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| The Medical Management of Gender Dysphoria using GnRHa; A review of the published evidence of the use GnRHa for gender dysphoria in adolescents | November 2024 |

# Newcastle Ottawa Scale Assessment for Case controlled studies

| **No** | **Country**  **Year** | **Reference** | **Selection**  **(max 1 star per item)** | | | | **Compatibility**  **(max 2 stars per item)** | **Exposure** | | | **Rating** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Case Definition Adequate** | **Representative-ness of Cases** | **Selection of controls** | **Definition of controls** | **Comparability cases & controls on the basis of design or analysis** | **Assessment of Exposure** | **Same method of Ascertainment** | **Non-response rate** |
| **10** | **USA**  **2021** | **(Nokoff et al., 2021a)** | Cases selected from GIS.  Diagnostic criteria not stated | Cases assumed to be representative of GD adolescents eligible for GnRHa | Cohort of children at same institution undergoing the same formal investigations | Cis-gender non exposed to GnRHa | Research conducted in the same institution undergoing the same investigations. Matched for age. | Medical / trial records | Same investigations reported. | Non-response not stated. | Good |
| **15** | **N’lands**  **2015** | **(Staphorsius. et al., 2015)** | Cases selected from GIS. Diagnosis based on DSM 4/5 | Cases assumed to representative of GD individuals eligible for GnRHa. | GD individuals matched for age Tanner stage and sex. | 1. Cisgender controls  2. Untreated GD | 1. Control group of cis gender friends of cases  2. Treated and untreated GD  Analysis adjusted for key variables. | Medical records | DEXA and MRI | 30 excluded but breakdown not provided. | Good |
| **17** | **N’lands**  **2020** | **(van de Grift et al., 2020)** | Cases selected from GIS.  Diagnosis based on DSM 4/5 | Cases assumed to be representative of GD individuals eligible for GnRHa | Same GIS clinic matched for age, CSH therapy and requesting surgery | GnRHa therapy excluded. | By design: Individuals enrolled in GIS clinic.  By Analysis: Age: Tanner status, Gender, | Medical records | Same investigations reported | Eligible cases = 316. Included for analysis = 200. | Good |

USA = United States of America, N’lands = Netherlands, GIS = Gender Identity Service, GD = gender Dysphoria, GnRHa = gonadotrophin releasing hormone analouge, DSM-4/5 = Diagnostic and Statistical manual, version 4 or 5, DEXA – Dual Emission X-ray Analysis.

# NOS Criteria Definitions for Case Control Studies

## Selection

### Case definition adequate

* Case definition of gender dysphoric individuals receiving GnRHa accepted as accurate on the basis of individuals being managed through GIS with diagnostic criteria. GnRHa administration occurs though injections or implants which reduces non-compliance due to self-medication risks. Duration of therapy for executive function, and cardiometabolic outcomes and surgical options acceptable based on limited information.

### Representativeness of cases

* Truly representative of the average adolescent with GD in Gender Identity Service Clinics for GnRHa. Diagnosis accepted if recognised method stated, or if the individual was managed through a specialist Gender Identity service. For the purpose of analysing medical complications of GnRHa, attendance through a publicly funded GIS clinic is accepted as being representative of individuals with GD receiving GnRHa. This assumption has not been applied for the analysis of psychosocial outcomes.

### Selection of controls

* Controls selected through the same GIS or for non-GD controls through the same institution, undergoing the same investigation

### Definition of controls

* Unexposed to GnRHa or without GD

## Comparability

### Comparability of cases and controls on the basis of design or analysis

* Study controls for primary outcome
* Study controls for secondary outcomes

## Exposure

### Ascertainment of Exposure

* Medical Notes

### Non-response Rate

* Same for both groups.

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor)

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

# Newcastle Ottawa Scale Assessment for Bone Mineral Density Cohort Studies

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study No** | **Country**  **/ Year** | **Reference** | **Selection of Study Groups** | | | | **Comparability of Cohorts** | **Ascertainment of Exposure / Outcome** | | | **Comment /Rating** |
| **Cases**  **Representa-tive** | **Selection of non-exposed cohort** | **Ascertainment of Exposure** | **Outcome not present at start of study** | **Assessment of Outcome** | **Follow-up duration** | **Follow-up Cohort** |
| **2** | **N’lands**  **2023** | **(Boogers et al., 2023)** | Retrospective GIS cohort with protocol | National Health and Nutrition Examination Surveys | GnRHa prescribed through GIS | Complete BMD-Z scores prior to GnRHa not provided. | BMD-Z score data not provided.  AMAB only included in study | BMD-Z score data not provided. | All > 1 year.  Mean (SD) > 2 years (0.7) | 157 eligible participants, 87 included. Excluded cohort not analysed. | **Poor**  Numerical BMD-Z-scores not provided Primary outcomes after GAHT |
| **3** | **UK**  **2021** | **(Carmichael et al., 2021)** | Prospective GIS cohort with protocol | Reference range for HABMD-Z-scores not provided | GnRHa prescribed through GIS | Longitudinal study with yearly assessment protocol to 3 years. | BMD-z scores not categorised by sex assigned at birth. | BMD z-scores from medical records | Longest follow up provided up to three years. | Prospective. 44 sequential cases. 1/44 lost at 12 months. | **Poor**  Lack of categorisation and reference range description. |
| **6** | **UK**  **2019** | **(Joseph et al., 2019)** | Retrospective GIS cohort with protocol | Reference range based on published UK norms for Caucasian subjects | GnRHa prescribed through GIS | Longitudinal study with yearly assessment protocol to 3 years. | BMD-Z scores provided  AMAB & AFAB analysed separately.  Narrow age range 12 – 14 years | BMD z-scores from medical records | All > 1 year up to 3 years | All eligible individuals enrolled during study period included | **Good** |
| **8** | **N’Lands**  **2015** | **(Klink. et al., 2015)** | Retrospective GIS cohort with protocol | BMD z-score National Health and Nutrition Examination Surveys  BAMD z-score published reference | GnRHa prescribed through GIS | Longitudinal study with yearly assessment protocol to initiation of GAHT till age 18 | Broad age range 11.4 – 18.3 years | BMD z-scores from medical records | GnRHa treatment median 1.3 years range 0.5 – 3.8 years | Follow-up data not provided. Primary endpoint 22 years | **Good**  Purpose of study to assess BMD after GnRHa and GAHT therapy at age 22 years. |
| **9** | **Canada**  **2021** | **(Navabi et al., 2021)** | Retrospective GIS cohort with protocol | BMD reference range based on published data | GnRHa prescribed through GIS | Longitudinal study with yearly assessment protocol to 3 years. | Age, Tanner status, bone age not reported for GnRHa subgroup.  AMAB & AFAB analysed separately. | BMD z-scores from medical records | GnRHa treatment median or range not provided for GnRHa subgroup. | Eligible = 198  Included = 172  FU = 87% | **Poor**  GnRHa cohort a sub-analysis of larger cohort. |
| **13** | **N’lands**  **2020** | **(Schagen et al., 2020)** | Prospective GIS cohort with protocol | BMD z-score National Health and Nutrition Examination Surveys  BAMD z-score published reference | GnRHa prescribed through GIS | Prospective study with baseline BMD data. | Analysis by early or late puberty based on Tanner stage. | BMD z-scores from medical records | GnRHa duration mean (SD) 2.0 ± 0.94 | 127 cases enrolled.  121 completed protocol. | **Good** |
| **16** | **N’lands**  **2019** | **(Stoffers et al., 2019)** | Prospective GIS cohort with protocol | BMD z-score National Health and Nutrition Examination Surveys  BAMD z-score published reference | GnRHa prescribed through GIS | Longitudinal study with yearly assessment protocol | Broad age range, pubertal development.  AFAB only included in study | BMD z-scores from medical records | All GnRHa > 6 mo.  GnRHa duration median (range) 8 (3-39) | 64 eligible, 62 included in analysis | **Poor** |
| **19** | **N’Lands**  **2017** | **(Vlot et al., 2017)** | Retrospective cohort with GIS protocol | Published reference range | GnRHa prescribed through GIS | Longitudinal study with yearly assessment protocol | Separate analysis for young and older individuals based on bone age. Small numbers (range 5 – 23) in each group. | BMD z-scores from medical records | Duration of GnRHa not provided. > 1 year in median age between baseline and initiation of GAHT. | Eligible individuals = 215  Included = 112  No analysis of excluded cases. | **Good** |

BMD = Bone Mineral Density, BMAD, Bone mineral areal density, DSM-4/5 = Diagnostic and Statistical manual, version 4 or 5, DEXA – Dual Emission X-ray Analysis, GIS = Gender Identity Service, GD = gender Dysphoria, GnRHa = gonadotrophin releasing hormone agonist, N’lands = Netherlands, UK = United Kingdom, , USA = United States of America.

# NOS Criteria definitions: BMD

## Selection

### Representativeness of cases

* Cohort considered representative of adolescents diagnosed with GD eligible for GnRHa if investigations undertaken as part of a specific protocol through a recognised GIS

### Description of non-exposed cohort

* Drawn from same cohort of adolescents with GD not treated with GnRHa an accepted control
* Comparison to validated published population reference ranges.

### Ascertainment of Exposure

* Medical record of having received GnRHa.

### Demonstration that outcome of interest was not present at start of study

* For longitudinal studies analysis prior to and after initiation of GnRHa treatment
* For cross sectional studies comparisons to validated published population reference ranges

## Comparability

### Comparability of cohorts

* For BMD studies, BMD-z scores or similar categorised by sex assigned at birth required
* Adjusted by age, Tanner status, bone age.

## Outcome

### Assessment of Outcome

* Independent Blind assessment
* Record linkage for data extracted from medical notes

### Adequate follow-up duration

* Minimum of 6 months for BMD studies.

### Adequate follow up of cohorts

* All subjects accounted for
* Small proportion (<15%) unlikely to influence results

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor)

Good quality: 3 or 4 stars in selection domain **AND** 1 or 2 stars in comparability domain **AND** 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain **AND** 1 or 2 stars in comparability domain **AND** 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

# Newcastle Ottawa Scale Assessment for Cardiometabolic Cohort Studies

| **Study No** | **Country**  **Year** | **Reference** | **Selection of Study Groups** | | | | **Comparability of Cohorts** | **Ascertainment of Exposure / Outcome** | | | **Comment / Rating** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cases**  **Representative** | **Selection of non-exposed cohort** | **Ascertainment of Exposure** | **Outcome not present at start of study** | **Assesment of Outcome** | **Follow-up duration** | **Follow-up Cohort** |
| **7** | **N’Lands**  **2019** | **(Klaver et al., 2020)** | Retrospective cohort with GIS protocol | Published relevant reference ranges | GnRHa prescribed through GIS | Longtitudinal study with baseline data. | AMAB and AFAB analysed separately  Linear mixed model regression with analaysis for missing values. | Data from medical records | Difference in mean duration of GnHRa monotherapy 1.8 yrs AMAB and 1.7 yrs AFAB. | Not provided | **Good** |
| **11** | **Israel**  **2020** | **(Perl et al., 2021)** | Retrospective cohort with GIS protocol | Published relevant reference ranges | GnRHa prescribed through GIS | Longtitudinal study protocol with baseline data. | Study only included AFAB adolescents. | Medical Records | All treated for > 2 months. | Small number of cases n= 15  3 missing data (20%) | **Poor**  **Time required for BP alterations unknown.** |
| **12** | **N’lands**  **2016** | **(Schagen et al., 2016)** | Retrospective cohort with GIS protocol | Reference range for creatinine not provided | GnRHa prescribed through GIS | Longtitudinal study protocol with baseline data. | AMAB and AFAB analysed separately.  Broad age range (11.6 – 17.9 years) | Medical Records | All at 1 year. | AMAB 28/36 (78%)    AFAB 29/41 (70%) | **Good** |
| **16** | **N’lands**  **2019** | **(Stoffers et al., 2019)** | Prospective GIS cohort with protocol | Reference range for Blood pressure not provided | GnRHa prescribed through GIS | Longtitudinal study with yearly assessment protocol | AFAB only included in study  Broad age range, pubertal development.  BP data during GnRHa unadjusted for age. | BP from medical records | All GnRHa > 6 mo.  GnRHa duration median (range) 8 (3-39) | 64 eligible, 62 included in analysis | **Poor**  **Primary aim of study was BMD.** |

# NOS Criteria definitions: Cardiometabolic

## Selection

### Representativeness of cases

* Cohort considered representative of adolescents diagnosed with GD eligible for GnRHa if investigations undertaken as part of a specific protocol through a recognised GIS

### Description of non-exposed cohort

* Drawn from same cohort of adolescents with GD not treated with GnRHa an accepted control
* Comparison to validated published population reference ranges.

### Ascertainment of Exposure

* Medical record of having received GnRHa.

### Demonstration that outcome of interest was not present at start of study

* For longitudinal studies analysis prior to and after initiation of GnRHa treatment
* For cross sectional studies comparisons to validated published population reference ranges

## Comparability

### Comparability of cohorts

* Cardiometabolic outcome z-scores or centiles categorised by sex assigned at birth required

## Outcome

### Assessment of Outcome

* Independent Blind assessment
* Record linkage for data extracted from medical notes

### Adequate follow-up duration

* Minimum of 3/12 follow-up for cardiometabolic outcomes.

### Adequate follow up of cohorts

* All subjects accounted for
* Small proportion (<15%) unlikely to influence results

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor)

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

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