolescents, and after 12 months of psychological support + 6 months of puberty suppression for immediately eligible GD adolescents); 18 months from the baseline (Time 3: after 18 months of psychological support for delayed eligible GD adolescents, and after 18 months of psychological support + 12 months of puberty suppression for immediately eligible GD adolescents).

Participants were compared with a sample of young individuals without observed psychological/psychiatric symptoms (N = 169), using the same methodology of this study, the CGAS scale [16]. This sample was part of a large naturalistic cohort



*GD-Related Discomfort*

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# Rivelazioni

The Tavistock and Portman NHS
NHS Foundation Trust

Board of Directors Part One

**Agenda and papers**
of a meeting to be held in public

2.00pm–4.40pm
Tuesday 23rd June 2015

Board Room,
Tavistock Centre,
120 Belsize Lane,
London, NW3 5BA

## Tavistock's Experimentation with Puberty Blockers: Scrutinizing the Evidence

Transgender Trend - March 5, 2019 - Health Professionals and Organisations - 24 Comments


**Tavistock's Experimentation with Puberty Blockers: Scrutinizing the Evidence**

*by Michael Biggs, Dept of Sociology, University of Oxford*

(2 March 2019)

# Il blocco puberale non riduce la disforia

The Tavistock and Portman NHS
NHS Foundation Trust

*Gender Dysphoria & Body Image*

No significant changes in gender dysphoria emerged, measured by UGDS, GII and RCGI. This suggests that the suppression of puberty does not impact positively on the experience of gender dysphoria. It will be interesting to see if the introduction of cross sex hormone produces different results.

For body image however, significant differences were found looking at both sexes separately between T0 and T1 (see Table 5). Natal boys were less dissatisfied with their primary sex characteristics after being on the blockers for 1 year ($F(1,12)=4.857$, $\rho<.05$), whereas natal girls appeared to be more dissatisfied with their secondary ($F(1,15)=5.509$, $\rho<.05$) and neutral sex characteristics ($F(1,15)=7.79$, $\rho<.05$).

Table 5: Gender Dysphoria and Body Image of adolescents before (T0) and 1 year on puberty supression (T1)

| | T0 | | | T1 | | | T0 - T1 significance | | Between-sex significance | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All (N=30) | Natal boys (N=14) | Natal girls (N=16) | All (N=30) | Natal boys (N=14) | Natal girls (N=16) | | | Natal boys | | Natal girls | |
| | *M (SD)* | *M (SD)* | *M (SD)* | *M (SD)* | *M (SD)* | *M (SD)* | *F (df, errdf)* | *ρ* | *F (df, errdf)* | *ρ* | *F (df, errdf)* | *ρ* |
| UGDS | 4.77 (.24) | 4.81 (.26) | 4.74 (.22) | 4.73 (.36) | 4.76 (.39) | 4.71 (.33) | .215 (1.29) | 0.647 | .159 (1,13) | 0.697 | .061 (1,15) | 0.808 |
| GII | 2.03 (.27) | 2.09 (.30) | 1.98 (.24) | 1.95 (.22) | 2.05 (.16) | 1.87 (.23) | 1.740 (1,27) | 0.198 | .124 (1,13) | 0.731 | 2.331 (1,14) | 0.149 |
| RCGI | 2.02 (.43) | 1.72 (.29) | 2.26 (.38) | 1.93 (.41) | 1.67 (.29) | 2.13 (.38) | 1.860 (1,26) | 0.184 | 0.17 (1,11) | 0.688 | 2.703 | 0.122 |
| Body Image Scale | | | | | | | | | | | | |
| *primary characteristics* | 4.49 (.47) | 4.55 (.42) | 4.44 (.51) | 4.36 (.50) | 4.17 (.51) | 4.51 (.45) | 1.445 (1,28) | 0.239 | 4.857 (1,12) | 0.048 * | 0.387 (1,15) | 0.543 |
| *secondary characteristics* | 2.96 (.70) | 2.84 (.73) | 3.06 (.69) | 3.07 (.77) | 2.53 (.76) | 3.52 (.43) | .365 (1,28) | 0.551 | 0.88 (1,12) | 0.367 | 5.509 (1,15) | 0.033 * |
| *neutral characteristics* | 2.44 (.74) | 2.71 (.65) | 2.22 (.75) | 2.70 (.68) | 2.54 (.85) | 2.82 (.50) | 2.176 (1,28) | 0.151 | 0.521 (1,12) | 0.484 | 7.79 (1,15) | 0.014 * |

M = Mean; SD = Standard deviation; UGDS = "Utrecht Gender Dysphoria Scale"with Range 0-5; GII = "Gender Identity Interview" RCGI = "Recalled Childhood Gender Identity"

Body Image Scale is a 5-point scale coded with 1 = very satisfied to 5 = very dissatisfied with body part

* Significant difference in mean between T0 and T1, $\rho < .05$

# Il blocco puberale non riduce il rischio suicidario

The Tavistock and Portman NHS
NHS Foundation Trust

*Self-harm*

Looking at two self-harm items measured by the YSR, a significant increase was found in the first item "I deliberately try to hurt or kill self". Adolescents had the option to score these items as: not true, sometimes true, often true. More adolescents tend to score this item in the "sometimes true - range" at T1 compared to T0, especially natal girls.

Table 4: Self harm items 18 and 91 from the Youth Self Report using Wilcoxon Test

| | T0 | | | T1 | | | T0 - T1 significance | | Between-sex significance | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All N=30 | Natal boys N=14 | Natal girls N=16 | All N=30 | Natal boys N=14 | Natal girls N=16 | | | Natal boys | | Natal girls | |
| | *M (SD)* | *M (SD)* | *M (SD)* | *M (SD)* | *M (SD)* | *M (SD)* | *Z* | *ρ* | *Z* | *ρ* | *Z* | *ρ* |
| Self harm items YSR: | | | | | | | | | | | | |
| *I deliberately try to hurt or kill myself* | .13 (.15) | .14 (.36) | .13 (.34) | .39 (.56) | .23 (.44) | .50 (.63) | -2.111 | 0.035 * | 0.447 | 6.55 | -2.449 | 0.014 * |
| *I think about killing myself* | .30 (.53) | .21 (.43) | .38 (.62) | .57 (.73) | .43 (.65) | .69 (.79) | -1.734 | 0.083 | -1.134 | 0.257 | -1.311 | 0.19 |

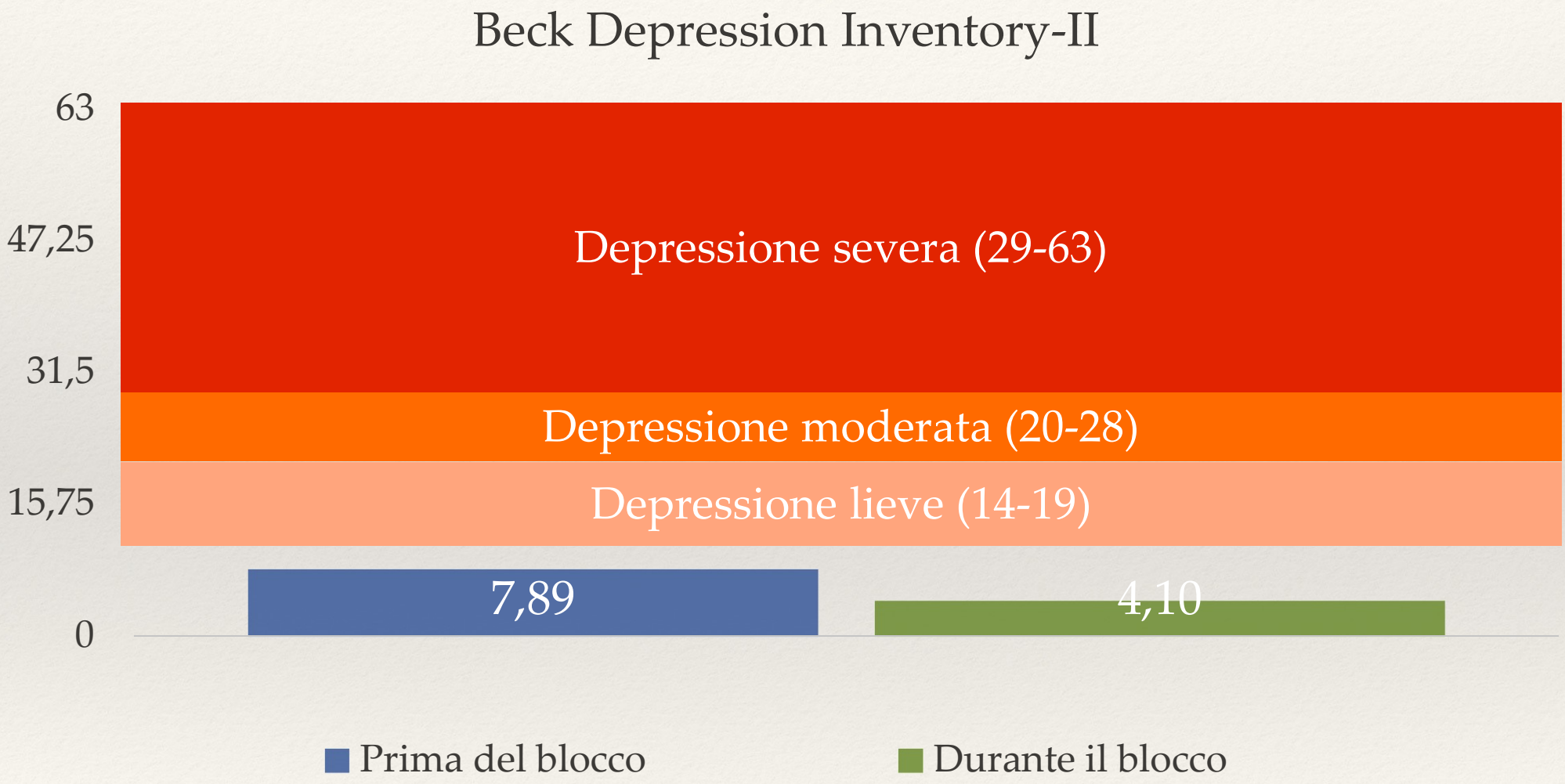
* Significant difference in mean between T0 and T1, $\rho < .05$

This Table shows the percentages of the scores given in T0 and T1.

Table 3: Self-harm reported by adolescents at T0 and T1

| | T0 | T1 |
|---|---|---|
| I deliberately try to hurt or kill myself | | |
| not true | 71.80% | 67.90% |
| sometimes | 18.90% | 32.10% |
| often true | 10.00% | 0% |
| I think about killing myself | | |
| not true | 65.90% | 58.60% |
| sometimes | 29.60% | 31.00% |
| often true | 4.50% | 10.30% |

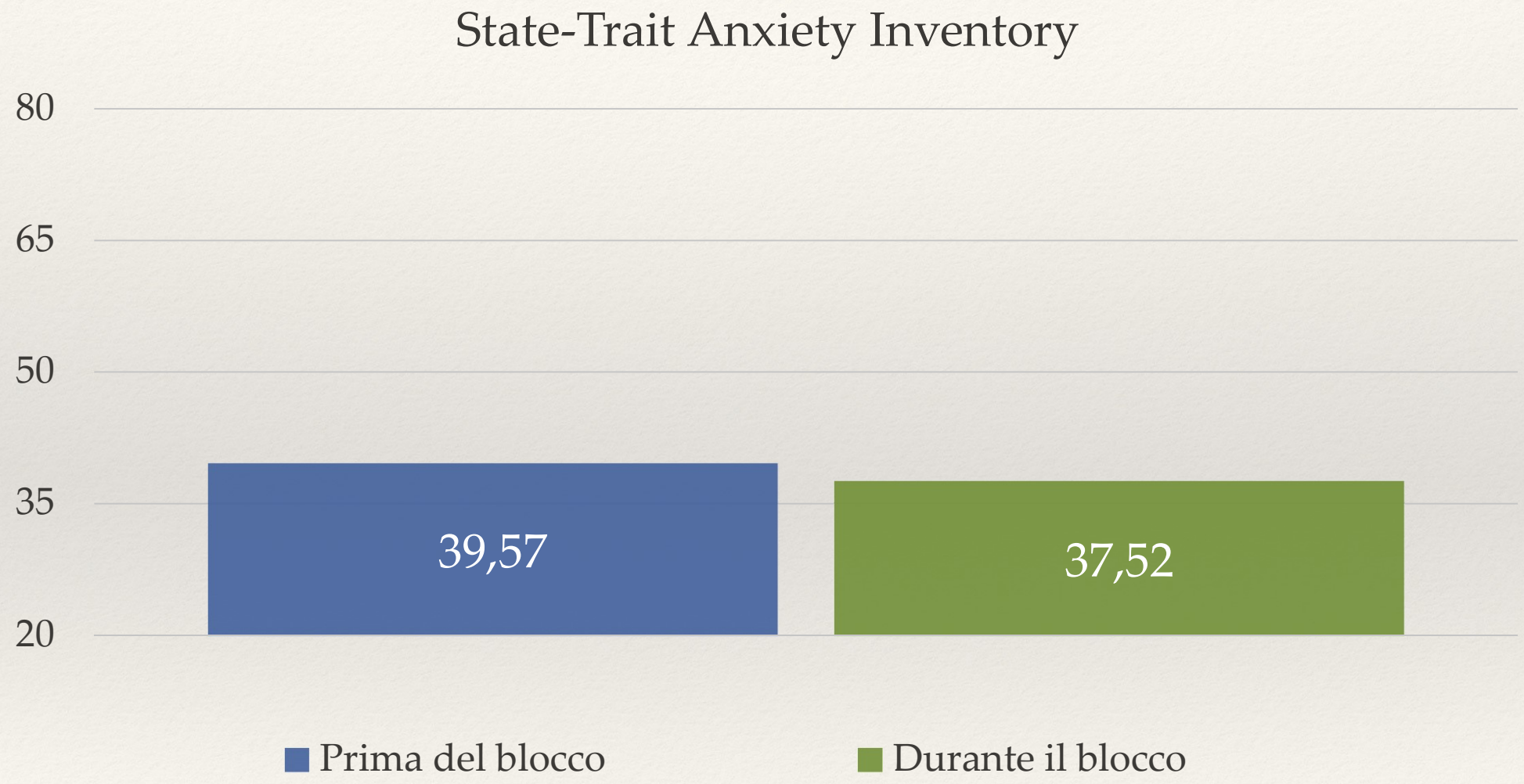
# Blocco puberale: effetto sulla depressione




De Vries ALC, et al. Pediatrics 2014; 134(4): 696-704.

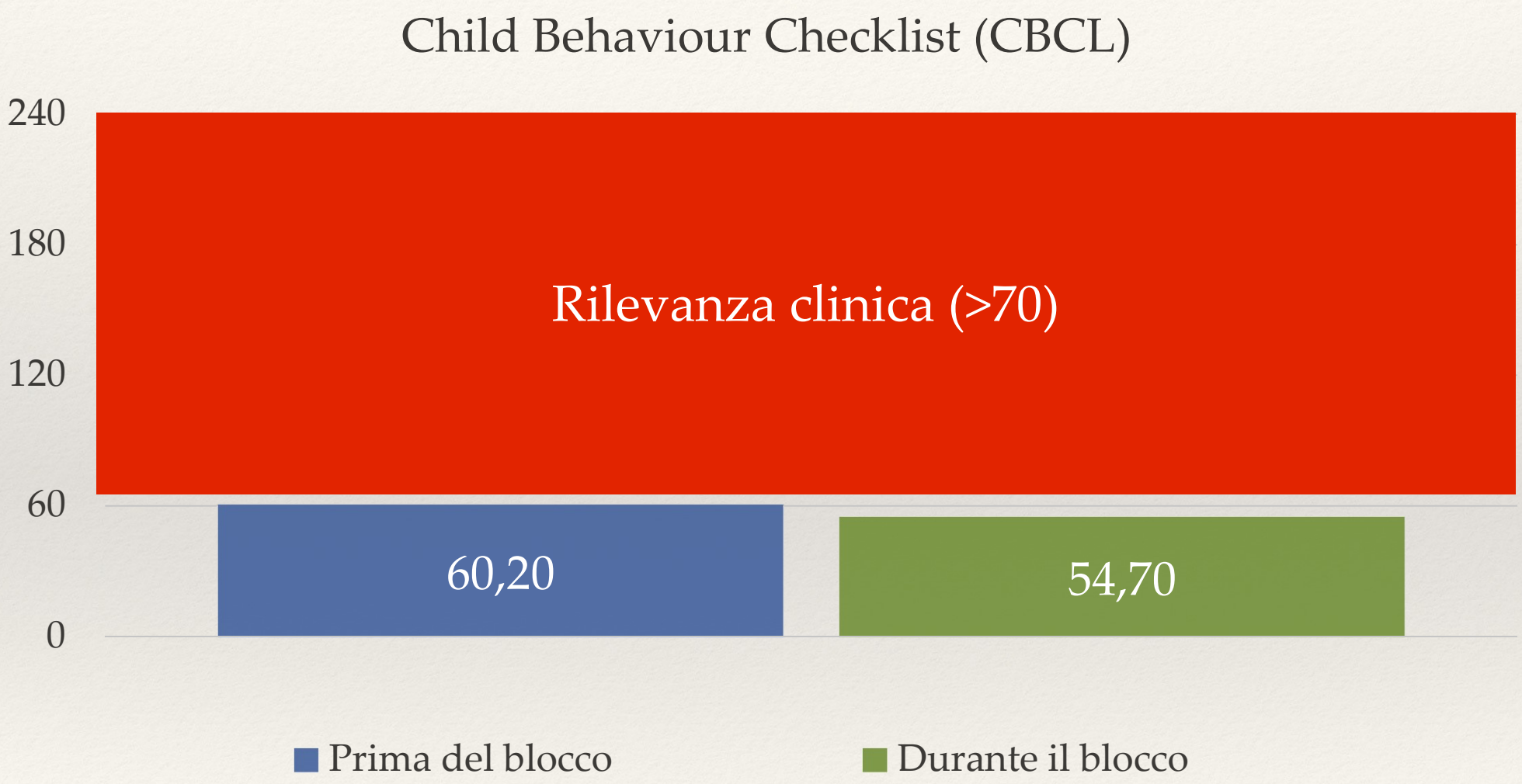
Beck AT, Steer RA, Brown GK. BDI-II: Beck Depression Inventory Manual. 2nd ed. San Antonio: Psychological Corporation; 1996.

# Blocco puberale: effetto sull'ansia



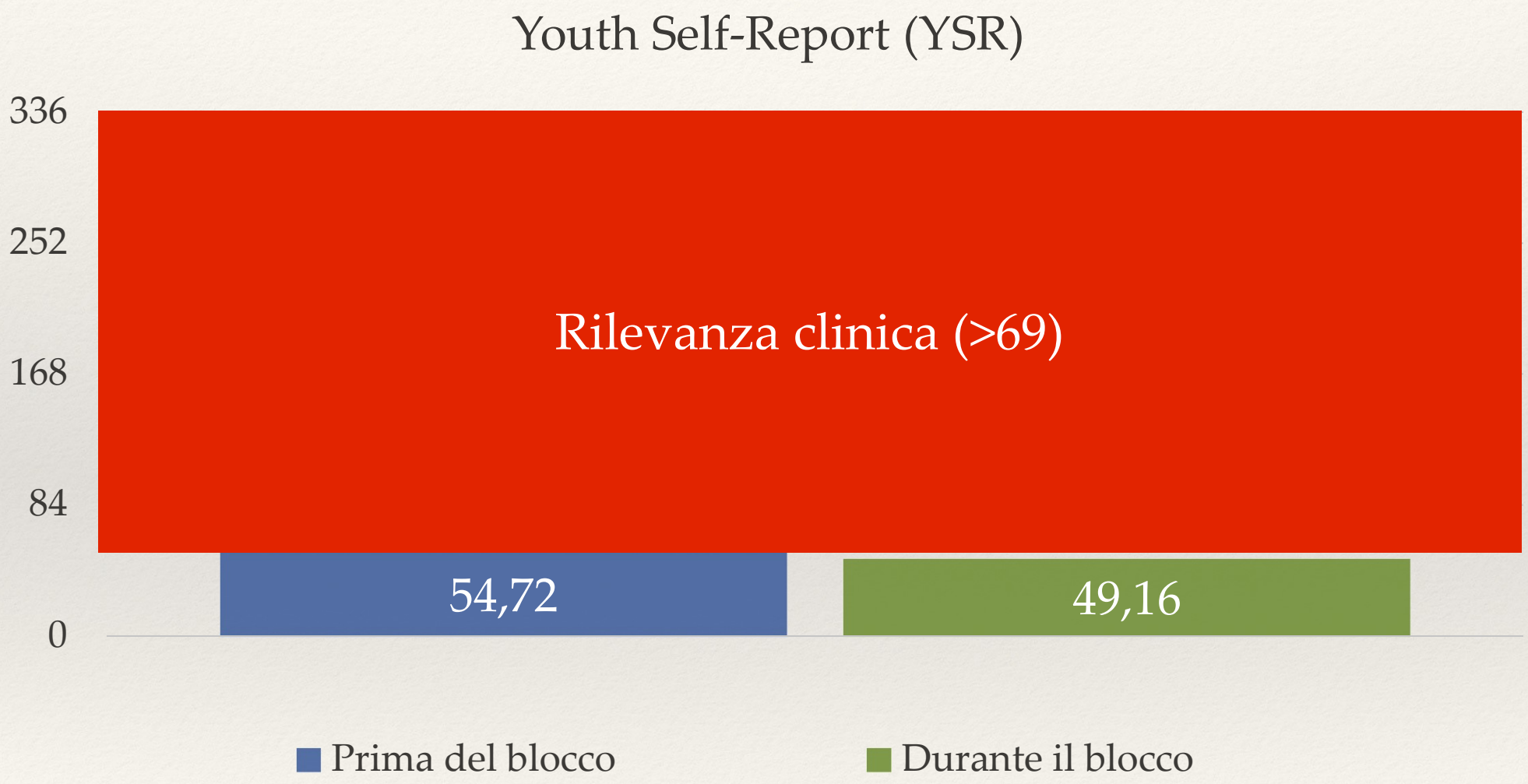

De Vries ALC, et al. Pediatrics 2014; 134(4): 696-704.

# Blocco puberale: effetto sui problemi di comportamento




De Vries ALC, et al. Pediatrics 2014; 134(4): 696-704.

# Blocco puberale: effetto sui problemi di comportamento




De Vries ALC, et al. Pediatrics 2014; 134(4): 696-704.
Achenbach, T.M., & Rescorla, L.A. (2001). Manual for the ASEBA School-Age Forms & Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

# Una motivazione immotivata

- La motivazione principale per il CNB a favore della TRP è la sofferenza del minore con DG, soprattutto per il timore di comportamenti autolesionistici e intenzioni suicidarie. Ma non vi è alcuna evidenza scientifica che quello con TRP sia il trattamento elettivo per queste situazioni.

CNB, 13 luglio 2018.

# Effetti fisici

1. Riduzione della densità minerale ossea (non compensato dalla terapia estrogenica nei MtF)
2. Rallentamento della crescita
3. Aumento della massa grassa
4. Riduzione della massa magra
5. Infertilità

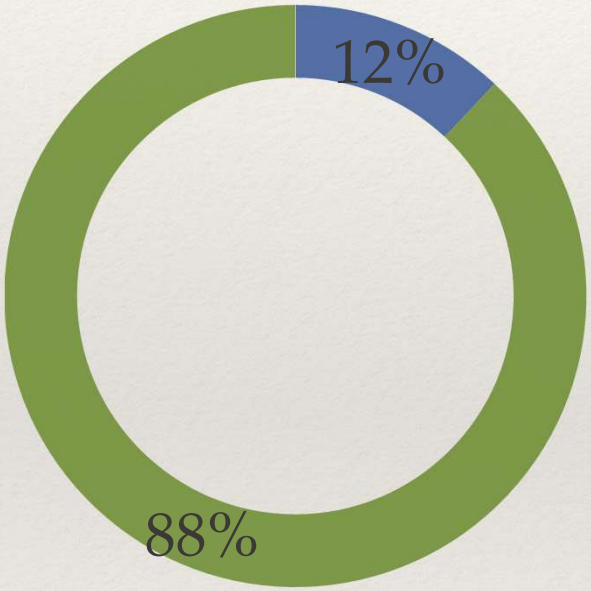
Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review

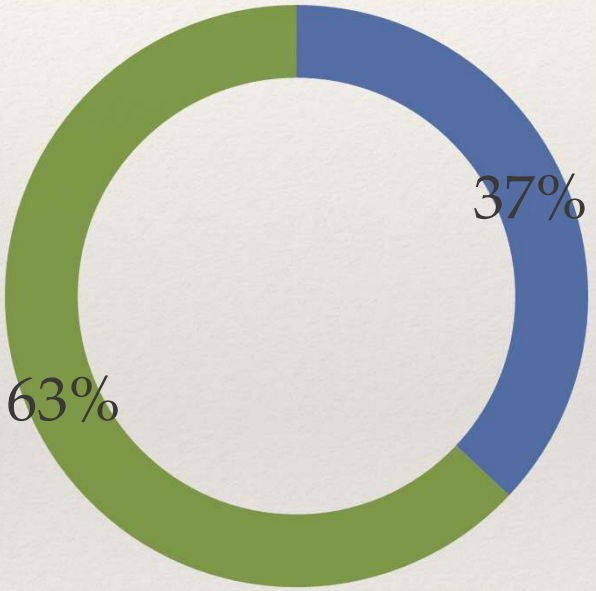
Denise Chew, BBmed,[a] Jemma Anderson, MBBS,[b] Katrina Williams, MBBS, MSc, PhD, FRACP, FAFPHM,[a,c,d] Tamara May, BA, BSc, GDipPsych, PGDipPsych, PhD,[a,c,d,e] Kenneth Pang, MBBS, BMedSc, FRACP, PhD[a,c,d,f,g]

Chew D, et al. Pediatrics 2018; 141(4): pii: e20173742. doi: 10.1542/peds.2017-3742. Epub 2018 Mar 7.

# Dare tempo

# Persistenti vs Desistenti




Drummond KD, et al. Developmental Psychology 2008; 44, 34–45.

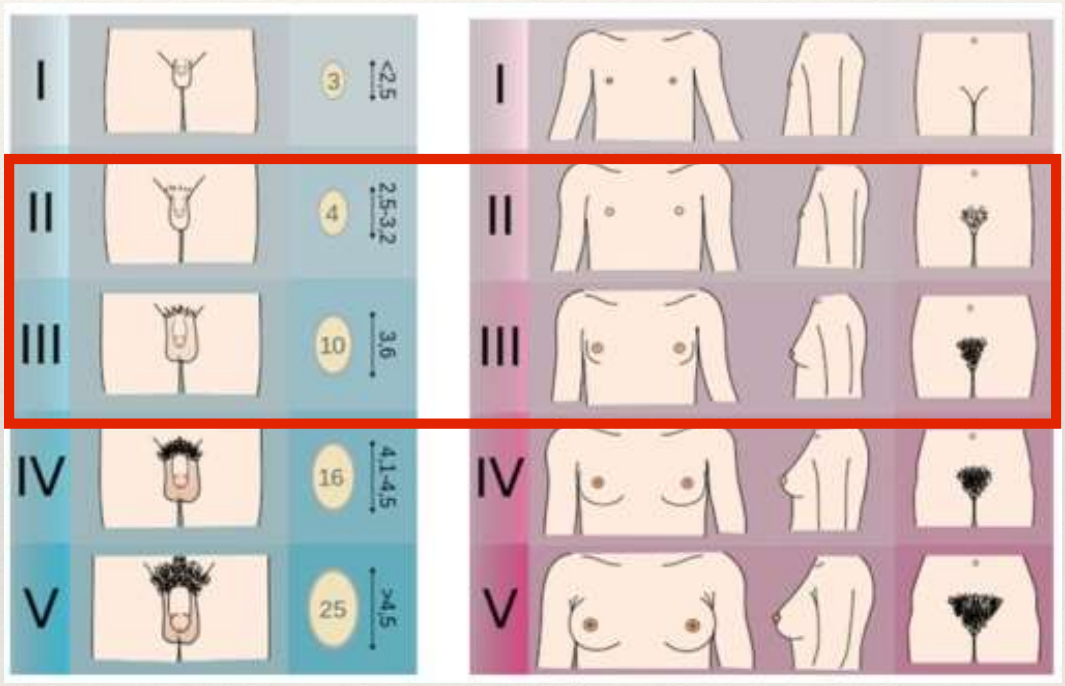
Steensma TD, et al. J American Academy of Child and Adolescent Psychiatry 2013; 52, 582-90.

# Età e Desistenza

[2] Il fenomeno della DG, sebbene ridotto numericamente, è in crescita. Si parla di una prevalenza dello 0,002-0,005% (2-5 casi su 100.000). Alcuni studi fatti sia in Olanda che in Canada indicano che nell'infanzia la DG non evolve necessariamente nella fase adolescenziale; mentre nel caso in cui la DG permanga nella fase iniziale della pubertà (adolescenza) raramente desiste e quasi tutti i soggetti con DG in adolescenza mantengono questa condizione nell'età adulta.

# Quando ?

- Le linee guida raccomandano di attuare il blocco puberale non prima dello stadio II di Tanner per verificare l'effetto dei cambiamenti puberali sulla disforia.




Hembree WC, et al. J Clin Endocrinol Metab 2017; 102: 3869–3903.

# La spinta biologica

*The adolescent development of desisters*

In desisters, the gender discomfort gradually decreased over the course of grades 7 and 8 (age 10 to 13). Both boys and girls indicated that their changing interests and friendships, and the physical changes during puberty made the gender discomfort diminish and eventually disappear. The desisters also reported that their first experience of falling in love and awareness of sexual attraction were factors that resulted in the disappearance of their gender dysphoria.

As for their preferences for gender-related activities and friendships, the desisters indicated that their gender atypical interests did not necessarily evaporate, but that they just became more receptive to gender typical interests. As a result, they developed more affiliation with children of their own gender, and more often engaged in same-gender friendships.

*"I cambiamenti fisici durante la pubertà facevano diminuire il disagio, facendolo talora scomparire".*

Steensma TD, et al. Clin Child Psychol Psychiatry. 2011; 16(4): 499-516.

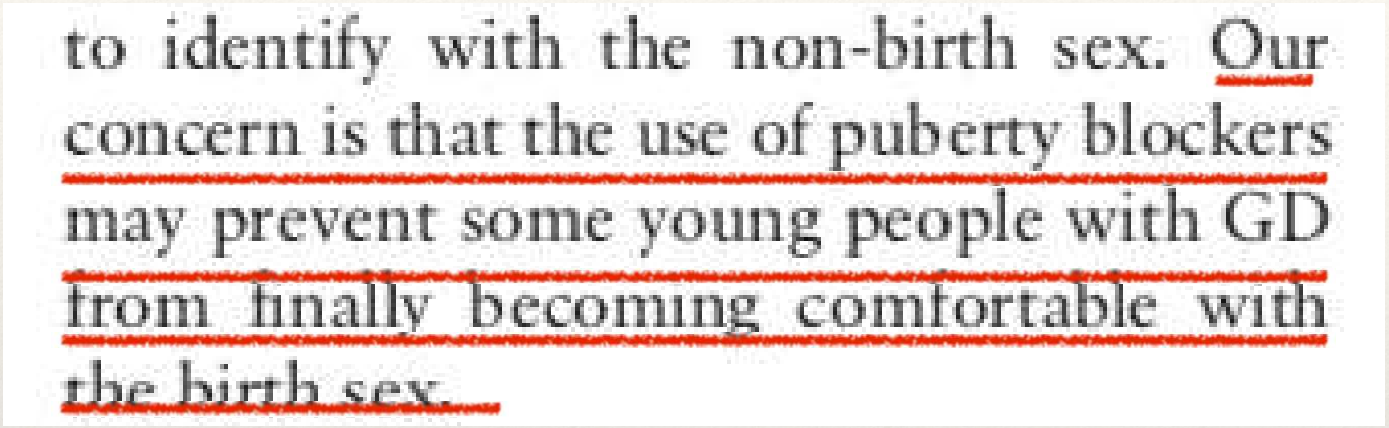
# La capacità di prevedere la persistenza è scarsa

In the combined group, the following variables collectively accounted for 58% of the variability in the persistence of gender dysphoria: Age at intake, childhood role transition, and both cognitive and affective responses to the gender identity interview. Once these variables were accounted for, responses to the gender identity questionnaire did not predict additional variance in persistence. Cognitive responses to the gender identity interview were

*"Le seguenti variabili spiegavano nel loro complesso il 58% della variabilità della persistenza della disforia di genere: l'età alla presentazione, la transizione di ruolo dall'infanzia e le risposte cognitive ed affettive all'intervista sull'identità di genere. Una volta che queste variabili venivano considerate, le risposte al questionario sull'identità di genere non prediceva ulteriore varianza della persistenza".*

Steensma TD, et al. J Am Acad Child Adolesc Psychiatry. 2013; 52(6):582-590.

# Dare tempo può non essere una scelta neutra



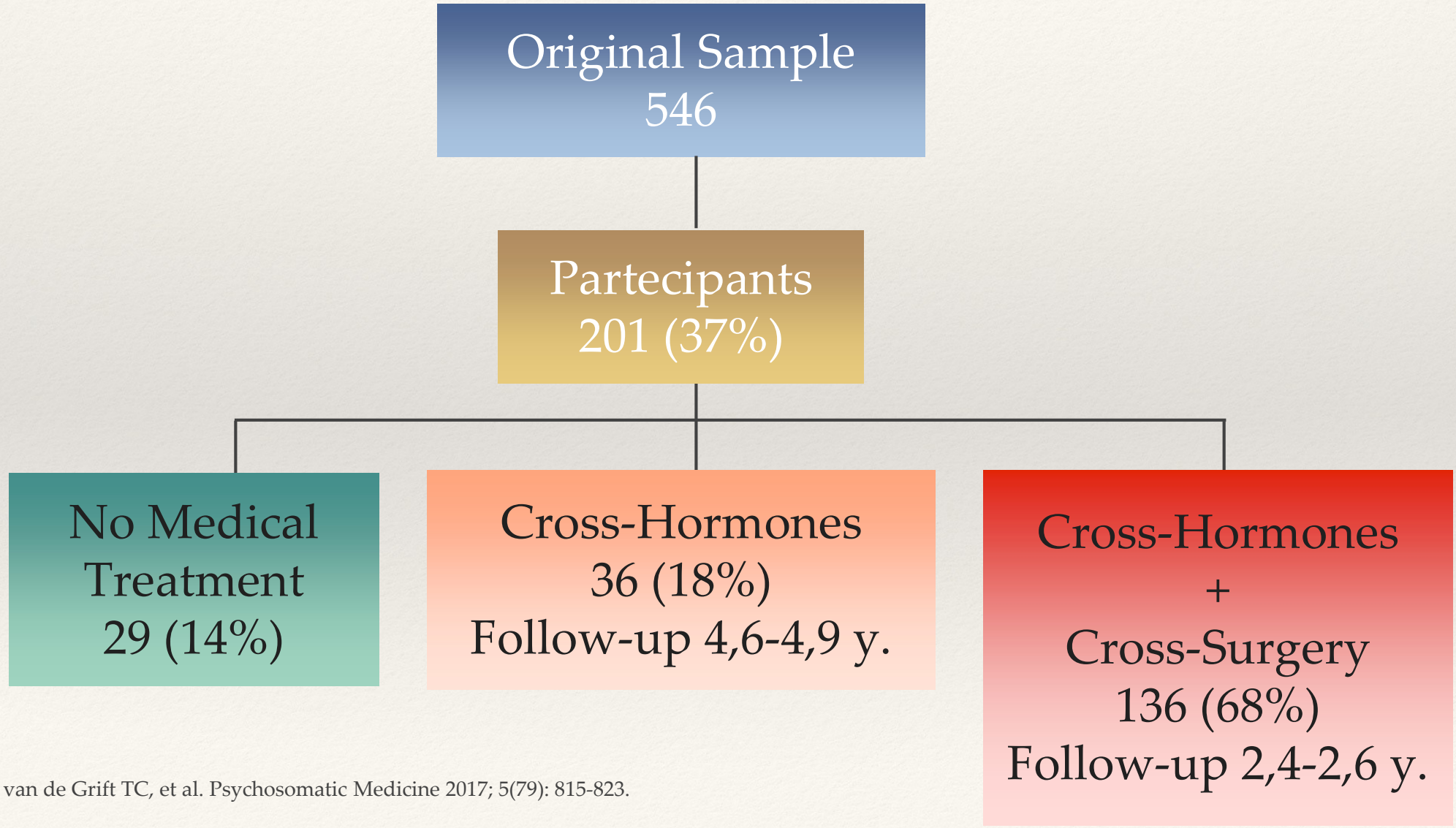
to identify with the non-birth sex. Our concern is that the use of puberty blockers may prevent some young people with GD from finally becoming comfortable with the birth sex.

*"La nostra preoccupazione è quella che l'uso dei bloccanti della pubertà possa impedire ad alcuni giovani con GD di raggiungere un benessere finale col proprio sesso di nascita".*

Richard C, et al. Arch Dis Child. 2019; 104(6): 611-612.

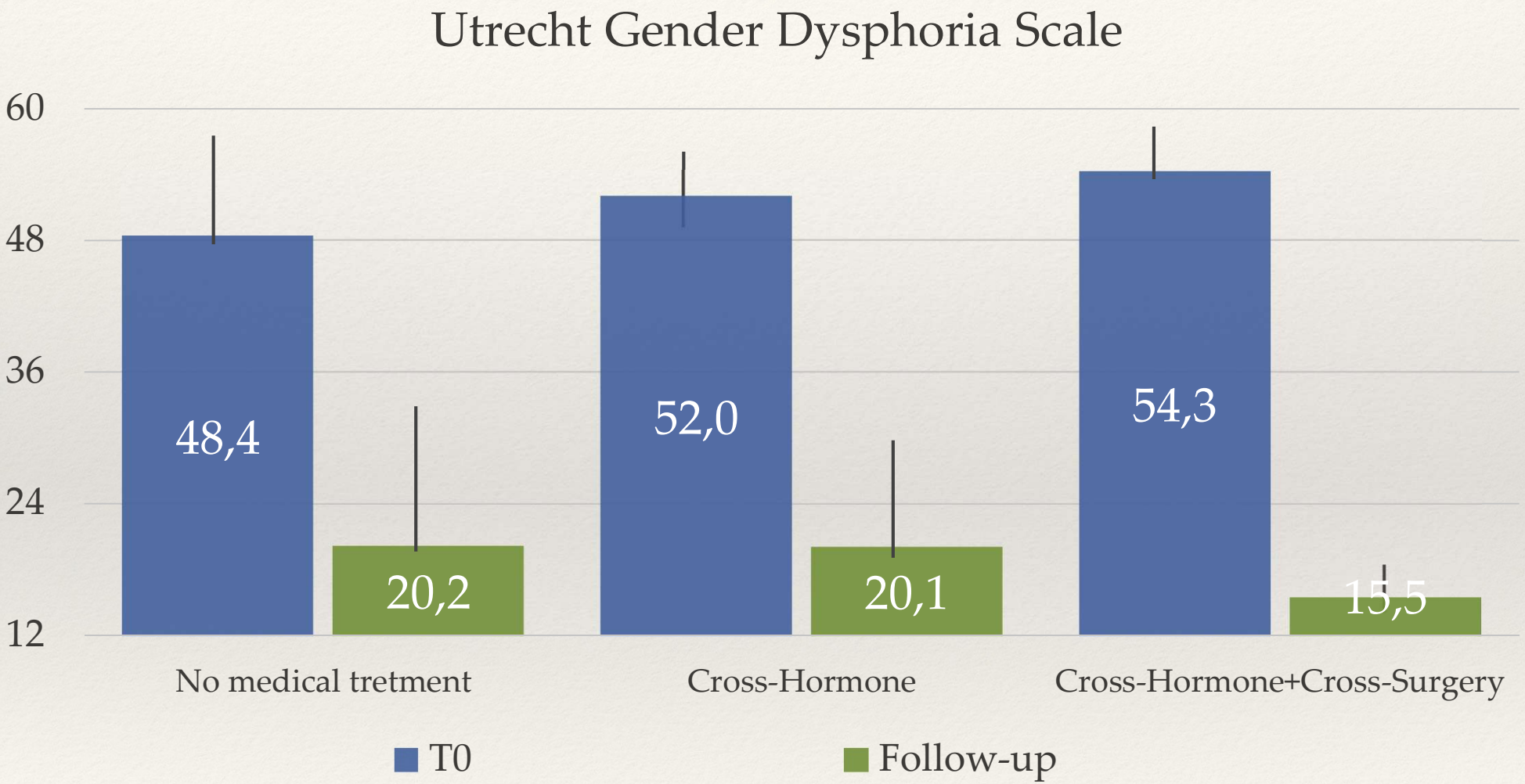
# Facilitare la transizione chirurgica

# Effetto della transizione sulla disforia di genere




van de Grift TC, et al. Psychosomatic Medicine 2017; 5(79): 815-823.

# Effetto della transizione sulla disforia di genere




van de Grift TC, et al. Psychosomatic Medicine 2017; 5(79): 815-823.

# Il risultato nel tempo: Olanda

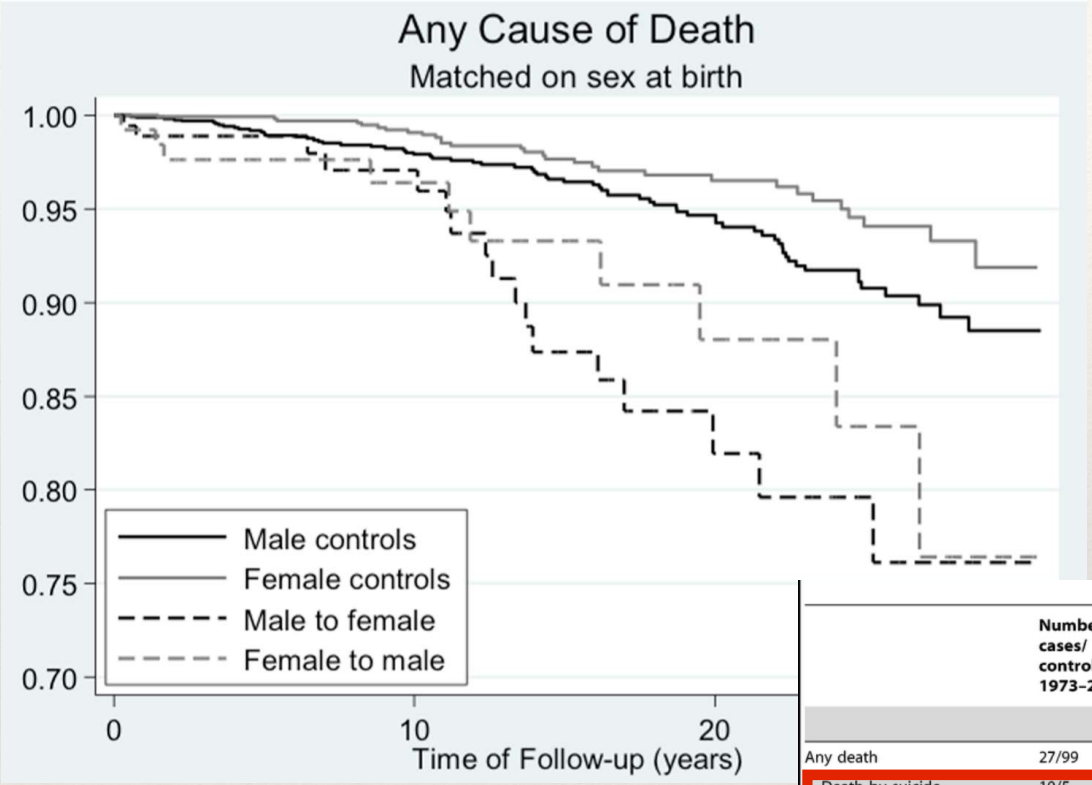
**Table 2** SMR adjusted for age and period of follow-up on hormone treatment by biological sex in 1331 male-to-female and female-to-male transsexual subjects.

| | Male-to-female transsexuals | | Female-to-male transsexuals | |
|---|---|---|---|---|
| **Cause of death** | Observed cases | SMR (95% CI) | Observed cases | SMR (95% CI) |
| Malignant neoplasm | 28 | 0.98 (0.88–1.08) | 5 | 0.99 (0.65–1.44) |
| Lung | 13 | 1.35 (1.14–1.58) | 1 | 1.06 (0.26–3.19) |
| Digestive tract | 3 | 0.42 (0.28–0.60) | 2 | 2.41 (0.90–5.18) |
| Hematological | 6 | 2.58 (1.97–3.30) | 1 | 2.86 (0.69–8.57) |
| Brain | 2 | 1.59 (0.95–2.46) | 0 | – |
| Other: kidney, melanoma, bone, and prostate in MtF. In FtM: leiomyosarcoma | 4 | 0.79 (0.57–1.07) | 1 | 0.77 (0.25–1.77) |
| Ischemic heart disease | 18 | 1.64 (1.43–1.87) | 1 | 1.19 (0.39–2.74) |
| Cerebrovascular accidents | 5 | 1.26 (0.93–1.64) | 0 | – |
| AIDS | 16 | 30.20 (26.0–34.7) | 0 | – |
| Endocrine/diabetes | 2 | 0.85 (0.41–1.32) | 0 | – |
| Respiratory system diseases | 4 | 0.85 (0.61–1.14) | 0 | – |
| Digestive system diseases | 3 | 1.01 (0.68–1.45) | 1 | 2.56 (0.62–7.69) |
| Genitourinary system disease (ESRD) | 1 | 1.21 (0.58–2.17) | 0 | – |
| Nervous system disease (MS) | 0 | | 1 | 3.57 (0.86–10.7) |
| External causes | 24 | 7.67 (6.84–8.56) | 2 | 2.22 (1.07–5.44) |
| Illicit drugs use | 5 | 13.20 (9.70–17.6) | 1 | 25.00 (6.00–32.5) |
| Suicide | 17 | 5.70 (4.93–6.54) | 1 | 2.22 (0.53–6.18) |
| Unknown/ill-defined symptoms | 21 | 4.00 (3.52–4.51) | 2 | 2.08 (0.69–4.79) |
| Total | 122 | 1.51 (1.47–1.55) | 12 | 1.12 (0.89–1.59) |

ESRD, end-stage renal disease; MS, multiple sclerosis.

Asscheman H, et al. European Journal of Endocrinology 2011; 164 635–642.

# Il risultato nel tempo: Svezia

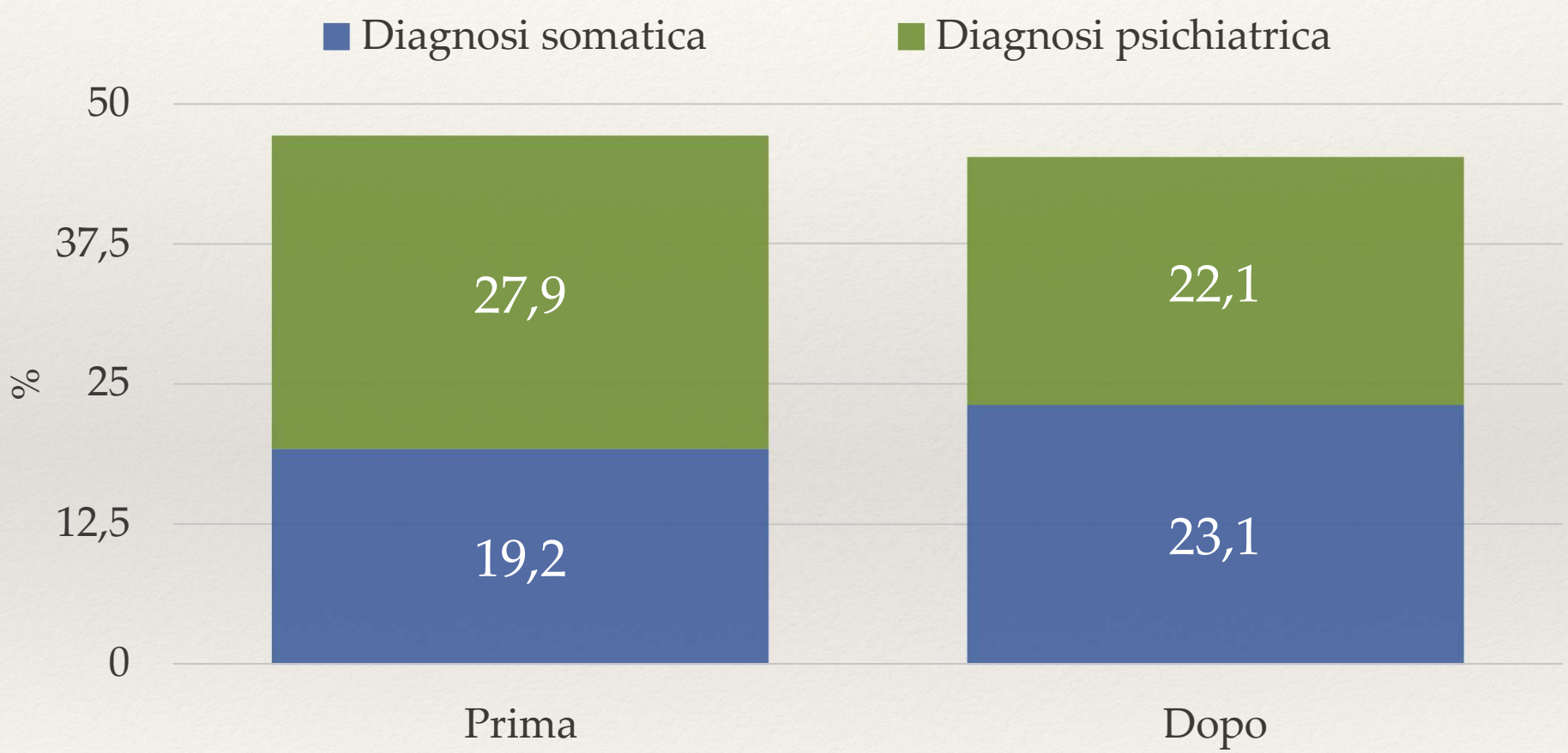



| | Number of events cases/ controls 1973–2003 | Outcome incidence rate per 1000 person-years 1973–2003 (95% CI) | | Crude hazard ratio (95% CI) 1973–2003 | Adjusted* hazard ratio (95% CI) 1973–2003 | Adjusted* hazard ratio (95% CI) 1973–1988 | Adjusted* hazard ratio (95% CI) 1989–2003 |
|---|---|---|---|---|---|---|---|
| | | 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

Dhejne C, et al. PLoS ONE 6(2): e16885.

# Il risultato nel tempo: Danimarca




Simonsen Rk, et al. Nord J Psychiatry. 2016; 70(4): 241-247.
Simonsen Rk, et al. Sex Med. 2016; 4(1): e60-8.

# Conclusioni

- Assenza di presupposti per un impiego clinico
- Assenza di presupposti per una sperimentazione clinica
- È opportuno che AIFA riapra il dossier.

# Slides aggiuntive

# Sospendere la triptorelina?

- **Dottoressa Petraglia:** "Non è definita la durata del piano terapeutico proposto. La maggior parte degli studi suggerisce la sospensione del blocco ormonale all'età di 16 anni, con l'avvio di un percorso di valutazione della persistenza della DG". (p. 5)

# Il blocco puberale non viene interrotto

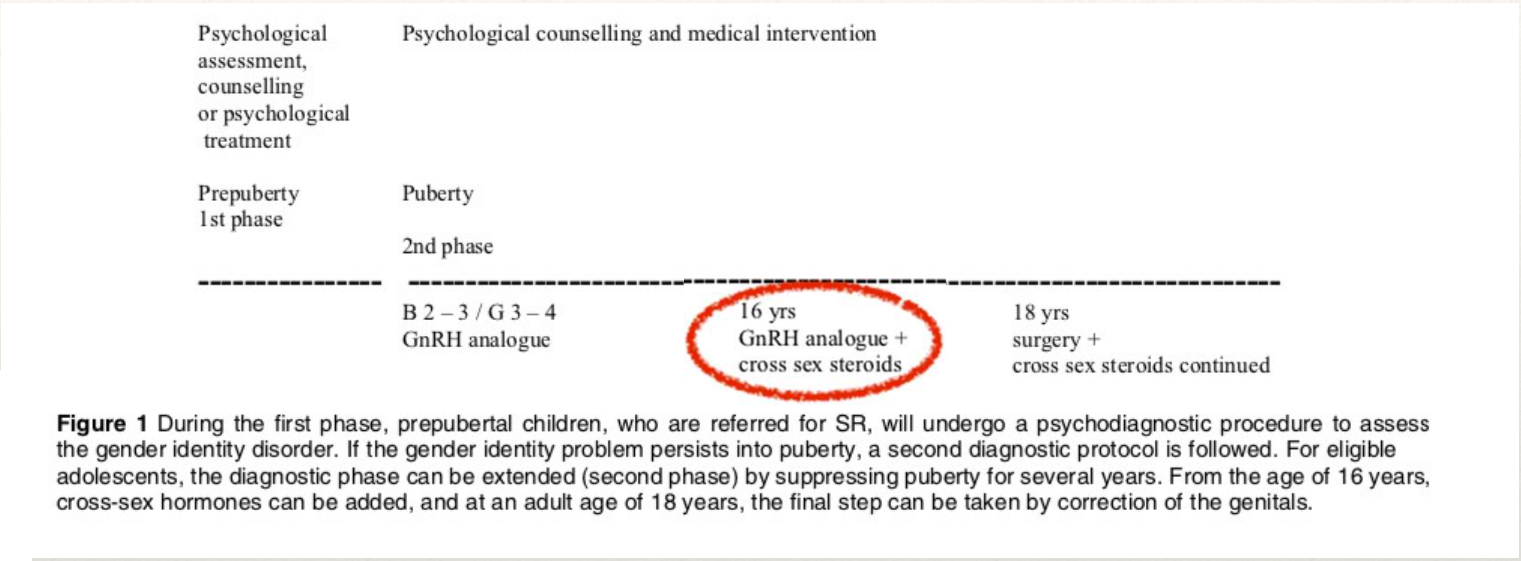



**Figure 1** During the first phase, prepubertal children, who are referred for SR, will undergo a psychodiagnostic procedure to assess the gender identity disorder. If the gender identity problem persists into puberty, a second diagnostic protocol is followed. For eligible adolescents, the diagnostic phase can be extended (second phase) by suppressing puberty for several years. From the age of 16 years, cross-sex hormones can be added, and at an adult age of 18 years, the final step can be taken by correction of the genitals.

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## Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects

Henriette A Delemarre-van de Waal and Peggy T Cohen-Kettenis

*Amsterdam Gender Clinic, Departments of Pediatrics and Medical Psychology, Institute for Clinical and Experimental Neuroscience, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands*

*(Correspondence should be addressed to H A Delemarre-van de Waal; Email: h.delemarre@vumc.nl)*

**Abstract**

Treatment outcome in transsexuals is expected to be more favourable when puberty is suppressed than when treatment is started after Tanner stage 4 or 5. In the Dutch protocol for the treatment of transsexual adolescents, candidates are considered eligible for the suppression of endogenous puberty when they fulfil the Diagnostic and Statistic Manual of Mental Disorders-IV-RT criteria for gender disorder, have suffered from lifelong extreme gender dysphoria, are psychologically stable and live in a supportive environment. Suppression of puberty should be considered as supporting the diagnostic procedure, but not as the ultimate treatment. If the patient, after extensive exploring of his/her sex reassignment (SR) wish, no longer pursues SR, pubertal suppression can be discontinued. Otherwise, cross-sex hormone treatment can be given at 16 years, if there are no contraindications. Treatment consists of a GnRH analogue (GnRHa) to suppress endogenous gonadal stimulation from B2–3 and G3–4, and prevents development of irreversible sex characteristics of the unwanted sex. From the age of 16 years, cross-sex steroid hormones are added to the GnRHa medication.

Preliminary findings suggest that a decrease in height velocity and bone maturation occurs. Body proportions, as measured by sitting height and sitting-height/height ratio, remains in the normal range. Total bone density remains in the same range during the years of puberty suppression, whereas it significantly increases on cross-sex steroid hormone treatment. GnRHa treatment appears to be an important contribution to the clinical management of gender identity disorder in transsexual adolescents.

*European Journal of Endocrinology* **155** S131–S137

### Introduction

Transsexuals are applying for sex reassignment (SR) surgery at increasingly younger ages. Yet clinicians are usually reluctant to start the SR procedure before adulthood. They assume that adolescents are not able to make a sensible decision about something as drastic as SR. They fear that the risk of postoperative regrets will be high and the treatment will have unfavourable physical, psychological or social consequences. Post-operative regret or any other unfavourable result of SR naturally is of serious concern to clinicians. However, the decision of what age to start SR should be a balanced one. There are two main reasons to consider early treatment as appropriate.

One reason for early treatment is that an eventual delay or arrest in emotional, social or intellectual development can be warded off more successfully when the ultimate cause of this arrest has been taken care of. Suffering from gender dysphoria without being able to present socially in the desired social role, and/or to stop the development of secondary sex characteristics usually leads to problems in these areas. Adolescents find it hard to live with a secret. Often have difficulties in connecting socially and romantically with peers while still in the undesired gender role, or the physical developments create an anxiety that limits their capacities to concentrate on other issues.

A second reason to start SR early is that the physical treatment outcome following interventions in adulthood is far less satisfactory than when treatment is started at an age at which secondary sex characteristics have not yet been (fully) developed. Looking like a man (woman) when living as a woman (man) creates barriers that are not easy to overcome. This is obviously an enormous and lifelong disadvantage. Indeed, Ross

This paper was presented at the 4th Ferring Pharmaceuticals International Paediatric Endocrinology Symposium, Paris (2006). Ferring Pharmaceuticals has supported the publication of these proceedings.



DOI: 10.1530/eje.1.02231
Online version via www.eje-online.org

# Il blocco puberale normalmente non viene interrotto

Il blocco della pubertà può continuare per alcuni anni, dopo di che bisogna decidere se interrompere la terapia ormonale o se proseguire per arrivare alla transizione femminilizzante o mascolinizzante. Il blocco della pubertà non porta necessariamente alla transizione sociale o al cambio di sesso.

The World Professional Association for Transgender Health 7a Versione1 | www.wpath.org
Standards of Care per la Salute di Persone Transessuali, Transgendere di Genere Non-Conforme

When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion. Gonadotropin secretion and endogenous production of testosterone may resume and interfere with the effectiveness of estrogen treatment, in transgender female adolescents (126, 127). Therefore, continuation of GnRH analog treatment is advised until gonadectomy. Given that GD/gender-incongruent adolescents may opt not to have gonadectomy, long-term studies are necessary to examine the potential risks of prolonged GnRH analog treatment. Alternatively, in transgender male adolescents, GnRH analog treatment can be discontinued once an adult dose of testosterone has been reached and the individual is well virilized. If uterine bleeding occurs, a progestin can be added. However, the combined use of a GnRH analog (for ovarian suppression) and testosterone may enable phenotypic transition with a lower dose of testosterone in comparison with testosterone alone. If there is a wish or need to discontinue GnRH analog treatment in transgender female adolescents, they may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see section 3.0 "Hormonal Therapy for Transgender Adults").

Hembree WC, et al. J Clin Endocrinol Metab, November 2017, 102(11):3869–3903.

# I GnRHa riducono la densità ossea

**Bone Mineral Density**

*GnRHas in Transfemale Adolescents*

Lumbar spine bone mineral density (BMD) *z* scores decreased after treatment with GnRHa monotherapy,[19,29,31] and this reduction was statistically significant in all[29,31] but 1 study.[19] When results were stratified by bone age, the mean reduction in *z* score was only significant (1.32) for individuals with a bone age <15 years.[31] Absolute lumbar spine BMD did not change over time, and thus the decrease in *z* scores after GnRHas likely reflects a failure to accrue BMD compared with age-matched peers. In 2 studies, researchers also examined BMD at the hip and femoral regions, which

*GnRHas in Transmale Adolescents*

There was a greater reduction in BMD in transmale adolescents treated with GnRHas than transfemale adolescents. Two studies revealed a significant decrease in absolute and *z* scores for lumbar spine BMD,[19,31] whereas another study revealed a significant reduction in only *z* scores.[29] In 1 study, researchers quantified the reduction in BMD *z* scores as being 0.79 for individuals with a bone age <14 years and 0.56 for individuals with bone ages ≥14 years.[31] Two studies also revealed statistically significant reductions in BMD *z* scores at the hip and femoral regions in transmale adolescents.[19,31]

Chew D, et al. Pediatrics 2018; 141(4):
pii: e20173742. doi: 10.1542/peds.2017-3742. Epub 2018 Mar 7

# I GnRHa riducono la densità ossea

*Estrogen*

Estrogen monotherapy was associated with significant increases in both absolute BMD and *z* scores in the lumbar spine,[29,31] but not the hip,[31] of transfemale adolescents previously treated with GnRHas. Furthermore, their *z* scores after 2 years of estrogen were still below that of age- and birth-assigned sex-matched norms.[31] Specifically, *z* scores in the spine were −1.10 and −0.66 in those with younger (<15 years) and older (≥15 years) bone ages, respectively.

*Testosterone*

Testosterone monotherapy led to a significant increase in both absolute BMD and *z* scores in the lumbar spine[29,31] and hip[31] of transmale adolescents, who had previously been on GnRHas. However, their *z* scores did not reach that of age- and birth-assigned sex-matched controls, aside from the *z* scores in the hip of individuals with older bone ages. Specifically, *z* scores in the spine and hip were −0.15 and −0.37, respectively, in those with younger (<15 years old) bone ages and −0.06 and 0.02, respectively, in those with older (≥15 years old) bone ages.

Chew D, et al. Pediatrics 2018; 141(4):
pii: e20173742. doi: 10.1542/peds.2017-3742. Epub 2018 Mar 7

# Nei maschi il blocco puberale sancisce l'infertilità

Should a trans female adolescent be commencing puberty suppression in early adolescence (Tanner stage 2-3) collection of mature sperm will usually not be possible since mature sperm are produced from mid puberty (Tanner stage 3-4). Unfortunately, this point in development often coincides with voice deepening, so most adolescents will find waiting for sperm maturation to occur unacceptable in the context of their gender dysphoria. Should the adolescent not have mature sperm for cryopreservation, testicular tissue cryopreservation can be offered as a potential means for reproduction in the future,[17] but is currently experimental and with limited availability across Australia outside of major capital cities.

Jornal de Pediatria - Vol. 77, Supl.2 , 2001 S141

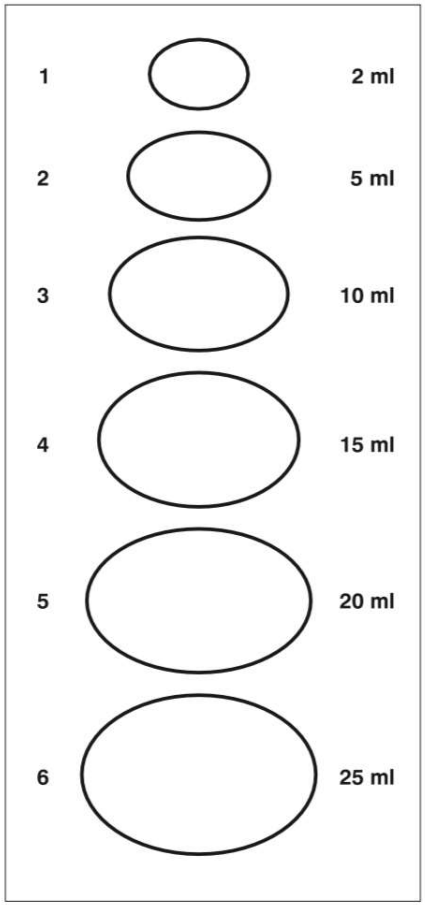


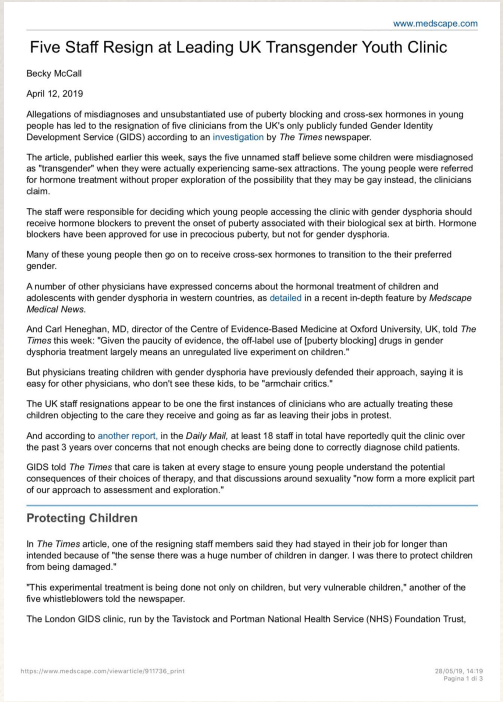

**Figure 5 -** Scheme for graphic measurement of testicular volume. The testicle is palpated and visually compared with the graphic models. Testicular volume is determined according to one of the six volumes or one of the intermediate volumes between two consecutive volumes depicted . The entire measurement scale includes 13 volumes: less than 2ml, 2ml, 3.5ml, 5ml, 7.5ml, 10ml, 12.5ml, 15ml, 17.5ml, 20ml, 22.5ml, 25ml, and greater than 25ml

# Persistenza negli adolescenti

Viceversa, la persistenza della disforia di genere nell'età adulta pare essere maggiore negli adolescenti. Non esistono studi prospettici precedenti, tuttavia, in uno studio di follow-up su 70 adolescenti con diagnosi di disforia di genere, ai quali furono somministrati ormoni per il blocco della pubertà, tutti proseguirono il percorso di riattribuzione di sesso a partire dalle terapie ormonali femminilizzanti/mascolinizzanti (de Vries, Steensma, Doreleijers & Cohen-Kettenis, 2010).

# Una “sperimentazione senza regole”

And Carl Heneghan, MD, director of the Centre of Evidence-Based Medicine at Oxford University, UK, told *The Times* this week: "Given the paucity of evidence, the off-label use of [puberty blocking] drugs in gender dysphoria treatment largely means an unregulated live experiment on children."



www.medscape.com

Five Staff Resign at Leading UK Transgender Youth Clinic

Becky McCall

April 12, 2019

Allegations of misdiagnoses and unsubstantiated use of puberty blocking and cross-sex hormones in young people has led to the resignation of five clinicians from the UK's only publicly funded Gender Identity Development Service (GIDS) according to an investigation by *The Times* newspaper.

The article, published earlier this week, says the five unnamed staff believe some children were misdiagnosed as "transgender" when they were actually experiencing same-sex attractions. The young people were referred for hormone treatment without proper exploration of the possibility that they may be gay instead, the clinicians claim.

The staff were responsible for deciding which young people accessing the clinic with gender dysphoria should receive hormone blockers to prevent the onset of puberty associated with their biological sex at birth. Hormone blockers have been approved for use in precocious puberty, but not for gender dysphoria.

Many of these young people then go on to receive cross-sex hormones to transition to the their preferred gender.

A number of other physicians have expressed concerns about the hormonal treatment of children and adolescents with gender dysphoria in western countries, as detailed in a recent in-depth feature by *Medscape Medical News*.

And Carl Heneghan, MD, director of the Centre of Evidence-Based Medicine at Oxford University, UK, told *The Times* this week: "Given the paucity of evidence, the off-label use of [puberty blocking] drugs in gender dysphoria treatment largely means an unregulated live experiment on children."

But physicians treating children with gender dysphoria have previously defended their approach, saying it is easy for other physicians, who don't see these kids, to be "armchair critics."

The UK staff resignations appear to be one the first instances of clinicians who are actually treating these children objecting to the care they receive and going as far as leaving their jobs in protest.

And according to another report, in the *Daily Mail*, at least 18 staff in total have reportedly quit the clinic over the past 3 years over concerns that not enough checks are being done to correctly diagnose child patients.

GIDS told *The Times* that care is taken at every stage to ensure young people understand the potential consequences of their choices of therapy, and that discussions around sexuality "now form a more explicit part of our approach to assessment and exploration."

**Protecting Children**

In *The Times* article, one of the resigning staff members said they had stayed in their job for longer than intended because of "the sense there was a huge number of children in danger. I was there to protect children from being damaged."

"This experimental treatment is being done not only on children, but very vulnerable children," another of the five whistleblowers told the newspaper.

The London GIDS clinic, run by the Tavistock and Portman National Health Service (NHS) Foundation Trust,

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