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a population-based cohort study

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Gender incongruence and timing of puberty: a population-based cohort study

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Objective: To study whether the timing of puberty in adolescents who reported gender incongruence (incongruence between birth-assigned sex and self-identified gender) was different from those adolescents who reported gender congruence.
Design: Population-based cohort study using data from the *Danish National Birth Cohort*.
Setting: Not applicable.
Patient(s): Birth-assigned boys and girls born between 2000 and 2003, who self-reported gender incongruence at 11 years (N = 10,046) and their pubertal developmental stages from age 11 years to every 6 months throughout puberty were included.
Intervention(s): Not applicable.
Main Outcome Measure: Mean age differences in months at reaching Tanner stages 2–5 for breast or genital development and pubic hair, voice break, first ejaculation, menarche, axillary hair, acne, and the average difference at attaining all pubertal milestones (primary outcome).
Result(s): In total, 549 (5.5%) adolescents reported part or full gender incongruence at 11 years. Tendencies toward earlier timing of puberty were observed in adolescents who reported part gender incongruence (average difference, birth-assigned boys: −3.2 months [95% confidence interval {CI}: −6.7; 0.3]; birth-assigned girls: −2.0 months [95% CI: −3.9; −0.1]). Tendencies toward earlier timing of puberty were observed in adolescents who reported full gender incongruence (average difference, birth-assigned boys: −2.4 months [95% CI: −5.0; 0.4]; birth-assigned girls: −1.9 months [95% CI: −5.1; 1.2]).
Conclusions: The results from this study indicated that birth-assigned boys and girls who reported either part or full gender incongruence tended to reach puberty slightly earlier than those adolescents who reported gender congruence at 11 years of age. Knowledge on the timing of puberty among adolescents who experience gender incongruence is essential to inform mutual decision-making in clinical settings. (Fertil Steril® 2022;118:938-45. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Gender incongruence, pubertal timing, gender identity, population-based

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Gender identity is defined as the individual's own perception of their gender, whether it corresponds with the individual's birth-assigned sex or not. Most children can already label and express their gender in early childhood (1), whereas some will believe a mismatch between their biologic sex assigned at birth and their self-identified gender. This is defined as gender incongruence (2). In recent decades, an increase in adolescents who experience gender incongruence has been observed. This rise may lead to increased need for counseling by health care professionals and ultimately therapy of different sorts (3, 4). Children

and adolescents who are gender incongruent may experience psychological difficulties as their secondary sex characteristics mature (5), and some may wish to delay or suppress puberty. Research on puberty, including knowledge about the timing of puberty among adolescents who are gender incongruent is limited. One study ($N = 696$ birth-assigned girls) with limited adjustment for important potential confounders found that birth-assigned girls who were gender incongruent, reached timing of puberty earlier than birth-assigned girls from the general population (6). Knowledge on the timing of puberty in adolescents who are gender incongruent is essential to inform mutual decision-making in clinical settings.

We investigated whether the timing of puberty in adolescents who reported gender incongruence was different from those who reported gender congruence. We used information from a large Danish Puberty Cohort with self-reported information on potential gender incongruence at 11 years of age and longitudinally collected information on multiple pubertal milestones.

MATERIALS AND METHODS

Study Sample

This study was based on data from the Danish National Birth Cohort (DNBC) (7), including its subcohort: the Puberty Cohort (8). Between 1996 and 2002, Danish women were invited to participate in the DNBC at their first antenatal visit at the general practitioner around gestational week 6–12. Approximately 60% of all the invited mothers were recruited, resulting in approximately 92,000 mothers. Around gestational week 17, the mothers were interviewed via telephone regarding lifestyle and health-related factors. At 11 years, the adolescent and the mother were invited to complete a follow-up questionnaire on the adolescent's health and well-being. In the 11-year follow-up questionnaire, for the first time, the adolescents were asked to report their pubertal development.

The Puberty Cohort was established in 2012. Live-born singletons born between 2000 and 2003 whose mothers participated in the first pregnancy interview in the DNBC and had not withdrawn from the DNBC before 2012 were eligible for the Puberty Cohort. Of the 56,641 eligible adolescents, 22,439 were sampled for the Puberty Cohort (8). To ensure a broad exposure contrast, the Puberty Cohort was sampled based on the prenatal exposures hypothesized to be important for onset of pubertal development and combined with a random sample of 8,000 adolescents. The sampling regime is described in detail elsewhere (9). Each adolescent sampled for the Puberty Cohort was invited to respond to a web-based questionnaire regarding their pubertal development every 6 months from 11.5–18 years of age or until full sexual maturation (defined as Tanner stage 5 for both pubic hair and breast or genital development). Of the 22,439 participants in the Puberty Cohort, 15,819 (70%) completed at least 1 questionnaire about pubertal development, whereas 10,046 participants also had information on gender incongruence available that was collected in the 11-year follow-up (Fig. 1).

Gender Incongruence

Information about gender incongruence was derived from the 11-year follow-up in DNBC and grouped into 3 exposure groups. The participants were asked: *"How true is this for you: I would rather be the opposite sex"* with response options: *"not true at all," "sometimes true," or "certainly true."* Participants were grouped as "gender congruent" (reference group) if they answered "*not true at all*"; as "partly gender incongruent" if they answered "*somewhat true*"; and "fully gender incongruent" if they answered "*certainly true*." The question was inspired by the *Youth Self-Report* questionnaire, a standardized self-report questionnaire designed to assess emotional and behavioral functioning in children and young adults aged between 11 and 18 years (10).

Timing of Puberty

The outcome was mean age at achieving self-reported pubertal milestones. In each questionnaire, the birth-assigned girls were asked about menarche *(yes or no, if yes: exact age in years and months)* and current stage of pubic hair and breast development (Tanner stages 1–5) (11). Birth-assigned boys were asked about voice break *(completely changed/partly changed/no/do not know)*, first ejaculation *(yes or no, if yes: exact age in years and months)*, and current stage of pubic hair and genital development (Tanner stages 1–5) (12). Both birth-assigned boys and girls were asked about axillary hair *(yes or no)* and acne *(yes or no)*. All questions about Tanner stages included a brief description and an illustration of each stage.

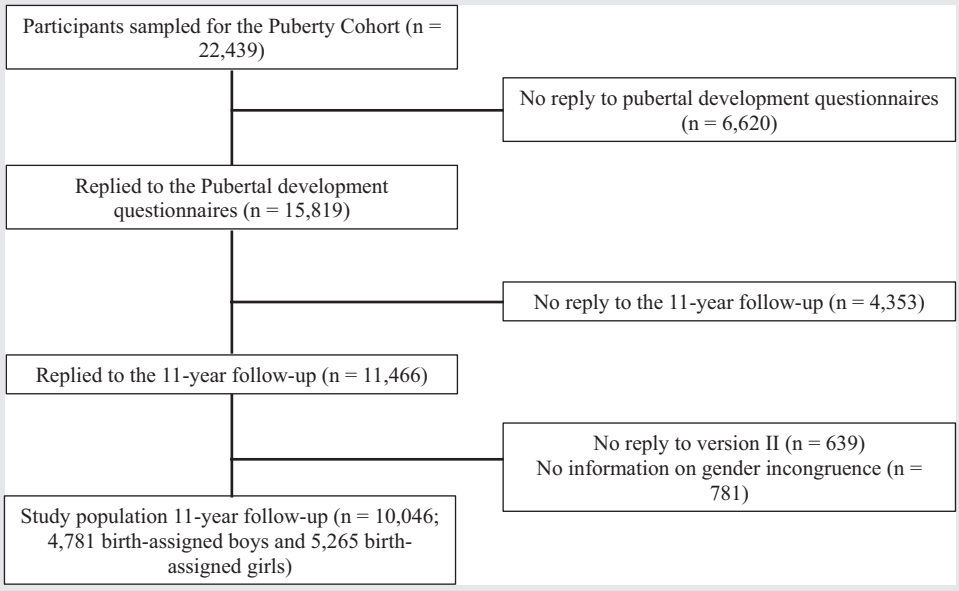
Covariates

The potential confounders were identified using directed acyclic graphs (13) (Supplemental Fig. 1, available online) based on previous literature suggesting gender incongruence to develop early in life (14, 15). The information on the following covariates were obtained from the first interview in the DNBC: maternal alcohol intake in first trimester *(yes or no)*, maternal smoking in first trimester *(yes or no)*, maternal age at menarche *(earlier than peers or same time as peers or later than peers)*, maternal prepregnancy body mass index *(kg/m^2: <18.5, 18.5-24.9, or ≥ 25.0)*, parental social class *(high-grade professional or low-grade professional or skilled worker or unskilled worker)*, and parental cohabitation *(living together or living apart)*. The information on parity (*first child or second or later child)* was obtained from the *Danish Medical Birth Registry.*

Statistical Analysis

The primary outcome was the mean age differences in months (with a 95% confidence interval [CI]) at achieving each pubertal milestone. As information about pubertal development was collected every 6 months from age 11–18 years, the outcome data were either left-, interval- or right-censored. Left-censored: if the pubertal milestone was achieved before the first questionnaire; interval censored: if the pubertal milestone was achieved between the 2 questionnaires; and

FIGURE 1



Flowchart of the study population.

Thomsen. Gender incongruence and puberty. Fertil Steril 2022.

right-censored: in case the pubertal milestone was not achieved when completing the last questionnaire. We used a multivariable regression model (STATA's -intreg- package) for censored time-to-event data assuming normally distributed residuals. The assumption of normally distributed residuals was visually inspected by plotting the nonparametric cumulative incidence function of the residuals based on the Turnbull estimator against the parametric cumulative function based on the normal distribution (16). This was checked in R x 64 3.3.1 (R core team, R Foundation for Statistical Computing, Vienna, Austria). The plots were compatible with the assumption.

Additionally, we obtained a single estimate of the average difference in age at attaining the pubertal milestone by simultaneously modeling all pubertal milestones using Hüber–White robust variance estimation, and thereby, accounting for the dependencies between the individual pubertal milestones and the risk of type I errors because of multiple testing (17, 18).

Inverse probability weights were used as sampling weights to accommodate the sampling strategy used for the Puberty Cohort (9) and as selection weights to minimize the risk of selection bias because of selective nonparticipation (19). The selection weights were calculated as the inverse probability of participation using a logistic regression model of participation status (*yes or no*). The maternal information (maternal alcohol in first trimester, cohabitation in pregnancy, maternal age at menarche, maternal prepregnancy body mass index, parity, maternal smoking in first trimester, cohabitation, and parental social class) obtained from the first interview in the DNBC were used as explanatory variables to predict participation. (Supplementary Data, available online). Sampling and selection weights were multiplied and included in all analyses. Robust variance estimation was used to account for the use of inverse probability weights and clustering of siblings in DNBC. All analyses were performed using STATA 16.1 (StataCorp, College Station, Texas) and all results are presented according to the *General Data Protection Regulation* (Regulation (EU), 2016/679 of 25 May 2018).

Ethics

The data collected within the DNBC were approved by the *Committee for Biomedical Research Ethics* in Denmark ([KF] 01-471/94) and in accordance with the Helsinki Declaration. According to Danish law, questionnaire and interview-based studies did not need approval by the ethical or scientific institution committees. Written informed consents were obtained from the mothers at enrollment on behalf of the adolescents until they reached 18 years. This study was approved by the *Danish Data Protection Agency* and the steering committee of the DNBC (2020-32).

RESULTS

Study Participants

At 11 years, 78 (1.6%) birth-assigned boys and 268 (5%) birth-assigned girls reported part gender incongruence, whereas 95 (2%) birth-assigned boys and 108 (2%) birth-assigned girls reported full gender incongruence (Table 1).

Main Analysis

The mean age difference with a 95% CI is presented for each pubertal milestone for birth-assigned boys (Fig. 2 and

TABLE 1

Descriptive characteristics according to gender incongruence in 10,046 children

	Gender congruent (n = 9,497)	Partly gender incongruent (n = 346)	Fully gender incongruent (n = 203)	Missing
	N (%)	*N* (%)	*N* (%)	(%)
Alcohol 1st trimester				<0.2
No	4,769 (50.3)	172 (49.7)	Approximately 100[b] (49.3)	
Yes	4,714 (49.7)	174 (50.3)	105 (50.7)	
Cohabitation in pregnancy				0.1
Living apart	177 (1.9)	9 (2.6)	6 (3.0)	
Living together	9,315 (98.1)	337 (97.4)	197 (97)	
Maternal age at menarche				0.7
Earlier than peers	2,355 (24.8)	99 (28.6)	57 (28.1)	
Same as peers	5,411 (57.0)	Approximately 195[b] (56.4)	Approximately 100[b] (49.8)	
Later than peers	1,660 (17.5)	54 (15.6)	42 (22.2)	
Maternal prepregnancy (kg/m^2)				<1.4
<18.5	605 (6.4)	29 (8.4)	10 (4.9)	
18.5–24.9	5,985 (63)	196 (56.7)	135 (66.5)	
≥25.0	2,782 (29.3)	113 (32.7)	Approximately 60[b] (29.5)	
Parity				0
First child	4,926 (51.9)	159 (46.0)	99 (48.8)	
Second or later child	4,571 (48.1)	187 (54.0)	104 (51.2)	
Smoking 1st trimester				0.1
No	7,113 (74.9)	233 (67.3)	142 (70)	
Yes	2, 352 (24.8)	Approximately 110[b] (31.7)	Approximately 60[b] (30)	
Social class				0.1
High grade	2,388 (25.1)	62 (17.9)	44 (21.7)	
Low grade	3,299 (34.7)	117 (33.8)	67 (33.0)	
Skilled worker	2,414 (25.4)	99 (28.6)	59 (29.1)	
Unskilled worker	1,344 (14.2)	Approximately 70[b] (19.7)	Approximately 35[b] (17.2)	
Birth-assigned sex				0
Boy	4,608 (48.5)	78 (22.5)	95 (46.8)	
Girl	4,889 (51.5)	268 (77.5)	108 (53.2)	
Child mental health complaints[a]				<0.1
Yes	835 (8.8)	74 (21.4)	33 (16.3)	
No	8,664 (91.2)	272 (78.6)	170 (83.3)	
BMI at 11 years of age (kg/m^2) (SD)	17.3 (2.5)	17.5 (2.6)	17.3 (2.6)	13.8

Note: BMI = body mass index; SD = Standard deviation

[a] Daily mental health complaints at 11 years included feeling sad, irritable or bad mood, nervousness and trouble falling asleep.

[b] Rounded up or down to nearest 5 because of local data regulation.

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Supplemental Table 1, available online) and birth-assigned girls (Fig. 3 and Supplemental Table 1).

Overall, we observed tendencies toward earlier timing of puberty in birth-assigned boys who reported part gender incongruence (average difference: −3.2 [95% CI: −6.7; 0.3] months) or full gender incongruence (average difference: −2.4 [95% CI: −5.0; 0.4] months) at 11 years, but with 95% CIs overlapping the null. (Fig. 2 and Supplemental Table 1).

Similarly, we observed tendencies toward earlier timing of puberty in birth-assigned girls who reported part gender incongruence (average difference: −2.0 [−3.9; −0.1] months) or full gender incongruence (average difference: −1.9 [−5.1; 1.2] months) (Fig. 3 and Supplemental Table 1).

DISCUSSION

Main Findings

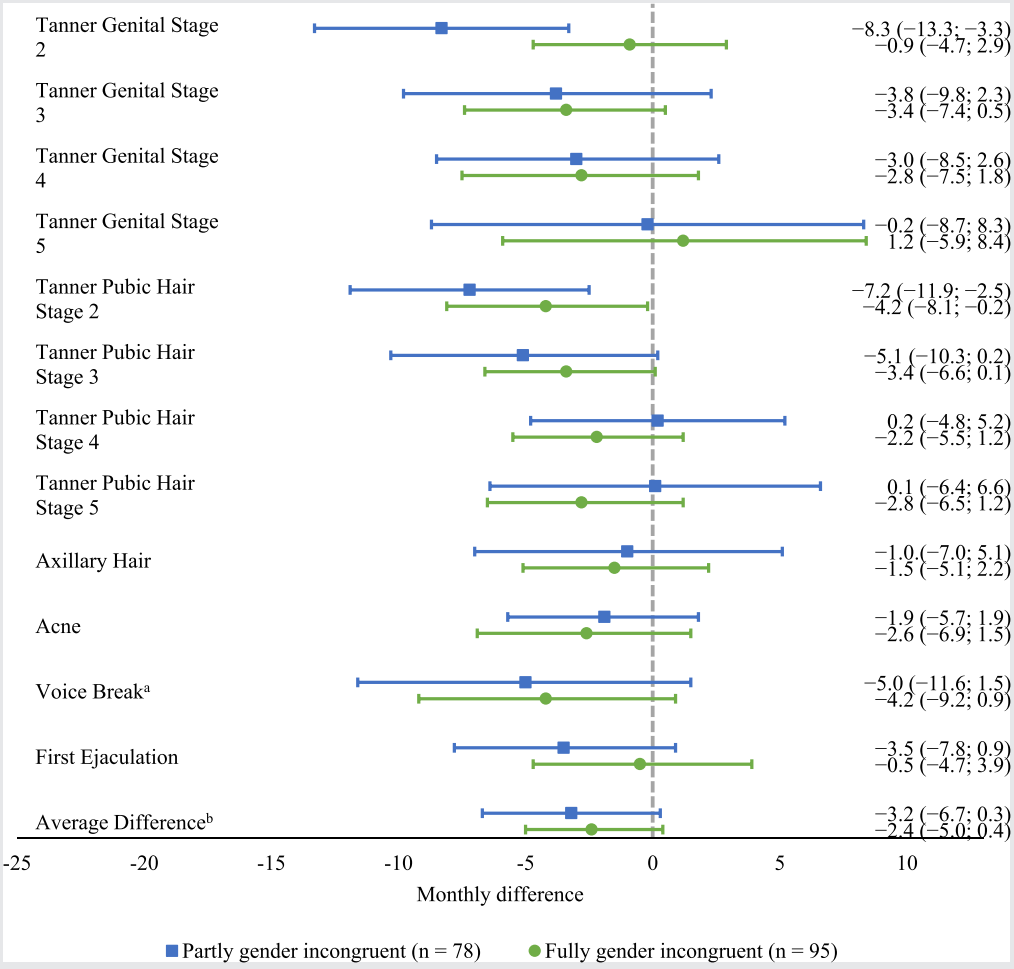
Our results suggest tendencies toward slightly earlier timing of puberty in birth-assigned boys and girls who reported either part or full gender incongruence at 11 years of age.

Strengths and Limitations

The strengths of this study were the large sample size, the collection of detailed information on various covariates, including socioeconomic and prenatal factors, and the measurement of multiple pubertal milestones for each adolescent collected longitudinally throughout puberty. In addition, it is a strength of our study that we used adolescents' perception of their own gender identity as opposed to parental perception about their child's gender identity, because parental perception might be more prone to bias because of stigma or culture.

Only 45% of the participants in the Puberty Cohort had information regarding potential gender incongruence available. The impact of gender incongruence on participation is unknown, but participation in the Puberty Cohort was not associated with a marker of age at pubertal development obtained from external registry data, which minimizes the risk of selection bias (20). Additionally, we had detailed information on prenatal factors potentially associated with participation, which was used to calculate the selection weights used in all analyses.

FIGURE 2



Adjusted mean age differences at attaining different pubertal milestones with a 95% confidence interval in months in timing of puberty according to gender incongruence in birth-assigned boys, Denmark, Puberty Cohort, $n = 4{,}645$. Adjusted for maternal alcohol in first trimester, cohabitation status, maternal age at menarche, maternal prepregnancy body mass index, maternal smoking in first trimester, parity, and parental social class.
[a]Number of observations: 4,553
[b]Number of observations: 4,545

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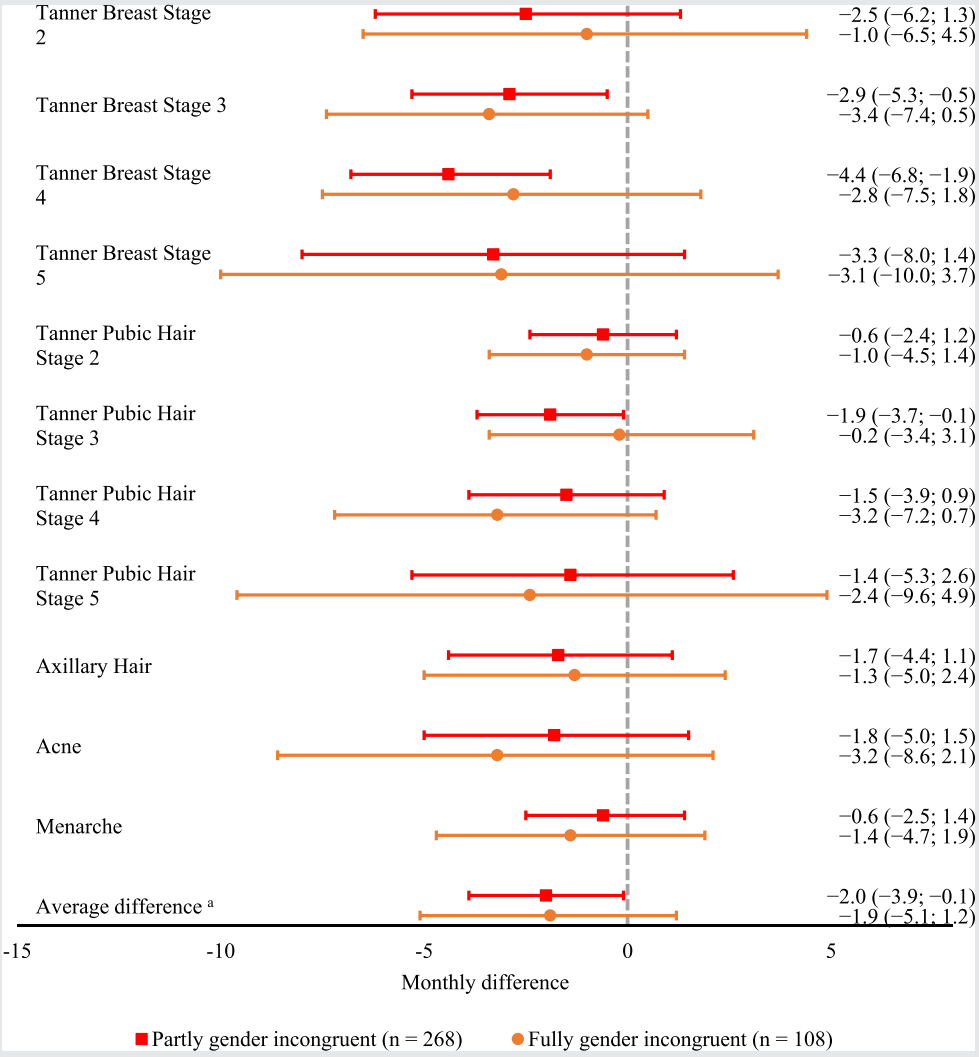
Gender incongruence was self-reported by the participants. The question on the exposure was not a direct measure for gender incongruence and might refer to a transitory "wish" rather than gender identity. The relatively high proportion of adolescents who reported part- or full gender incongruence at 11 years could indicate that this is the case, because the adult prevalence of gender incongruence in Denmark is estimated to be only 0.5 % (21). Further, we cannot rule out that adolescents who had entered the initial stages of puberty at the time of reporting might have been more aware of their gender incongruence because of the bodily changes they were undergoing. This may have led to bias away from the null hypothesis.

In contrast to clinical examination, self-reported data on pubertal development may reduce the risk of nonparticipation but comes at the risk of misclassification (8). The information on the pubertal development was self-reported by the participants every 6 months, minimizing the risk of recall bias. The Tanner stages in the Puberty Cohort have been validated previously and showed fair-to-moderate agreement between self-reported Tanner stages and those obtained by clinical Tanner staging determined by health care professionals (22). As adolescents who experience gender incongruence in general report high body dissatisfaction with their secondary gender characteristics (5, 23), we cannot rule out the risk of differential misclassification of the pubertal milestones. However, we believe it is unlikely that they systematically overreport or underreport their pubertal development, and potential measurement error of the outcome is most likely nondifferential.

Although we have adjusted for multiple potential confounders, it is not possible to rule out residual confounding or bias because of unknown factors. For example, we were not able to adjust for prenatal androgen exposure, although

FIGURE 3



Adjusted mean age differences at attaining different pubertal milestones with a 95% confidence interval in months in timing of puberty according to gender incongruence among birth-assigned girls, Denmark, Puberty Cohort, n = 5,128. Adjusted for maternal alcohol in first trimester, cohabitation status, maternal age at menarche, maternal prepregnancy body mass index, maternal smoking in first trimester, parity, and parental social class.

[a]Number of observations: 5,116

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this has been suggested as a common cause of both early timing of puberty (24, 25) and gender identity development (26), potentially leading to unmeasured confounding.

In Denmark, a gender identity clinic that offers puberty suppression to minors was not established until 2016 (27). Most likely, none of the adolescents in our study has received treatment, and suppression of puberty or cross-hormone therapy has most likely not affected our results.

Interpretation

Timing of puberty in adolescents who are gender incongruent has been investigated in 1 study in birth-assigned girls. Sumia et al. (6) (N = 696) used recalled age at menarche as the outcome measure and reported earlier timing of puberty for gender incongruent birth-assigned girls. Our results are consistent with their finding. The biologic mechanisms underlying our findings remain to be settled, and more research is needed to understand the biologic mechanism between gender incongruence and the timing of puberty.

CONCLUSION

We observed that adolescents who reported either part or full gender incongruence at 11 years tended to reach puberty slightly earlier than adolescents who reported gender congruence

Although the magnitude of the observed monthly difference in timing of puberty is small and most results

overlapping the null, our findings provide new knowledge to health care professionals about tendencies in timing of puberty in birth-assigned boys and girls who are experiencing gender incongruence.

Children and adolescents who are gender incongruent may be more likely to experience psychological challenges during the maturation of their secondary gender characteristics and some of these adolescents may wish to delay or suppress the development of puberty (5, 28). As health care professionals observe an increase in the number of adolescents, who wish to begin treatment options such as puberty suppression and cross-sex therapy (4, 27, 29), knowledge on the timing of puberty in this population is essential to inform mutual decision-making in clinical settings. The guidelines recommend initiating puberty suppression around Tanner stage 2 (30). Health care professionals should be aware of the declining trend toward earlier puberty in the general population and that adolescents who are gender incongruent, may tend to experience puberty slightly earlier than adolescents who are gender congruent.

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Incongruencia de género y momento de la pubertad: un estudio de cohorte basado en la población.

Objetivo: Estudiar si el momento de la pubertad en adolescentes que reportaron incongruencia de género (incongruencia entre el sexo asignado al nacer y el género autoidentificado) fue diferente de aquellos adolescentes que reportaron congruencia de género.

Diseño: Estudio de cohorte poblacional utilizando datos de la *Cohorte Nacional de Nacimiento de Dinamarca*.

Ámbito: No aplicable.

Paciente(s): Se incluyeron niños y niñas asignados como tales en el momento del nacimiento, nacidos entre 2000 y 2003, que autoinformaron incongruencia de género a los 11 años (N=10.046), y sus etapas de desarrollo puberal desde los 11 años hasta cada 6 meses durante la pubertad.

Intervención(es): No aplicable.

Medición de resultado principal: Diferencias de edades promedio en meses al alcanzar las etapas de Tanner 2-5 para el desarrollo mamario o genital y del vello púbico, rotura de la voz, primera eyaculación, menarquia, vello axilar, acné y la diferencia promedio al alcanzar todos los hitos puberales (resultado principal).

Resultado(s): En total, 549 adolescentes (5,5%) informaron incongruencia de género total o parcial a los 11 años. Se observaron tendencias hacia una pubertad más temprana en adolescentes que informaron incongruencia parcial de género (diferencia promedio, en los asignados como niños al nacer: -3,2 meses [intervalo de confianza del 95 % {IC}: -6,7; 0,3]; en las asignadas como niñas al nacer: -2,0 meses [IC 95%: -3,9; -0,1]). Se observaron tendencias hacia una pubertad más temprana en adolescentes que reportaron incongruencia total de género (diferencia promedio, en los asignados como niños al nacer: -2,4 meses [IC del 95 %: -5,0; 0,4]; en las asignadas como niñas al nacer: -1,9 meses [IC del 95 %: -5.1; 1.2]).

Conclusiones: Los resultados de este estudio indicaron que los asignados como niños y niñas al nacer que reportaron incongruencia de género total o parcial tendieron a alcanzar la pubertad un poco antes que aquellos adolescentes que reportaron congruencia de género a los 11 años de edad. Conocer el momento de la pubertad entre los adolescentes que experimentan incongruencia de género es esencial para informar la toma mutua de decisiones en contextos clínicos.