G.19 Bone mineral density

Review question: What is the most effective strategy to monitor for the identification of reduced bone mineral density in people with Cystic Fibrosis?

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
Full citation Baker, J. F., Putman, M. S., Herlyn, K., Tillotson, A. P., Finkelstein, J. S., Merkel, P. A., Body composition, lung function, and	Sample size n=63 adults with CF Mean age (SD): 31.7 (8.0) years (18 to 57) 50.9% male Characteristics	Prognostic test/ tool/ factor Low baseline BMD, defined as z-score ≤ -1 Very low baseline BMD, defined as z-score ≤ -2 Standard dual-energy X-ray absorptiometry (DXA) on a QDR4500A model (Hologic Inc, Bedford, MA)	Sample selection Subjects underwent scanning to measure BMD and a medical interview to obtain history information Data collection DXA scanning at the PA spine to measure BMD using	Results Change in posterior-anterior spine BMD at 2 years z-score ≤1 at baseline not significantly and independently associated with	Limitations The methodological limitations were assessed using a critical appraisal tool for the evaluation of the quality of prognosis studies in systematic reviews (Hayden et al. 2006):

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prevalent and progressive bone deficits among adults with cystic fibrosis, Joint, Bone, Spine: Revue du RhumatismeJoint Bone Spine, 83, 207-11, 2016 Ref Id 457420 Country/ies where the study was carried out United States of America Study type Retrospective case series Aim of the study To assess independent predictors of baseline and 2-year changes in bone mineral density in adults with CF. Study dates Unclear. Source of funding Veterans Affairs Clinical Science Research & Development	Adults with CF from Massachusetts General Hospital Cystic Fibrosis Care Center Inclusion criteria Elevated sweat chloride level or mutational analysis diagnostic for cystic fibrosis Exclusion criteria Organ transplant recipients		QDR4500A model (Hologic Inc, Bedford, MA) Physical examination Medical interview: medical history, physical activity, menstrual/pubertal development, fracture history Laboratory assessments Lung spirometry Activity level: interview Scans performed using a QDR4500A model (Hologic Inc, Bedford, MA) Data analysis Multivariate model adjusting for: age, gender, fat-free max index and height Group comparisons: Chi2 tests and t-tests or non-parametric equivalents for non-normally distributed data Body composition variables: multiple variable models to adjust for height and gender. Correlations and univariate linear regression: to evaluate factors associated with BMD Z-core Hypothesis driver linear regression models: to identify predictors of change in PA spine BMD Z-score GEE marginal models with correlation structures: to	greater BMD loss (p-value = 0.81) z-score ≤2 at baseline not significantly and independently associated with greater BMD loss (p-value = 0.47)	Study participation The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. PARTLY (date of recruitment unclear, random sample from CF care centre) Study attrition Loss to follow-up (from sample to study population) is not associated with key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. UNSURE (60% followed up at 2 years, no explicit reasons for loss provided other than subjects without follow up scan at 2 years were significantly younger with lower baseline Z-scores) Prognostic factor measurement The prognostic factor of interest is adequately measured in study

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National Center for Research Resources National Institute of Arthritis and Musculoskeletal and Skin Diseases CF foundation			evaluate longitudinal change in PA spine BMD Z-score Follow-up repeat scan performed at 2 years (data available for n=39)		participants to sufficient to limit potential bias. YES (every image reviewed by bone densitometrist) Outcome measurement The outcome of interest is adequately measured in study participants to sufficiently limit potential bias. PARTLY (outcomes clearly defined. No detail on blind measurements) Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. YES (multivariable and longitudinal models adjusted for age, gender, FFMI, height) Analysis The statistical analysis is appropriate for the design of the study, limiting potential for the

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					presentation of invalid results. YES Other information Subjects that did not have a repeat PA spine DXA were significantly younger and tended to have lower baseline PA spine z-scores.
Full citation Bhudhikanok, G. S., Wang, M. C., Marcus, R., Harkins, A., Moss, R. B., Bachrach, L. K., Bone acquisition and loss in children and adults with cystic fibrosis: a longitudinal study, Journal of Pediatrics, 133, 18-27, 1998 Ref Id 366725 Country/ies where the study was carried out United States of America Study type	Sample size n=47 children and young people with CF (26 females and 15 males) Characteristics Mean age, range: 20.6 years (8.4 to 48.5 years)30 female, 19 male Boy and young males n=9 Adult males n=6 Girls and young females n=11 Adult females n=15 Inclusion criteria A diagnosis of CF based on elevated sweat chloride concentrations	Prognostic test/ tool/ factor Baseline lumbar spine BMD (z-score for age and sex) • Males o Children and young people < 18 years: -1.0±0.9 o Adults ≥ 18 years: -2.5±1.4 • Females o Children and young people < 18 years: -1.5±1.5 o Adults ≥ 18 years: -1.9±1.6 Baseline femoral neck BMD (z-score for age and sex) • Males o Children and young people < 18 years: -0.8±0.6 o Adults ≥ 18 years: -2.5±0.8 • Females	Sample selection Data collection Anthropometric and clinical data: assessed by protocols and questionnaires Disease severity: Shwachman-Kulczycki score Laboratory assessment BMD: DXA (QDR 1000W, Hologic Corporation, Waltham) for lumbar spine, left proximal femur and whole body, BMAD was calculated to estimate volumetric bone density for the spine and hip. Percentage change in BMD and absolute change in BMD Z-score were calculated. Data analysis Wilcoxon rank-sum test: to compare changes in BMD and BMD Z-score One sample t-test: to test for changes in clinical and	Results Change in lumbar spine BMD (z-score for age and sex) at mean 17 months follow-up Males Children and young people < 18 years: -0.2±0.5; ns Adults ≥ 18 years: 0.1±0.2; ns Females Children and young people < 18 years: -0.6±0.8; p<0.05 Adults ≥ 18 years: 0.1±0.3; ns Change in femoral neck BMD (z-score for age and sex) at mean 17 months follow-up Males	Limitations The methodological limitations were assessed using a critical appraisal tool for the evaluation of the quality of prognosis studies in systematic reviews (Hayden et al. 2006): Study participation The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. PARTLY (explicit inclusion/exclusion criteria not listed) Study attrition Loss to follow-up (from sample to study

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Prospective case series Aim of the study To determine patterns of bone mineral acquisition in children and young adults with cystic fibrosis and to identify clinical and laboratory correlates of change in bone mineral density. Study dates July 1992 - July 1993 Source of funding None listed.	after pilocarpine iontophoresis. Exclusion criteria Not reported	o Children and young people < 18 years: -2.0±1.6 o Adults ≥ 18 years: -2.2±1.6 Baseline femoral neck BMD (z-score for age and sex) Males Children and young people < 18 years: -0.8±0.6 Adults ≥ 18 years: -2.5±0.8 Females Children and young people < 18 years: -2.0±1.6 Adults ≥ 18 years: -2.2±1.6 Baseline whole body BMD (z-score for age and sex) Males Children and young people < 18 years: -0.3±0.5 Adults ≥ 18 years: -2.0±1.2 Females Children and young people < 18 years: -1.3±1.2	bone measure at baseline and follow-up Scatterplots and nonparametric Spearman's rank correlations: to examine associations between outcome variables and anthropometric and clinical factors Multiple regression: to evaluate association of predictor variables with outcome variables, to compare BMAD and biochemical markers of bone turnover SAS v6.09 and 6.11 for Unix. Follow-up Mean 17 months (11 to 25 months) (data available for n=41) after initial evaluation	Children and young people < 18 years: -0.2±0.4; ns Adults ≥ 18 years: -0.2±0.4; ns Females Children and young people < 18 years: -0.3±0.8; ns Adults ≥ 18 years: 0.1±0.4; ns Change in femoral neck BMD (z-score for age and sex) at mean 17 months follow-up Males Children and young people < 18 years: -0.6±0.4; p<0.005 Adults ≥ 18 years: 0.1±0.3; ns Females Children and young people < 18 years: -0.4±0.3; p<0.005 Adults ≥ 18 years: -0.0±0.2; ns	population) is not associated with key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. YES (reasons for loss to follow-up given) Prognostic factor measurement The prognostic factor of interest is adequately measured in study participants to sufficient to limit potential bias. YES Outcome measurement The outcome of interest is adequately measured in study participants to sufficient to limit potential bias. PARTLY (wide range of follow-up time: 11 to 25 months) Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the

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		Adults ≥ 18 years: -1.3±1.2			prognostic factor of interest. UNSURE (treatment not documented over the course of longitudinal study) Analysis The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. YES Overall quality: Other information
Full citation Brenckmann, C., Papaioannou, A., Freitag, A., Hennessey, R., Hansen, S., Ioannidis, G., Webber, C., Adachi, J., Osteoporosis in Canadian adult cystic fibrosis patients: a descriptive study, BMC Musculoskeletal Disorders, 4, 13, 2003	Sample size n=40 adult CF patients attending a tertiary care hospital Characteristics Mean age (SD): 28.7 (8.4) Range: 19-52 Inclusion criteria Symptomatic and genetic diagnosis of CF Exclusion criteria Not reported	Prognostic test/ tool/ factor Baseline mean (SD) z-scores: Left hip BMD: -0.9 (1.1) Right hip BMD:-1.0 (1.1) Lumbar spine BMD: -1.1 (1.3) Baseline mean (SD) gm/cm2: Total BMD: 1.2 (0.1)	Sample selection Data collection Clinical and laboratory data was obtained from a clinic database and pharmaceutical data from in-patient pharmacy DXA scanning of the lumbar spine, femoral neck and total hip to measure BMD using Hologic QDR4500A machine T and Z-scores were calculated. WHO criteria for T-score was used: -1.0 to -2.5 indicates osteopenia and < -2.5 indicates osteoporosis	Results BMD annual change: Change in hip BMD: Left hip: -3.01% (95% CI -4.76 to -1.26) Right hip: -3.06% (95% CI -4.69 to -1.43) Change in lumbar spine BMD: -0.86% (95% CI -2.46 to 0.75) Change in total body BMD (n=21): 0.0% (SD 1.4%)	Limitations The methodological limitations were assessed using a critical appraisal tool for the evaluation of the quality of prognosis studies in systematic reviews (Hayden et al. 2006): Study participation The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
Ref Id 329545 Country/ies where the study was carried out Canada Study type Observational study Aim of the study To evaluate the prevalence of osteoporosis, the prevalence of non-vertebral fractures, and the change in bone mineral density in adult cystic fibrosis patients receiving care at a tertiary hospital Study dates 1999 Source of funding None listed			Scans were performed in two consecutive years for 21 patients Data analysis Paired two-tailed one-sample t-tests and 95% CI: to determine if mean changes in BMD were significantly different from baseline Follow-up Scans were performed in two consecutive years for 27 patients		results. UNCLEAR (all CF patients attending a tertiary hospital, inclusion/exclusion criteria details sparse) Study attrition Loss to follow-up (from sample to study population) is not associated with key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. YES (prevalence study limited loss to follow-up) Prognostic factor measurement The prognostic factor of interest is adequately measured in study participants to sufficient to limit potential bias. YES Outcome measurement The outcome of interest is adequately measured in study participants to sufficient to limit potential bias. PARTLY (no mention of review methodology)

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					Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. NO (The majority of patients measured for annual change in BMD had the second scan for clinical reasons and were receiving additional treatment and therefore the sample for this measurement is skewed) Analysis The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. (UNSURE) Overall quality: Other information Subgroup analysis was not possible as sample size was too small. N=21 participants were receiving oral or IV corticosteroids

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Full citation Haworth, C. S., Selby, P. L., Horrocks, A. W., Mawer, E. B., Adams, J. E., Webb, A. K., A prospective study of change in bone mineral density over one year in adults with cystic fibrosis, Thorax, 57, 719-23, 2002 Ref Id 366737 Country/ies where the study was carried out United Kingdom Study type Prospective case series Aim of the study To identify appropriate therapeutic strategies and the optimal time for intervention Study dates April - December 1997 Source of funding	Sample size n=114 adults with cystic fibrosis Characteristics Mean (SD) age: 25.1 (6.9) years (15 to 49) Young cohort ≤ 24 years n=55 Adult cohort ≥ 25 years n=59 Inclusion criteria Confirmed diagnosis of CF by raised sweat chloride test, gene analysis or an appropriate cystic fibrosis phenotype. Exclusion criteria Not reported	Prognostic test/ tool/ factor Details reported in a previous study: Lumbar spine BMD Femoral neck BMD Total hip BMD QCT and DXA DXA scans performed using: Hologic QDR 4500A densitometer (Hologic Inc., Bedford, MA, USA) Baseline lumbar spine BMD (mg/ml by CQT): Young cohort ≤ 24 years: 176.1 (166.9 to 185.2) Adult cohort ≥ 25 years: 170.8 (161.3 to 180.3) Baseline lumbar spine BMD (g/cm2 by DXA): Young cohort ≤ 24 years: 0.918 (0.8882 to 0.953) Adult cohort ≥ 25 years: 0.942 (0.909 to 0.975) Baseline femoral neck BMD (g/cm2 by DXA): Young cohort ≤ 24 years: 0.839 (0.801 to 0.877) Adult cohort ≥ 25 years: 0.781 (0.756 to 0.819) Baseline total hip BMD (g/cm2 by DXA):	Sample selection All patients attending Manchester Adult Cystic Fibrosis Unit Data collection BMD assessed on recruitment and follow up by DXA, SXA, QCT Biochemical measurements Clinical assessment: FEV and anthropomorphic measurements, questionnaire to assess physical activity Data analysis Analysis using SPSS v7.0 One sample t-test or Wilcoxon signed rank test: to determine significance of annual change in BMD Independent sample t-tests: to identify whether differences in BMD annual change between specific patient groups Spearman's rank correlations: to identify clinical and biochemical correlates of BMD annual change at skeletal site Follow-up 114 patients re-attended for BD a median of 12 (12-13) months after their initial BMD assessment	Results Annual change in lumbar spine BMD (mg/ml by CQT): Young cohort ≤ 24 years: -1.7% (-4.4 to 1.1) Adult cohort ≥ 25 years: 0.7% (-1.5 to 2.8) Annual change in lumbar spine BMD (g/cm2 by DXA): Young cohort ≤ 24 years: -0.9% (-2.0 to 0.2) Adult cohort ≥ 25 years: -0.0% (-1.3 to 1.2) Annual change in femoral neck BMD (g/cm2 by DXA): Young cohort ≤ 24 years: -2.5% (-3.8 to -1.2); p-value <0.001 Adult cohort ≥ 25 years: -1.9% (-2.9 to -0.8); p-value <0.001 Annual change in total hip BMD (g/cm2 by DXA): Young cohort ≤ 24 years: -2.2% (-3.3 to -1.0); p-value <0.001	Limitations The methodological limitations were assessed using a critical appraisal tool for the evaluation of the quality of prognosis studies in systematic reviews (Hayden et al. 2006): Study participation The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. YES Study attrition Loss to follow-up (from sample to study population) is not associated with key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. UNSURE (reasons stated for study withdrawal but BMD Z scores at each site were lower in patients who dropped out)

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Cystic Fibrosis Research Trust, UK		Young cohort ≤ 24 years: 0.917 (0.880 to 0.953 Adult cohort ≥ 25 years: 0.881 (0.844 to 0.918)		Adult cohort ≥ 25 years: -1.5% (-2.4 to -0.6); p=0.001	Prognostic factor measurement The prognostic factor of interest is adequately measured in study participants to sufficient to limit potential bias. YES Outcome measurement The outcome of interest is adequately measured in study participants to sufficient to limit potential bias. YES Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. UNSURE Analysis The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. PARTLY (multiple correlations used at p<0.05)

Study details	Participants	Prognostic test/ tool/ factor	Methods	Outcomes and results	Comments
					Overall quality: Other information
Full citation Papaioannou, A., Kennedy, C. C., Freitag, A., O'Neill, J., Pui, M., Ioannidis, G., Webber, C., Pathak, A., Hansen, S., Hennessey, R., Adachi, J. D., Longitudinal analysis of vertebral fracture and BMD in a Canadian cohort of adult cystic fibrosis patients, BMC Musculoskeletal Disorders, 9, 125, 2008 Ref Id 329956 Country/ies where the study was carried out Canada Study type Retrospective case series	Sample size N=49 adults with CF Characteristics Mean age (SD): 25.2 (9.4) years 42.9% male Inclusion criteria Moderate to severe respiratory impairment At least one chest radiograph or DXA scan in previous year CF confirmed by positive sweat test and DNA analysis Exclusion criteria Patients accepted on lung-transplant list or received prior organ transplant	Prognostic test/ tool/ factor DXA Baseline mean (SD) T-score/ Z-score: Lumbar spine BMD: -0.80 (1.10) Proximal femur BMD: -0.57 (0.97) Whole body BMD: -0.71 (1.11)	Sample selection All patients who attended Adult Cystic Fibrosis Clinic at McMaster University Medical Centre during 2002 Data collection Radiology review: first and last chest radiograph between 1996 and 2003 selected for review Bone densitometry: scans of lumbar spine, proximal femur and whole body taken using standard dual-energy X-ray absorptiometry (DXA) on a QDR4500A model (Hologic Inc, Bedford, MA, USA) taken 2-5 times during the study BMD measurements reported as T- (adult) or Z-scores (≤19 years) Clinical/laboratory variables recorded Data analysis Analysis using SPSS v13.0 Multi-variable regression model: to estimate percent BMD change per year, with 2-sided p-value of < 0.05 for significance	Results Overall rate of bone loss at mean 4.3 years follow-up: Lumbar spine BMD: -0.73% Proximal femur BMD: -1.93% Whole body BMD: -0.40%	Limitations The methodological limitations were assessed using a critical appraisal tool for the evaluation of the quality of prognosis studies in systematic reviews (Hayden et al. 2006): Study participation The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. YES Study attrition Loss to follow-up (from sample to study population) is not associated with key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. YES (those excluded were transplant recipients or lack of scans)

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Aim of the study To examine: longitudinal changes in BMD the rate of vertebral fractures in adults with CF Study dates 2002 Source of funding Ontario Thoracic Society			Mann-Whitney U-test: to test differences in baseline characteristics between fracture vs non-fracture patients Fisher's exact test: to examine differences between proportions Follow-up Mean (SD): 4.03 (1.45) years (data available for n=10)		Prognostic factor measurement The prognostic factor of interest is adequately measured in study participants to sufficient to limit potential bias. PARTLY (clinic data was retrospective and coincident if performed within 1 year) Outcome measurement The outcome of interest is adequately measured in study participants to sufficient to limit potential bias. PARTLY (clinic data was retrospective and coincident if performed within 1 year) Confounding measurement and account Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. PARTLY (wide age range in sample size and use of steroid and Vit

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					D supplementation not controlled for) Analysis The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. YES Other information
Full citation Schulze, K. J., Cutchins, C., Rosenstein, B. J., Germain-Lee, E. L., O'Brien, K. O., Calcium acquisition rates do not support age-appropriate gains in total body bone mineral content in prepuberty and late puberty in girls with cystic fibrosis, Osteoporosis International, 17, 731-40, 2006 Ref Id 330050 Country/ies where the study was carried out	Sample size N=18 Characteristics Prepubertal and pubertal girls and young females with CF Inclusion criteria Not reported Exclusion criteria Not reported	Prognostic test/ tool/ factor Baseline mean±SD gender and age matched z-scores: Lumbar spine BMD: -0.40±1.13 Whole body BMD: -0.29±1.01 Standard dual-energy X-ray absorptiometry (DXA) on a QDR4500A model (Hologic Inc, Bedford, MA, USA)	Sample selection Patients who had completed baseline assessment of bone parameters in the original study were invited to return for follow-up assessment n=18 Data collection Medical survey: fracture history, physical exercise, hospitalizations Pubertal stage assessment using Tanner stage Clinical and laboratory assessment: anthropometric measures and FEV1, hormone levels BMD: DXA using a QDR4500A model and age-matched Z-scores determined for lumbar spine and total body bone mineral content from Hologic database	Results Change between baseline and follow-up (mean±SD follow-up 2.13±1.16; range 1.06 to 4.10 years) Lumbar spine BMD: -0.46±0.94 Whole body BMD: -0.45±1.16	Limitations The methodological limitations were assessed using a critical appraisal tool for the evaluation of the quality of prognosis studies in systematic reviews (Hayden et al. 2006): Study participation The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results. YES Study attrition Loss to follow-up (from sample to study population) is not

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United States of America Study type Aim of the study to assess calcium accretion rates and changes in lumbar spine BND and total body mineral content to examine predictors of these parameters to understand effectors of bone health over time in children with CF Study dates Original study: July 1999 - October 2001 Follow-up: 1-4 years later Source of funding Cystic Fibrosis Foundation and National center for Research Resources/General clinical Research Center, JHH			Data analysis STATA v8.0 Regression analysis: to identify determinants of LS BMD Z-score, TBBMC Z-score and their changes over time ANOVA with Scheffe's multiple comparisons tests: to determine measures of BM by pubertal groups at baseline or follow-up ANCOVA: to assess changes in BM by pubertal groups Paired t-test: to assess significance in subject characteristics between baseline and follow-up measurements T-tests: within pubertal groups to determine if measures of LS and TBBMC Z-score changes over time differed from zero Follow-up Mean time: 2.13±1.14 years (range 1.6 to 4.10)		associated with key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias. YES (reasons given for loss to follow-up) Prognostic factor measurement The prognostic factor of interest is adequately measured in study participants to sufficient to limit potential bias. UNSURE (clear description of prognostic factor measurement but scan follow up ranged from 1-4 years) Outcome measurement The outcome of interest is adequately measured in study participants to sufficient to limit potential bias. UNSURE (clear description of prognostic factor measurement but scan follow up ranged from 1-4 years) Confounding measurement and account

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					Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest. UNSURE (longitudinal study - treatment regimes) Analysis The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results. YES Other information Although the study reported data stratified by pubertal status, this was not reported in the review as sample size was very low (range 2 to 7). Significant differences were found by pubertal stage at baseline.