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| Supplementary material: Addendum to *Impact of Puberty Blockers in Gender-Dysphoric Adolescents: An evidence brief* | November 2024 |

Table 1: Studies on epidemiology and physical health included in the addendum

| **Study and country** | **Type of article** | **Study type** | **Study aim** | **Treatment** | **Comment** | **Quality[[1]](#footnote-1)** |
| --- | --- | --- | --- | --- | --- | --- |
| **Physical** | | | | | |  |
| Boogers LS, Reijtenbagh SJP, Wiepjes CM, et al. 2023. Time course of body composition changes in transgender adolescents during puberty suppression and sex hormone treatment. *Journal of Clinical Endocrinology and Metabolism*. DOI: 10.1210/clinem/dgad750.  Netherlands | Peer-reviewed original research  American College of Obstetricians and Gynecologists study | Retrospective longitudinal observational | Body composition | Triptorelin 3.75 mg 1 × per 4 weeks, or 11.25 mg 1 × per 10 to 12 weeks | In both transgender boys and transgender girls, treatment with GnRHa resulted in a decrease in lean mass z-scores and an increase in fat mass z-scores. | Good |
| Fisher AD, Ristori J, Romani A, et al. 2023. Back to the future: is GnRHa treatment in transgender and gender diverse adolescents only an extended evaluation phase? *Journal of Clinical Endocrinology and Metabolism* 109(6): 1565–79. DOI: 10.1210/clinem/dgad729.  Italy | Peer-reviewed original research | Prospective longitudinal observational | Relationship between psychological wellbeing and body composition | Triptorelin 3.75 mg every 28 days, interval adjustments based on clinical and laboratory data | Psychological improvement in transgender and gender diverse adolescents on GnRHa seems to be related to the objective body changes induced by a GnRHa. | Poor |
| Perl L, Elkon-Tamir E, Segev-Becker A, et al. 2021. Blood pressure dynamics after pubertal suppression with gonadotropin-releasing hormone analogs followed by estradiol treatment in transgender female adolescents: a pilot study. *Journal of Pediatric Endocrinology and Metabolism* 34(6): 741–5. DOI: 10.1515/jpem-2021-0172.  Israel | Peer-reviewed original research | Retrospective longitudinal observational | Cardiovascular | Decapeptyl 3.75 mg every 4 weeks | Based on the findings in this pilot study, the authors suggest that pubertal suppression with GnRHa may increase DBP in transgender male adolescents, but it does not cause hypertension. | Good |
| Roy MK, Bothwell S, Kelsey MM, et al. 2024. Bone density in transgender youth on gender-affirming hormone therapy. *Journal of the Endocrine Society* 8(5). DOI: 10.1210/jendso/bvae045.  United States | Peer-reviewed original research | Cross-sectional (secondary analysis of data) | Bone health | GnRHa schedule not reported | Total body BMD z-scores ascertained by DXA were slightly below average for female and male norms, but still in the normal range, including for those who were on GnRHa monotherapy. | Poor |
| van der Loos MATC, Vlot MC, Klink DT, et al. 2023. Bone mineral density in transgender adolescents treated with puberty suppression and subsequent gender-affirming hormones. *JAMA Pediatrics* 177(12): 1332–41. DOI: 10.1001/jamapediatrics.2023.4588.  Netherlands | Peer-reviewed original research | Prospective longitudinal observational | Bone health  Primary aim to assess gender-affirming hormone treatment | Triptorelin 3.75 mg, every 4 weeks  or 11.25 mg every 10 to 12 weeks | For individuals AMAB, the z-scores were already lower than 0 at the start of a GnRH agonist treatment and further decreased during that treatment. For AFAB individuals, the BMD z-scores decreased after the start of GnRH agonist treatment. | Good |
| Waldner R, Doulla M, Atallah J, et al. 2023. Leuprolide acetate and QTc interval in gender-diverse youth. *Transgender Health* 8(1): 84–8. DOI: 10.1089/trgh.2021.0102.  Canada | Peer-reviewed original research | Retrospective cross-sectional observational research | Cardiac | Leuprolide. Dose not stated | No gender-diverse youth on leuprolide acetate demonstrated clinically significant prolonged QTc. Analysis by assigned or affirmed gender was not possible. | Poor |
| **Fertility** | | | | | |  |
| No studies identified | | | | | |  |
| **Epidemiology** | | | | | | **Quality[[2]](#footnote-2)** |
| Gutiérrez K, Moreno M, Sierra JA, et al. 2024. Characteristics of the paediatric population with gender incongruence attending specialized care in Cali, Colombia: an observational, descriptive and retrospective study. *Child and Adolescent Psychiatry and Mental Health* 18(1): 1. DOI: 10.1186/s13034-023-00689-6.  Colombia | Peer-reviewed original research | Observational retrospective | Age at development of gender dysphoria/incongruence | GnRHa schedule not described | The median age of onset of gender incongruence was 10 years (IQR: 5–13 years). The median time elapsed between the reported onset of gender incongruence and the first consultation with a multidisciplinary gender-affirming team was 3 years (IQR: 1–10 years). | 93% |

Table 2: Papers included after full review – impact of puberty blockers on mental health and wellbeing outcomes

| **Study** | **Outcomes** | **GRADE quality** | **Risk of bias** |
| --- | --- | --- | --- |
| Fisher AD, Ristori J, Romani A, et al. 2023. Back to the future: is GnRHa treatment in transgender and gender diverse adolescents only an extended evaluation phase? *Journal of Clinical Endocrinology and Metabolism* 109(6): 1565–79. DOI: 10.1210/clinem/dgad729. | Gender dysphoria  Anxiety  Depression  Quality of life  Suicidality | Very low  Very low  Very low  Very low  Very low | Critical  Critical  Critical  Critical  Critical |
| McGregor K, McKenna JL, Williams CR, et al. 2024. Association of pubertal blockade at Tanner 2/3 with psychosocial benefits in transgender and gender diverse youth at hormone readiness assessment. *Journal of Adolescent Health* 74(4): 801–7. DOI: 10.1016/j.jadohealth.2023.10.028. | Quality of life / social wellbeing  Self-harm  Suicidality | Low  Very low  Very low | Moderate  Serious  Serious |
| McPherson S, Freedman DEP. 2024. Psychological outcomes of 12–15-year-olds with gender dysphoria receiving pubertal suppression in the UK: assessing reliable and clinically significant change. *Journal of Sex and Marital Therapy* 50(3): 315–25. DOI: 10.1080/0092623X.2023.2281986. | Quality of life / social wellbeing | Very low | Critical |
| van der Miesen AIR, Steensma TD, de Vries ALC, et al. 2020. Psychological functioning in transgender adolescents before and after gender-affirmative care compared with cisgender general population peers. *Journal of Adolescent Health* 66(6): 699–704. DOI: 10.1016/j.jadohealth.2019.12.018. | Suicidality | Very low | Serious |

Table 3: Papers included after full review – targeted mental health and wellbeing interventions

|  |  |  |
| --- | --- | --- |
| **Study** | **Intervention** | **Quality** |
| Morgan H, van Hall HW, Moore JK, et al. 2024. A pilot group program for parents of trans young people at a specialized pediatric gender diversity service. *LGBTQ+ Family: An Interdisciplinary Journal*. DOI: 10.1080/27703371.2024.2347495. | Parent/carer targeted  Psychologist-facilitated group designed for parental/carer understanding and acceptance of and support for their child | Low |
| Mackie G, Patlamazoglou L, Lambert K. 2023. The experiences of Australian transgender young people in school counseling: an interpretative phenomenological analysis. *Psychology of Sexual Orientation and Gender Diversity* 10(2): 337–49. DOI: 10.1037/sgd0000544. | Adolescent targeted  School-based counselling at secondary school level | High |

# Active clinical trials on puberty blockade in gender-dysphoric adolescents

Table 6 describes active clinical trials on puberty blockade in gender-dysphoric adolescents, which were all identified through ClinicalTrials.gov. No additional trials relevant to GnRHa therapy for gender dysphoria were identified in the Australian New Zealand Clinical Trials Registry[[3]](#footnote-3) or European Union Clinical Trials Register.[[4]](#footnote-4) It is likely that other studies are under way across jurisdictions that may not have been registered on any of these sites.

Table 6: Active clinical trials on puberty blockade in gender-dysphoric adolescents

| **Trial name** | **Trial number** | **Status** | **Aim** | **Study type** | **Cohort** | **Location** |
| --- | --- | --- | --- | --- | --- | --- |
| **Epidemiology** | | | | | | |
| Gender Dysphoria: Epidemiological Data (DyGenEpi) | ClinicalTrials.gov ID NCT04573127 | Unknown | To conduct a retrospective study in a single academic regional transgender referral centre. Data from the cohort follow-up in CHRU de Nancy. | Observational | All individuals (any age) with a diagnosis of gender dysphoria attending a specialist gender clinic. | France |
| **Cardiometabolic** | | | | | | |
| Puberty Blockade and Hormone Therapy in Transgender Youth (PUBErTY) | ClinicalTrials.gov ID NCT04596592 | Completed; no results reported | To study the effects of pubertal blockade and hormone therapy on cardiometabolic risk markers in transgender adolescents. | Prospective observational | Transgender males (AFAB), who:   * are aged 13–16 years at the time of enrolment * if on a GnRHa, have had more than six months exposure * plan to start testosterone clinically in less than six months. | United States |
| The Relation of GnRH Treatment to QTc Interval in Transgender Females | ClinicalTrials.gov ID NCT03078829 | Terminated: No results posted | To assess the effect of GnRH agonist treatment on QTc interval in transfemale youth. | Prospective observational | Transgender females 10 years or older:   * child * adult * older adult | United States |
| Pubertal Blockade and Estradiol Effects on Cardiometabolic Health for Transitioning Youth (PUBERTY) | ClinicalTrials.gov ID NCT04596592 | Recruiting | To evaluate the effect of estradiol with or without a prior GnRHa on insulin sensitivity and vascular function in transgender females compared with cisgender controls. | Prospective observational | People who identify as a transgender female who:   * were aged 13–16 years at the time of enrolment * if on a GnRHa, have had more than six months exposure * plan to start estradiol clinically in less than four months. | United States |
| **Bone health** | | | | | | |
| Skeletal Health and Bone Marrow Composition among Youth |  | Active | To identify the effects of pubertal blockade on bone density and size in paediatric transgender individuals. | Interventional (non-randomised) | Individuals aged 9–14 years identifying as transgender or binary. | United States |
| Skeletal Health and Bone Marrow Composition among Youth | ClinicalTrials.gov ID NCT04203381 | Recruiting | To examine bone marrow composition (by MRI) in 40 transgender youth and bone density and body composition before and after pubertal blockade, compared with healthy participants. | Observational longitudinal study  Multi-centre | Children aged 9–14 years with a diagnosis of gender dysphoria cared for at a specialist gender clinic. | United States |
| **Fertility** | | | | | | |
| Ovarian Tissue Cryopreservation in the Setting of Gender-affirming Therapy | ClinicalTrials.gov ID NCT05863676 | Recruiting | * To optimise techniques for cryopreservation of ovarian tissues, including determining efficacy of cryopreservation techniques. * To investigate factors affecting ovarian tissue and follicles, such as previous treatment with leuprolide acetate, or hormone therapy. | Prospective observational | * Transmales (AFAB) aged nine years or older with a diagnosis of gender dysphoria. * Patients aged nine years or older who are on or about to start puberty blockers or hormone treatment. * Patients over the age of 18 years about to undergo oophorectomy. | United States |
| Testicular Tissue Cryopreservation in the Setting of Gender-affirming Therapy | ClinicalTrials.gov ID NCT05829928 | Recruiting | * To optimise techniques for processing and cryopreserving testicular tissue. * To determine the presence and number of germ cells (sperm precursors) in the patients’ testicular tissue. * To develop next-generation cell- and tissue-based therapies for preserving fertility and treating infertility. | Longitudinal observational | * Transfemales (AMAB) aged nine years or older with a diagnosis of gender dysphoria. * Patients aged nine years or older who are on or about to start puberty blockers or hormone treatment. * Patients over the age of 18 years about to undergo orchidectomy. | United States |
| Fertility Preservation for Transfeminine Adolescents Via Semen Cryopreservation or Testicular Sperm Extraction (TESE) | ClinicalTrials.gov ID NCT06400199 | Recruiting | To identify and predict parameters for successful TESE procedures or semen cryopreservation more accurately and to evaluate the decision-making process and the experience of postponing or temporarily discontinuing puberty suppression to undergo successful fertility preservation. | Observational cohort | Transfemales: Adolescents with gender dysphoria aged 9–18 years. | Netherlands |
| **Mental health and wellbeing** | | | | | | |
| Evaluation of the Effectiveness of Hormonal Treatment in Adolescents Suffering From Gender Dysphoria (TRANSADO) | ClinicalTrials.gov ID NCT06351501 | Not yet recruiting | To assess the psychological benefits of starting gender-affirming hormones in early as opposed to late puberty.[[5]](#footnote-5) | Multicentre randomised open trial with blinded assessment | * Experimental arm: Adolescents with confirmed gender dysphoria who are starting gender-affirming hormone treatment at 14 years (+/– 6 months); 4 years follow-up (to age 18). * Control arm: Adolescents with confirmed gender dysphoria who are starting gender-affirming hormone treatment at 16 years (+/– 6 months); 2 years follow-up (to age 18 years). | France |

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1. Newcastle Ottawa Scale. [↑](#footnote-ref-1)
2. Crowe Critical Appraisal Tool. [↑](#footnote-ref-2)
3. URL: [**anzctr.org.au/**](https://www.anzctr.org.au/) (accessed 12 June 2024). [↑](#footnote-ref-3)
4. URL: [**clinicaltrialsregister.eu/ctr-search/search**](https://www.clinicaltrialsregister.eu/ctr-search/search) (accessed 12 June 2024). [↑](#footnote-ref-4)
5. Although this study does not assess GnRHa, it is a randomised trial assessing the impact of hormonal treatment started in early or late puberty and so it has implications for puberty blockade. [↑](#footnote-ref-5)