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# Bone mineral density in a cohort of adolescents during use of norethisterone enanthate, depot-medroxyprogesterone acetate, or combined oral contraceptives and after discontinuation of norethisterone enanthate

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## Abstract

**Background—**Depot-medroxyprogesterone acetate (DMPA), norethisterone enanthate (NET-EN) and combined oral contraceptives (COCs) have been shown to have a negative effect on bone mineral density (BMD) in adolescents. The aim of this study was to investigate BMD in 15-to 19-year-old new users of DMPA, NET-EN and COCs.

**Study Design—**This 5-year longitudinal study followed-up new users of DMPA (n=115), NET-EN (n=115), and COCs (n=116), and 144 nonuser controls. BMD was measured at the distal radius using dual x-ray absorptiometry.

**Results—**BMD increased in all groups (annual percent increase: nonusers, 1.49%; DMPA, 1.39%; NET-EN, 1.03%; COCs, 0.84%) during follow-up ($p<0.001$). There was evidence for lower BMD increases per annum in NET-EN ($p=.050$) and COC ($p=.010$) users compared to nonusers but no difference between DMPA and nonusers ($p=.76$). In 14 NET-EN discontinuers, an overall reduction of 0.61% per year BMD was followed upon cessation by an increase of 0.69% per year ($p=.066$).

**Conclusion—**This study suggests that BMD increases in adolescents may be less in NET-EN and COC users; however, recovery of BMD in NET-EN users was found in the small sample of adolescents followed post-discontinuation.

## Introduction

Depot-medroxyprogesterone acetate (DMPA) has been found to have a negative effect on bone mineral density (BMD) in adult premenopausal women (Curtis and Martins, 2006; Wanichsetakul et al, 2002; Petitti et al, 2000; Scholes et al, 1999;; Cundy et al, 1991) and in adolescents (Cromer et al, 2008; Clark et al, 2006; Scholes et al, 2005; Cromer et al, 2004; Lara-Torre et al, 2004; Scholes et al, 2004; Busen et al, 2003; Cromer et al, 1996). Limited data on the effect of norethisterone enanthate (NET-EN) have found a negative effect on BMD in adult (Rosenburg, et al, 2007) and adolescent users (Beksinska, et al 2007). A comprehensive review concluded that combined oral contraceptive (COC) use in adult premenopausal women was not associated with changes in BMD (Martins, et al, 2006). However, emerging data show that BMD may be compromised in adolescent users of low-dose COCs (Hartard, et al, 2006; Cromer, et al, 2004; Polatti et al, 1995).


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Studies that have followed women after discontinuation of DMPA have found that BMD recovers in adult pre-menopausal women within approximately 2-3 years of cessation of the method (Kaunitz, et al, 2008; Scholes, et al, 2002). Two studies have followed-up adolescent users of DMPA post-discontinuation (Clark et al, 2006; Scholes et al, 2005), and in both these studies, a significant increase in BMD was found in adolescents who discontinued DMPA. No longitudinal data are available on recovery of BMD in adolescent NET-EN and low-dose COC users. More evidence is needed to show if the recovery of BMD found in adult users of hormonal contraception is replicated in adolescents. The objective of this study was to determine if long-term use of hormonal contraceptives (COC, DMPA and NET-EN) compared to non-use, was associated with a change in bone mass in women aged 15-19 years.

## Subjects and methods

This was a prospective longitudinal study of adolescents aged 15 to 19 years who had never used hormonal contraception prior to recruitment to the study. Initiators of DMPA, NET-EN, COCs, and nonusers of contraception were enrolled from a family planning clinic in Durban, South Africa. The study cohort was recruited between July 2000 and July 2002 and follow-up continued until April 2006. All DMPA users were started on a regimen of 150 mg every 12 weeks and NET-EN users on 200 mg every 8 weeks. Both DMPA and NET-EN was administered intramuscularly. The COCs used by women included a range of formulations, with almost all (93%) using low-dose formulations containing between 30-40 mcg of estrogen. Women were eligible to participate if they had not lactated or delivered in the past 6 months, were not currently or had never used medication known to affect calcium metabolism for more than 3 months, and did not have a chronic disease affecting calcium metabolism. At the baseline visit, participants' height, weight and blood pressure were measured using a standard protocol and a questionnaire was administered to elicit information on demographic characteristics, regularity of the menstrual cycle, smoking, diet, exercise and caffeine and alcohol intake.

Forearm BMD was measured by dual energy x-ray absorptionmetry (DXA model DTX-200, Osteometer MediTech A/S Co, Rodovre, Denmark). BMD was measured in grams per square centimetre ($g/cm^2$) at the distal radius in the forearm. The DXA equipment was standardized daily using a phantom as prescribed by the manufacturer's instructions. Accuracy to the standard during the recruitment and follow-up period was 0.53%.

Study participants were followed-up at approximately six-monthly intervals. Forearm BMD, height and weight were measured at each follow-up visit. History of contraceptive use since last visit was recorded. Those recruited between July 2000 and April 2001 and who continued to participate until the end of the study completed 5 years of follow-up. Those recruited after April 2001 who continued until the end of the study, completed between 4 and 5 years of follow-up. Follow-up could not continue beyond April 2006 when project funding came to an end. Women continued the same follow-up schedule even if they stopped, changed or started another contraceptive method in order to investigate issues of recovery of BMD post-discontinuation of a hormonal method.

The characteristics of women in the study were quantified as means ± SD, medians, or percentages. The study was powered to detect a half standard deviation difference in bone mass between users and nonusers of hormonal contraceptives. This would be of biological significance as this difference is expected to translate into a large difference in the risk of fracture in older women. Information on the mean and standard deviation of cross-sectional measurements of forearm bone mass in white, European, premenopausal women reported by Nordin (Nordin, 1987) was used to estimate sample size. A sample of 63 participants per

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contraceptive group was required assuming a two-tailed statistical test with a significance level of 5% and power of 80%. Allowing for 10-15% loss to follow-up per year, this sample was increased to at least 110 women in each group to ensure adequate numbers in long-term follow-up. The nonuser group was over recruited compared to other groups as, in addition to loss to follow-up, it was anticipated that some of these women would commence a method of contraception or become pregnant.

Differences in BMD between contraceptive groups, and the associations between BMD and selected characteristics of the study participants by contraceptive group were assessed using one-way analysis of variance and multiple variable linear regression. BMD was measured in users and discontinuers. Follow-up of all women was cumulated up to their last visit, or up to the visit preceding a visit at which they reported a change in contraceptive method, whichever occurred first.

Interim analysis of this study found that BMI was significantly associated with radius BMD (Beksinska, et al, 2007). To assess the effect of contraceptive method on radius BMD, and to allow for within subject correlation of responses whilst controlling for the confounding effect of changes in BMI, we used random effects linear regression methods with radius BMD at the time of a study visit as the response variable, and contraceptive method, duration of follow-up and BMI at time of the visit as explanatory variables (STATA V.10, College Station, TX, USA). Differences in rate of change in radius BMD per year between methods were calculated by including interaction terms in the model for method and follow-up time. Additionally, we investigated whether change in radius BMD varied between two time periods by including an interaction term between follow-up time up to the last visit occurring before 2.5 years and follow-up time between 2.5 and 5 years, for each user-group separately. These two time periods were chosen as the literature indicates that the greatest loss of BMD as a result of hormonal contraceptive use occurs over the first 2 years of use (Tang,et al, 2000) and then loss continues at a slower rate and appears to stabilize. Finally, we investigated BMD in women who discontinued hormonal contraception.

Ethical approval was granted by the University of the Witwatersrand, Human Subjects Research Committee (protocol number M981001), and by the Scientific and Ethical Review Group of the World Health Organization (WHO).

## Results

In total, 490 women aged 15-19 years were recruited. All women including those in the DMPA, NET-EN and COC groups had no past use of hormonal contraception before recruitment into the study. Baseline information about these women is summarized in Table 3.3.1. Mean age was just under 18 years and most women were still in full-time education. The majority of women were African except in the COC group, which included 22% women of Indian origin and 21% Coloured. More than a quarter of women (29.3%) in the DMPA user group had ever been pregnant compared to low prevalence of pregnancy in the other groups. COC users were more likely to be smokers than other method users, although smoking generally was low across all groups.

In total, 277 women continued with the same method of contraception for at least two follow-up visits, while the rest had changed method or stopped using contraception. Total same-method follow-up time was 648 person-years in these 277 participants. Women who continued in the study using a different method of contraception, or stopped using contraception, were included up to the visit they changed method. Overall, 64% of woman continued in the study for between 2-3 years and 43% completed between 4-5 years of follow-up depending on time of recruitment. Main reasons for discontinuation from the

study included pregnancy, illness that could have affected BMD such as tuberculosis, loss to follow-up and moving out of the area.

Table 3.3.2 shows mean BMD and BMI at enrolment for each group. Radius BMD was similar in all four contraceptive user groups at baseline (p=.196). The regression model showed that BMI was the only baseline characteristic associated with radius BMD (p<0.001). BMI increased consistently by 0.11 $kg/m^2$ per year (95% CI 0.04 to 0.18) in all user groups with no evidence of differences in growth between groups (p=0.14).

Radius BMD increased in all groups during follow-up (Table 3.3.3), even after adjusting for changes in BMI (p<.001) with an overall increase for all women combined of 1.39% per annum (95% CI 1.19 % to 1.59 %). In nonusers, BMD increased by 1.49% per annum; in the DMPA, NET-EN and COC users, the increases were less 1.39% (p=.76), 1.03 % (p=.05) and 0.84% (p=.01), respectively (Table 3.3.3). There was moderate to strong evidence for smaller increases per annum in NET-EN (p=.050) and COC (p=.010) users compared to nonusers. There was no evidence for a difference in BMD between DMPA and nonusers (p=.76) (Table 3.3.3).

There was no evidence of a difference in change in radius BMD in the two time periods (up to 2.5 years and 2.5 years and longer) in any of the four study groups (DMPA p=0.105, NET-EN p=0.7, nonusers p=0.46, COC p=0.06).

We investigated changes in BMD in a group of 14 NET-EN users who discontinued use of the method without restarting another method during the course of the study. An overall reduction in radius BMD of 0.61% (95% CI= −2.53% to 1.34%) per year was seen in the 14 NET-EN users during use of the method, followed upon cessation of method by an increase of 0.69% (95% CI= −0.18% to 1.56%) per year. After adjusting for BMI, there was some evidence of a difference in rate of BMD change pre and post use of NET-EN (p=0.066). Most COC and DMPA discontinuers restarted other methods, thus there were too few to conduct a group analysis.

## Discussion

Our results show that radius BMD increased during follow-up in the nonuser and all three user groups after adjusting for BMI. There was some evidence of less increase in NET-EN and COC groups compared to the nonuser group. Our results confirm those obtained from an interim analysis of this study (Beksinska, et al, 2007) in regard to NET-EN. However, in the preliminary analysis, COC users did not show any differences in BMD growth from nonusers, possibly because the interim analysis lacked power. In the only other study that has previously investigated the effect of NET-EN use (Rosenburg, et al, 2007), BMD was measured in the left calcaneus in a large cross-sectional sample of adult premenopausal women. NET-EN users had similar values to DMPA users and these were both significantly lower compared to never users.

We found no evidence of any change in BMD growth in the period up to 2.5 years of use compared to the period from 2.5 years of use. Several studies have reported that the rate of loss of BMD in DMPA users is greatest in the first two years of use (Clark, et al, 2006; Curtis and Martins, 2006; Scholes, et al, 2005; Tang, et al, 2000). Only one of these studies has investigated rate of change in adolescents (Scholes, et al, 2005).

Several longitudinal studies have found that adolescent users of low-dose COCs may gain bone mass at a slower rate compared to nonusers (Hartard et al, 2006; Cromer, et al 2004; Polatti, et al, 1995). The COC formulations in our study were similar to those reported in these studies. Our study also showed that COC users gained BMD at a slower rate than

nonusers. Although DMPA users had a lower yearly increase in BMD compared to nonusers, this was not significant. Other studies measuring BMD at central sites such as the hip and spine have found that adolescent DMPA users have lower BMD values compared to nonusers (Cromer et al, 2008; Clark et al, 2006; Scholes et al, 2005; Cromer et al, 2004; Lara-Torre et al, 2004; Scholes et al, 2004; Busen et al, 2003; Cromer et al, 1996). Studies using the forearm as a site of BMD measurement have generally not found significant differences between DMPA users and controls (Bahamondes, et al, 1999; Tharnprisarn, et al, 2002). Our study has found similar results to others measuring the forearm with respect to DMPA. The forearm may be more sensitive to the effect of NET- EN and COC and it may be that these results would be magnified if measured at a central site such as the hip or spine. No studies have measured BMD at central sites in NET-EN users.

Our study shows some evidence of a recovery in growth in BMD in a very small sample of NET-EN discontinuers who did not use another method of contraception after cessation. The cross-sectional study that investigated women who commenced NET-EN during adolescence (18 years and younger) and then ceased using the method (Rosenburg, et al, 2007), found no difference in BMD values between those who had ceased use 2-3 years before and never users regardless of whether they were early starters (adolescents) or late starters (post-adolescence). It was not possible to make any statement about BMD recovery in the COC and DMPA discontinuers in our study as numbers were so small.

DMPA suppresses estradiol production, leading to estrogen deficiency (Ortiz, et al, 1977). This leads to greater bone resorption and hence loss of BMD. There is less information on NET-EN and the mechanisms by which it could affect BMD. Studies on NET alone have not found negative effects on BMD (Horowitz, et al, 1993; Eldred, et al, 1992; Riis, et al, 1990). There is now limited data available on recovery of BMD in women who commence DMPA in adolescence (Clark, et al, 2006; Scholes, et al, 2005). This is the first longitudinal study which has included NET-EN users and discontinuers. Further evidence is needed to ensure that any losses of BMD as a result of DMPA and NET-EN in adolescence are fully recovered and peak bone mass is not compromised. Until that time, the recommendations for DMPA and NET-EN in adolescents will continue to caution long-term use in young women.

The third edition (2004) of the World Health Organization's Medical Eligibility Criteria for contraceptive Use (WHO, 2004) has changed the classification of use of DMPA and NET-EN for women below 18 years and above 45 years from category 1 (no restriction for the use of the contraceptive method), to category 2 (advantages of using the method generally outweigh the theoretical or proven risks). This is backed up in the document by a number of statements reporting on current evidence of the effect of DMPA on BMD. The WHO has recommended that in the absence of evidence on NET-EN, the same restrictions should apply to NET-EN users.

Our study shows that although BMD continues to increase in adolescent users of NET-EN and COCs, these increases are lower than in nonusers. Although the percent yearly increase in DMPA users was lower than nonusers, there was no evidence of a difference and this may have been because this group had the lowest number of years at risk included in the analysis.

## Limitations

Longitudinal studies of adolescent users of hormonal contraception are often limited by method discontinuation. This was the case in our study where few women remained on hormonal contraception for more than two years without a change of method or stopping use of contraception altogether. Concerns regarding long-term use of DMPA and NET-EN in adolescents should take this into consideration as many young women will have discontinued use before the 2-year review suggested on the patient labelling. Our study has

used the forearm as its site of measurement which may be less sensitive than the hip and spine to changes in BMD resulting from hormonal contraceptive use.

## References


[1]. Petitti DB, Piaggio G, Mehta S, Cravioto MC, Meirik O. Steroid hormone contraception and bone mineral density: a cross-sectional study in an international population. The WHO Study of Hormonal Contraception and Bone Health. Obstet Gynaecol. 2000; 95:736–743.

[2]. Scholes D, Lacroix AZ, Ott SM, Ichikawa LE, Barlow WE. Bone mineral density in women using depot medroxyprogesterone acetate for contraception. Obstet Gynaecol. 1999; 93:233–238.

[3]. Wanichsetakul P, Kamudhamas A, Watanaruagkovit P, Siripakam Y, Visutakul P. Bone mineral density at various anatomic bone sites in women receiving combined oral contraceptives and depot-medroxyprogesterone acetate for contraception. Contraception. 2002; 65:407–410. [PubMed: 12127638]

[4]. Curtis KM, Martins SL. Progestogen-only contraception and bone mineral density. Contraception. 2006; 73:470–487. [PubMed: 16627031]

[5]. Cundy T, Evans M, Roberts H, Waltie D, Ames R, Reid IR. Bone density in women receiving depot medroxyprogesterone acetate for contraception. BMJ. 1991; 303:13–16. [PubMed: 1830502]

[6]. Scholes D, Lacroix AZ, Ichikawa LE, Barlow WE, Ott SM. The association between depot medroxyprogesterone acetate contraception and bone mineral density in adolescent women. Contraception. 2004; 69:99–104. [PubMed: 14759613]

[7]. Cromer BA, Blair J. McArdle, Mahan JD, Zibners BS, Naumovski Z. A prospective comparison of bone density in adolescent girls recieving depot medroxyprogesterone accetate (Depo-Provera), levenogesterol (Norplant), or oral contraceptives. J Pediatr. 1996; 129:671–676. [PubMed: 8917232]

[8]. Busen NH, Britt RB, Rianon M. Bone mineral density in a cohort of adolescent women using depot medroxyprogesterone acetate for one to two years. J Adolesc Health. 2003; 32:257–259. [PubMed: 12667729]

[9]. Lara-Torre E, Edwards CP, Perlman S, Hertweck SP. Bone mineral density in adolescent females using depot medroxyprogesterone acetate. J Pediatr Adolesc Gynecol. 2004; 17:17–21. [PubMed: 15010034]

[10]. Cromer BA, Stager M, Bonny A, et al. Depot medroxyprogesterone acetate, oral contraceptives and bone mineral density in a cohort of adolescent girls. J Adolesc Health. 2004; 35:434–441. [PubMed: 15581522]

[11]. Cromer BA, Bonny A, Stager M, et al. Bone mineral density in adolescent females using injectable or oral contraceptives: a 24-month prospective study. Fertil Steril. 2008 Epub ahead of print.

[12]. Scholes D, Lacroix AZ, Ichikawa LE, Barlow WE, Ott SM. Change in bone mineral density among adolescent women using and discontinuing depot medroxyprogesterone acetate contraception. Arch Pediatr Adolesc Med. 2005; 159:139–144. [PubMed: 15699307]

[13]. Clark MK, Sowers MR, Levy B. Bone mineral density loss and recovery during 48 months in first-time users of depot medroxyprogesterone acetate. Fertil Steril. 2006; 86:1466–1474. [PubMed: 16996507]

[14]. Rosenburg L, Zhang Y, Constant D, et al. Bone status after cessation of use of injectable progestin contraceptives. Contraception. 2007; 76:425–431. [PubMed: 18061699]

[15]. Beksinska ME, Kleinschmidt I, Smit J, Farley TMM. Bone mineral density in adolescents using norethisterone enanthate, depot-medroxyprogerterone acetate, or combined oral contraceptives for contraception. Contraception. 2007; 75:438–443. [PubMed: 17519149]

[16]. Martins SL, Curtis KM, Glasier AF. Combined hormonal contraception and bone health: a systematic review. Contraception. 2006; 73:445–469. [PubMed: 16627030]

[17]. Hartard M, Kleimond C, Wiseman M, Weissenbacher ER, Felsenberg D, Erben RG. Detrimental effect of oral contraceptives on parameters of bone mass and geometry in a cohort of 248 young women. Bone. 2007; 40:444–450. [PubMed: 16965947]

[18]. Polatti F, Perotti F, Felippa N, Gallina D, Nappi RE. Bone mass and long-term monophasic oral contraceptive treatment in young women. Contraception. 1995; 51:221–224. [PubMed: 7796586]

[19]. Kaunitz AM, Miller PD, Rice V. Montgomery, Ross D, McClung MR. Bone mineral density in women aged 25–35 years receiving depot-medroxyprogesterone acetate: recovery following discontinuation. Contraception. 2006; 74:90–99. [PubMed: 16860045]

[20]. Scholes D, LaCroix AZ, Ichikawa LE, Barlow WE, Ott SM. Injectable hormone contraception and bone density: results from a prospective study. Epidemiology. 2002; 13:581–587. [PubMed: 12192229]

[21]. Nordin BEC. The definition and diagnosis of osteoporosis. Calcif Tissue Int. 1987; 40:57–58. [PubMed: 3105834]

[22]. Tang OS, Tang G, Yip PS, Li F. Further evaluation on long-term depot-medroxyprogesterone acetate use and bone mineral density; a longitudinal cohort study. Contraception. 2000; 62:161–164. [PubMed: 11137068]

[23]. Bahamondes L, Perotti M, Castro S, Faundes D, Petta C, Bedone A. Forearm bone density in users of Depo-Provera as a contraceptive method. Fertil Steril. 1999; 71:849–852. [PubMed: 10231044]

[24]. Tharnprisarn W, Taneepanichskul S. Bone mineral density in adolescent and young Thai girls receiving oral contraceptives compared with depot medroxyprogesterone acetate: a cross-sectional study in young Thai women. Contraception. 2002; 66:101–103. [PubMed: 12204782]

[25]. Ortiz A, Hiroi F, Stanczyk FZ, Goebelsmann V, Mishell DR. Serum medroxyprogesterone acetate (MPA) concentrations and ovarian function following intramuscular injection of depo-MPA. J Clin Endocrinol Metab. 1977; 44:32–38. [PubMed: 833262]

[26]. Eldred JM, Haynes PJ, Thomas EJ. A randomized double blind placebo controlled trial of the effects on bone metabolism of the combination of nafarelin acetate and norethisterone. Clin Endcrinol. 1992; 37:354–359.

[27]. Horowitz M, Wishart JM, Need AG, Morris HA, Nordin BEC. Effects of norethisterone on bone related biochemical variables and forearm bone mineral in postmenopausal osteoporosis. Clin Endocrinol. 1993; 39:649–655.

[28]. Riis BJ, Christiansen C, Johansen JS, Jacobson J. Is it possible to prevent bone loss in young women treated with luteinizing hormone-releasing hormone agonists? J Clin Endocrinol Metab. 1990; 70:920–924. [PubMed: 2138631]

[29]. World Health Organization. Medical eligibility criteria for contraceptive use, third edition. Department of Reproductive Health and Research. World Health Organization; Geneva (Switzerland): 2004.

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**Table 3.3.1**

**Socio-demographic, lifestyle and reproductive characteristics of subjects aged 15-19 years by contraceptive user group, at baseline.**

| Characteristics | DMPA (n=115) | NET-EN (n=115) | COC (n=116) | Non user controls (n=144) | P value |
|---|---|---|---|---|---|
| Mean age, years (SD) | 17.8 (1.4) | 17.4 (1.3) | 17.8 (1.0) | 17.4 (1.2) | 0.0002 |
| Mean highest education grade (SD) | 10.9 (1.5) | 10.5 (1.5) | 11.3(0.8) | 10.3 (1.4) | 0.0001 |
| Marital status, % | | | | | |
| Married/cohabiting | 5.3 | 5.2 | 10.3 | 12.8 | 0.0001 |
| Reg partner-not cohabiting | 92.1 | 83.8 | 87.1 | 63.5 | |
| Casual partner | 2.6 | 5.2 | 2.6 | 23.0 | |
| No partner | 0 | 0.9 | 0 | 0.7 | |
| Employment status % | | | | | |
| Employed full/part-time | 6.2 | 2.6 | 9.5 | 2.7 | <0.0001 |
| Unemployed | 11.4 | 10.5 | 8.5 | 7.4 | |
| Student/scholar | 82.5 | 86.8 | 79.1 | 98.8 | |
| Ethnicity % | | | | | |
| African | 94 | 89 | 57 | 92 | <0.0001 |
| Coloured | 5 | 7 | 21 | 4 | |
| Indian | 1 | 4 | 22 | 4 | |
| Ever pregnant % | 29.3 | 3 | 6 | 2 | <0.0001 |
| Ever lactated % | 16.7 | 0.9 | 2.6 | 1.4 | |
| Lactation (yrs) median | <1 | <1 | <1 | <1 | |
| Mean age at menarche, years(SD) | 13.9±1.3 | 13.8±1.2 | 13.6±1.48 | 13.5±1.29 | 0.19 |
| Exercise | | | | | |
| No regular exercise (%) | 78.1 | 72.8 | 64.9 | 77.7 | 0.0001 |
| At least once a week (%) | 21.9 | 27.2 | 35.1 | 22.3 | |
| Dieted in last 6 months (%) | 3.5 | 2.6 | 5.3 | 2.0 | 0.54 |
| Ever smoked cigarettes (%) | 9.6 | 11.3 | 27.3 | 4.8 | < 0.001 |
| Current smoker (%) | 6.0 | 7.0 | 13.9 | 3.4 | 0.006 |

DMPA= depot medroxyprogesterone acetate; NET-EN = Norethisterone enanthate; COC= combined oral contraceptive SD= standard deviation;

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**Table 3.3.2**
**Mean BMD and BMI at admission by contraceptive group**

| Variable | DMPA n=115 | NET-EN n=115 | COC n=116 | Nonuser n=144 | p value |
|---|---|---|---|---|---|
| Radius BMD g/cm$^2$ | 0.459 (0.06) | 0.446 (0.06) | 0.460 (0.05) | 0.455(0.05) | 0.196 |
| Body weight (kg) | 59.1 (12.1) | 59.5 (9.8) | 56.7 (11.4) | 59.7 (11.6) | 0.13 |
| Height (cm) | 154.8 (5.2) | 156.1 (5.7) | 156.2 (7.5) | 155.9 (7.3) | 0.3 |
| BMI (kg/m$^2$) | 24.63 (4.77) | 24.31 (3.75) | 23.18 (4.97) | 24.61 (5.85) | 0.097 |

BMD= bone mineral density; BMI=body mass index

Data are expressed as mean ± SD

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**Table 3.3.3**

**Factors associated with radius BMD at study visit, estimated from random effects liner regression model.**

| Variable | % change in BMD (95% CI) per annum | % change in BMD per method relative to non user (p) | N | Time at risk (years) |
|---|---|---|---|---|
| Use of contraceptive method, per year * | | | | |
| Non user (reference) | 1.49 (1.25-1.72) | 0 | 96 | 311 |
| DMPA, | 1.39 (0.79-1.98) | −0.10 (p=0.76) | 51 | 76 |
| NET-EN | 1.03 (0.63-1.44) | −0.45 (p=0.050) | 71 | 146 |
| COC | 0.84 (0.39-1.28) | −0.65(p=0.010) | 59 | 116 |
| Effect of BMI, per unit change in BMI (% per $kg/m^2$) † | 0.267 (0.157-0.377) | | 277 | 648 |

*Adjusted for BMI

†Adjusted for contraceptive method