14 Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H. Coronary-heart-disease risk and impaired glucose tolerance: the Whitehall study. *Lancet* 1980;i: 1373-6.
15 Modan M, Halkin H, Almog S, Lusky A, Eshkol A, Shefi M, *et al.* Hyperinsulinemia: a link between hypertension, obesity and glucose intolerance. *J Clin Invest* 1985;75:809-17.
16 Ducimetiere P, Eschwege E, Papoz L, Richards JL, Claude JR, Rosselin G. Relationship of plasma insulin levels to the incidence of myocardial infarction and coronary artery disease mortality in a middle aged population. *Diabetologia* 1980;19:205-10.
17 Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, *et al.* Insulin resistance in essential hypertension. *N Engl J Med* 1987;317:350-7.
18 Pollare T, Lithell H, Selinus I, Berne C. A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N Engl J Med* 1989;321:868-73.
19 Rooney DP, Neely RDG, Ennis CN, Bell NP, Sheridan B, Atkinson AB, *et al.* Insulin action and hepatic glucose cycling in essential hypertension. *Metabolism* 1992;41:317-24.
20 DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979;237: E214-23.
21 Neely RDG, Rooney DP, Atkinson AB, Sheridan B, Ennis CN, Trimble ER, *et al.* Underestimation of glucose turnover determined using [6-^{3}H]glucose tracer in non-steady state: the role of a tritiated tracer impurity. *Diabetologia* 1990;33:681-7.
22 Neely RDG, Rooney DP, Bell PM, Bell NP, Sheridan B, Atkinson AB, *et al.* Influence of growth hormone on glucose–glucose 6 phosphate cycle and insulin action in normal humans. *Am J Physiol* 1992;263:E980-7.
23 Somogyi M. Determination of blood sugar. *J Biol Chem* 1945;160:69-73.
24 Hales CN, Randle PJ. Immunoassay of insulin with insulin antibody precipitate. *Biochem J* 1963;88:137-46.
25 Steele R, Wall JS, De Bodo RC, Altszuler N. Measurement of size and turnover rate of body glucose pool by the isotope dilution method. *Am J Physiol* 1956;187:15-25.
26 De Bodo RC, Steele R, Altszuler N, Dunn A, Bishop JS. On the hormonal regulation of carbohydrate metabolism; studies with C14 glucose. *Recent Prog Norm Res* 1963;19:445-88.
27 Hills M, Armitage P. The two-period cross-over clinical trial. *Br J Clin Pharmacol* 1979;8:7-20.
28 Murphy MB, Lewis PJ, Kohner E, Schumer B, Dollery CT. Glucose intolerance in hypertensive patients treated with diuretics: a fourteen-year follow-up. *Lancet* 1982;ii:1293-5.
29 Bengtsson C, Blohme G, Lapidus L, Lindquist O, Lundgren H, Nystrom E, *et al.* Do antihypertensive drugs precipitate diabetes? *BMJ* 1984;289: 1495-7.
30 Rapaport MI, Hurd HF. Thiazide-induced glucose intolerance treated with potassium. *Arch Intern Med* 1964;113:405-8.
31 Fajan SS, Floyd JC, Knopt RF, Rull J, Gunstche EM, Conn JW. Benzothiazidine suppression of insulin release from normal and abnormal islet cell tissue in man. *J Clin Invest* 1966;45:481-93.
32 Beardwood DM, Alden JS, Graham CA, Beardwood JT, Marble A. Evidence for a peripheral action of chlorothiazide in normal man. *Metabolism* 1965;14:561-7.
33 Bowen H, Moorehouse J. Glucose turnover and disposal in maturity onset diabetes. *J Clin Invest* 1973;52:3033-45.
34 Firth RG, Bell PM, Marsh HM, Hansen I, Rizza RA. Postprandial hyperglycemia in patients with non insulin dependent diabetes mellitus. Role of hepatic and extrahepatic tissues. *J Clin Invest* 1986;77:1525-32.
35 DeFronzo RA. Pathogenesis of type 2 (non-insulin dependent) diabetes mellitus: a balanced overview. *Diabetologia* 1992;35:389-97.
36 Gerich JE. Is muscle the major site of insulin resistance in type 2 (non-insulin-dependent) diabetes mellitus? *Diabetologia* 1991;34:607-10.
37 Grimm RH Jr, Leon AS, Hunninghake DB, Lenz K, Hannan P, Blackburn H. Effects of thiazide diuretics on plasma lipids and lipoproteins in mildly hypertensive patients: a double blind controlled trial. *Ann Intern Med* 1981;94:7-11.
38 Ames RP, Hill P. Elevation of serum lipids during diuretic therapy of hypertension. *Am J Med* 1976;61:748-57.

(Accepted 27 April 1994)

Exercise, smoking, and calcium intake during adolescence and early adulthood as determinants of peak bone mass

Matti J Välimäki, Merja Kärkkäinen, Christel Lamberg-Allardt, Kalevi Laitinen, Esko Alhava, Jorma Heikkinen, Olli Impivaara, Pekka Mäkelä, Juni Palmgren, Riitta Seppänen, Ilkka Vuori, and the Cardiovascular Risk in Young Finns Study Group

Abstract

***Objective*—To evaluate the contribution to peak bone mass of exercise, smoking, and calcium intake in adolescents and young adults.**

***Design*—Prospective cohort study with end point measurement (bone mineral density) after 11 years' follow up for lifestyle.**

***Setting*—Five university hospital clinics.**

***Subjects*—264 (153 females, 111 males) subjects aged 9 to 18 years at the beginning of the follow up and 20 to 29 years at the time of measurement of bone mineral density.**

***Main outcome measure*—Bone mineral density of lumbar spine and femoral neck by dual energy x ray absorptiometry; measures of physical activity and smoking and estimates of calcium intake repeated three times during follow up.**

***Results*—In the groups with the lowest and highest levels of exercise the femoral bone mineral densities (adjusted for age and weight) were 0·918 and 0·988 g/cm² for women (P=0·015, analysis of covariance) and 0·943 and 1·042 g/cm² for men (P=0·005), respectively; at the lumbar spine the respective values were 1·045 and 1·131 (P=0·005) for men. In men the femoral bone mineral densities (adjusted for age, weight, and exercise) were 1·022 and 0·923 g/cm² for the groups with the lowest and highest values of smoking index (P=0·054, analysis of covariance). In women the adjusted femoral bone mineral density increased by 4·7% together with increasing calcium intake (P=0·089, analysis of covariance). In multiple regression analysis on bone mineral density of the femoral neck, weight, exercise, age, and smoking were independent predictors for men; with weight, exercise, and age for women. These predictors together explained 38% of the variance in bone mineral density in women and 46% in men. At the lumbar spine, weight, smoking, and exercise were predictors for men; and only weight for women.**

***Conclusions*—Regular exercise and not smoking is important in achieving maximal peak bone mass in adolescents and young adults.**

Correspondence to:
Dr M Välimäki, Third Department of Medicine, Helsinki University Central Hospital, FIN-00290 Helsinki, Finland.

BMJ 1994;309:230-5

Introduction

Peak bone mass in young adults is a major determinant of bone mass later in life.[1] Thus even though most osteoporotic fractures occur in elderly people, the risk of osteoporosis may be profoundly affected by events in early life. Genetic factors play a major part in the determination of peak bone mass, accounting for up to 80% of the variance,[2] but 20% or more may be due to environmental factors, including exercise, smoking, and calcium intake.

The role of these lifestyle factors in adolescents and young adults as determinants of peak bone mass has, however, been examined in only a few studies,[3-10] and environmental factors during youth were estimated by retrospective surveys,[3 5-7] an extremely crude method of assessment. Furthermore, bone mineral content or density was usually measured only at radial or vertebral sites[3 4 6-8] and not at the femoral sites, which are most important with regard to osteoporotic hip fractures later in life. To date, the role of calcium intake in achieving peak bone mass has been most convincingly supported by prospective interventional studies[8 10] and that of exercise in a cross sectional study of children aged 5-14.[9] The effect of smoking has not been studied in these age groups.

The cardiovascular risk in young Finns study was originally designed to obtain information on risk factors for coronary heart disease and their determinants in childhood. The study began in 1980 with

Third Department of Medicine, University of Helsinki, Helsinki
Matti J Välimäki, *endocrinologist*

Minerva Foundation Institute for Medical Research, Helsinki
Merja Kärkkäinen, *research fellow*
Christel Lamberg-Allardt, *senior fellow*
Riitta Seppänen, *research fellow*

Research Unit of Alcohol Diseases, University of Helsinki, Helsinki
Kalevi Laitinen, *research fellow*

Department of Surgery, Kuopio University Central Hospital, Kuopio
Esko Alhava, *professor*

Osteoporosis Clinic, Deaconess Institute of Oulu, Oulu
Jorma Heikkinen, *senior lecturer*

Research and Development Unit, Social Insurance Institution, Turku
Olli Impivaara, *senior research officer*

Department of Obstetrics and Gynaecology, University of Helsinki, Helsinki
Pekka Mäkelä, *senior lecturer*

National Public Health Institute, Helsinki
Juni Palmgren, *statistician*

UKK Institute for Health Promotion Research, Tampere
Ilkka Vuori, *professor*

3596 male and female subjects, aged 3 to 18. For over 10 years information was collected on variables such as diet, exercise, and smoking. In 1991 we measured bone mineral density of the lumbar spine and the femoral neck in 264 of these subjects, aged 20 to 29, and related it to the prospectively collected data on their lifestyle.

Subjects and methods

CARDIOVASCULAR RISK IN YOUNG FINNS STUDY

In the cardiovascular risk in young Finns study Finnish children and adolescents from different parts of Finland with varying degrees of risk for coronary heart disease were recruited. They came from different socioeconomic backgrounds and living conditions. Sampling took place in the five Finnish cities with medical schools—namely, Helsinki, Kuopio, Oulu, Tampere, and Turku—and in selected rural communities in their vicinity by using the Social Insurance Institution's population register of non-institutionalised people born in 1962, 1965, 1968, 1971, 1974, and 1977 and living in the community in question. The study was started in 1980 with 3596 participants, who were then aged from 3 to 18. Only half the subjects had dietary interviews at the beginning of the study. These interviews were repeated in 1986, when the participants were 9 to 24 years old. Data on exercise and smoking were collected from all participants in the years 1980 and 1986.

SUBJECTS IN BONE MINERAL DENSITY STUDY

From the original study we invited 671 subjects, all at least 20 years old, to participate in the bone mineral density study, which was accepted by the ethics committee of Helsinki University Central Hospital; 345 (51%) agreed to participate. After exclusion of eight subjects with diseases known to affect calcium and bone metabolism and 73 with incomplete previous data on exercise, and smoking, 264 participants were finally accepted for the study, 111 men and 153 women. They represented four age cohorts in the original study, born in the years 1962, 1965, 1968, and 1971, and were 29, 26, 23, and 20 at the time of the measurement of bone mineral density in 1991. In Oulu and Tampere only the youngest age cohort was studied. (For the number of subjects in each age cohort see table I.)

Of the 407 subjects who either did not participate or were excluded, 212 were men and 195 women. In 1986 they did not differ from the participants with regard to weight, height, calcium intake, or smoking, but they were physically less active ($P=0{\cdot}004$, analysis of variance) than those finally enrolled.

STUDY DESIGN

Each participant underwent measurement of bone mineral density of the lumbar spine and hip and described current calcium intake, exercise, and smoking habits. Weight and height were recorded.

MEASUREMENT OF BONE MINERAL DENSITY

Bone mineral density was measured at the femoral neck and from the second to the fourth lumbar vertebrae by using dual energy x ray absorptiometry (DEXA). A Hologic QDR-1000 (Hologic, Waltham, United States) densitometer was used in Helsinki; Lunar DPX (Lunar Radiation, Madison, Wisconsin) equipment in Kuopio and Oulu; and Norland XR-26 densitometers (Norland, Fort Atkinson, Wisconsin) in Turku and Tampere. The coefficient of variation for precision of the bone mineral density measurements in the lumbar vertebrae and femoral neck varied from 0·9% to 1·7% and from 1·1% to 2·5%, respectively, for the densitometers used.

To combine bone mineral density values obtained from different manufacturers' instruments, data produced by Hologic and Lunar densitometers were adjusted to Norland values by using the following linear regression equations. For L2-L4: with Hologic adjusted$=0{\cdot}984\times$original$+0{\cdot}039$ and with Lunar adjusted$=1{\cdot}027\times$original$-0{\cdot}136$; for the femoral neck: with Hologic adjusted$=1{\cdot}126\times$original$-0{\cdot}066$ and with Lunar adjusted$=0{\cdot}907\times$original$-0{\cdot}004$.

To produce these equations nine healthy women with different bone mineral densities were measured with densitometers of the three different brands.[11] Values produced by densitometers from the same manufacturer (in Kuopio and Oulu from Lunar and in Turku and Tampere from Norland) were practically identical and their data were combined without any correction.

ESTIMATION OF LIFESTYLE FACTORS

Physical activity was estimated by asking about weekly frequency of physical activity exceeding 30 minutes per performance.[12] This same question was asked in 1980, 1986, and 1991. In subsequent calculations having two or more weekly sessions was called 1 and less than two sessions was called 0. The sum parameter of exercise—that is, the sum of the three years' answers—ranging from 0 to 3, was calculated for each subject for correlations with bone mineral density.

Smoking behaviour was estimated in 1980, 1986, and 1991.[13] The answer "yes" to daily smoking was called 1 and the answer "no" 0. The sum of the three answers was determined for each subject to be used in subsequent calculations.

In 1980 and 1986 information on food consumption was collected from a 48 hour recall interview in which detailed information was obtained on the type and amount of food eaten by the subject during the two days before the interview.[14] Dietary calcium intake was calculated by using special computer programs.[14] In 1991 a food frequency method was used for the same purpose. The mean calcium intake for 1980, 1986, and 1991 was calculated. The use of calcium supplement was negligible.

STATISTICAL ANALYSIS

Results are expressed as means (SD). Analysis of variance was used to study comparability of the age cohorts and to examine the significance of differences in bone mineral densities between groups by age or sex. To examine the relation between bone mineral density and other variables, Pearson product moment correlation coefficients and their significances were calculated. In evaluating dependence of bone mineral density on different lifestyle factors analysis of covariance was used.

Covariates selected were those previously considered strong confounding factors of bone mineral density and which were also found to be significant determinants of bone mineral density in the present study (age and weight) or which were found to have a significant association with bone mineral density in the present study and which could theoretically confuse results of calcium intake, smoking, and bone mineral density (exercise). Furthermore, multiple linear stepwise regression analysis was used to determine significant predictors of bone mineral density. Because body weight and scan area have an effect on the measured bone mineral density and because different brands of densitometers were used, body weight, scan area, brand of densitometer, and interaction of brand with body weight (brand × weight) and with scan area (brand × area) were first entered into the multiple regression model. This was done to adjust for their effect on bone mineral density. The analysis was also done without these forced variables. BMDP statistical

TABLE I—*Basic characteristics (mean (SD)) of subjects in four age cohorts*

Birth year	No of women	No of men	Body weight (kg) in 1991		Height (cm) in 1991		Mean calcium intake* (mg/day)		Smoking† (score 0-3)		Exercise† (score 0-3)	
			Women	Men	Women	Men	Women	Men	Women	Men	Women‡	Men§
1962	38	21	60 (9·7)	76 (10·4)	165 (6·0)	179 (6·1)	996 (262)	1444 (438)	1·03 (1·07)	0·85 (0·81)	1·33 (1·02)	1·52 (1·12)
1965	24	25	63 (8·6)	76 (10·4)	167 (5·6)	181 (5·7)	1083 (256)	1384 (344)	1·17 (0·76)	1·24 (1·09)	1·59 (0·90)	1·64 (1·07)
1968	34	23	59 (7·6)	75 (12·5)	166 (5·9)	179 (6·6)	1038 (340)	1441 (392)	0·91 (0·84)	1·18 (1·01)	1·97 (1·00)	1·87 (0·81)
1971	57	42	59 (8·9)	76 (10·5)	167 (5·1)	180 (5·8)	1049 (259)	1463 (488)	0·89 (0·76)	0·93 (0·79)	1·89 (0·95)	2·17 (0·80)

*Mean of intake in 1980, 1986, and 1991. †Sum parameter based on interviews in 1980, 1986, and 1991 (see text). ‡P=0·025, §P=0·041 for differences between age cohorts, analysis of variance.

TABLE II—*Mean (SD) bone mineral density (g/cm²) at lumbar spine (L2-L4) and hip in four age cohorts. Data adjusted to Norland values (see text)*

Birth year	L2-L4			Hip		
	Women	Men	P value for difference between sexes	Women*	Men†	P value for difference between sexes
1962	1·050 (0·137)	1·098 (0·128)	0·19	0·885 (0·122)	0·930 (0·110)	0·16
1965	1·063 (0·117)	1·099 (0·117)	0·28	0·918 (0·128)	0·994 (0·139)	0·05
1968	1·053 (0·111)	1·100 (0·131)	0·15	0·937 (0·123)	1·030 (0·162)	0·02
1971	1·049 (0·100)	1·108 (0·151)	0·02	0·939 (0·103)	1·077 (0·152)	0·00

*P=0·132, †P=0·002 for differences between age cohorts, analysis of variance.

TABLE III—*Mean (SD) bone mineral density (g/cm²) at lumbar spine and hip at various levels of sum parameter of exercise (see text). Both non-adjusted and adjusted (for age and weight) values are given*

Site of measurement	Sum parameter of exercise (score)			
	0 (18 women, 10 men)	1 (41 women, 29 men)	2 (47 women, 37 men)	3 (39 women, 34 men)
Non-adjusted L2-L4:				
Women	1·050 (0·134)	1·028 (0·100)	1·056 (0·114)	1·058 (0·103)
Men‡	1·071 (0·102)	1·058 (0·144)	1·088 (0·111)	1·162 (0·140)
Non-adjusted hip:				
Women†	0·866 (0·087)	0·886 (0·111)	0·933 (0·123)	0·962 (0·108)
Men‡‖	0·925 (0·105)	0·984 (0·152)	1·007 (0121)	1·097 (0·166)
Adjusted L2-L4:				
Women	1·082 (0·107)	1·054 (0·106)	1·079 (0·106)	1·079 (0·107)
Men‖	1·045 (0·132)	1·022 (0·124)	1·054 (0·124)	1·131 (0·125)
Adjusted hip:				
Women§	0·918 (0·101)	0·924 (0·100)	0·966 (0·100)	0·988 (0·100)
Men‖	0·943 (0·137)	0·930 (0·128)	0·951 (0·129)	1·042 (0·130)

*P=0·010, †P=0·004, ‡P=0·001, analysis of variance, §P=0·015, ‖P=0·005, analysis of covariance.

software in a VAX/VMS minicomputer was used in the analyses.

Results

BASIC CHARACTERISTICS

No significant differences between the age cohorts in weight and height existed in 1991. Mean calcium intake was also similar, varying from 996 mg to 1083 mg daily for women and from 1384 mg to 1463 mg for men. On the basis of the sum parameter daily smoking was equally common in the four age cohorts and for both sexes. The two youngest age groups of women (P=0·025, analysis of variance) and men (P=0·041, analysis of variance) took the most exercise (table I).

DEPENDENCE OF BONE MINERAL DENSITY ON AGE AND WEIGHT

Bone mineral density at the lumbar spine did not change with age, but for both sexes bone mineral density at the femoral neck was higher the younger the age cohort (men P=0·002, women P=0·132, analysis of variance; table II).

Dependence of hip bone mineral density on weight was found in all the age cohorts and for both sexes (r values for all women 0·43, $P<0·001$, for all men 0·32, $P<0·001$). At the lumbar spine the relation between bone mineral density and weight was less evident in individual age cohorts, but after combination of all the data for both sexes it was significant ($r=0·29$, $P<0·001$ for women; $r=0·27$, $P<0·01$ for men). When the rough data presented in table II were corrected for body weight (analysis of covariance) the inverse correlation between age and bone mineral density of the hip was significant for both sexes ($r=0·24$, P=0·002 for women; $r=0·37$, $P<0·001$ for men).

DEPENDENCE OF BONE MINERAL DENSITY ON EXERCISE

At the hip, bone mineral density adjusted for weight (analysis of covariance) correlated positively with the sum parameter of exercise in the four age cohorts for both sexes and at the lumbar spine in men. When all the age groups were combined significant relations were found at the hip for women ($r=0·30$, 95% confidence interval 0·15 to 0·44, $P<0·001$) and men ($r=0·36$, 0·19 to 0·51, $P<0·001$). At the lumbar spine the respective correlation coefficient for men was 0·29 (0·11 to 0·45, $P<0·01$).

When the subjects were divided into four groups in which the sum parameter value varied from 0 to 3, age and weight adjusted bone mineral density at the hip was higher the greater the activity index (analysis of covariance; P=0·015 for women; P=0·005 for men; table III). At the lumbar spine the same was true for men (P=0·005). In the groups with the lowest and highest index values the femoral bone mineral densities (adjusted for age and weight) were 0·918 (SD 0·101) and 0·988 (0·100) g/cm² for women (percentage difference 7·6%) and 0·943 (0·137) and 1·042 (0·130) g/cm² for men (percentage difference 10·5%), respectively; at the lumbar spine the respective values were 1·045 (0·132) and 1·131 (0·125) g/cm² (percentage difference 8·2%) for men.

DEPENDENCE OF BONE MINERAL DENSITY ON SMOKING

Men in all four age cohorts showed inverse correlations between bone mineral density adjusted for weight and the sum parameter of smoking at the lumbar spine and the hip. Correlation coefficients ranged from −0·18 to −0·46 at the lumbar spine and from −0·10 to −0·63 at the femoral neck. For all men combined, the respective r values were −0·27 (−0·44 to −0·09, $P<0·01$) and −0·28 (−0·44 to −0·10, $P<0·01$). Smoking and exercise were, however, slightly intercorrelated in men ($r=0·19$, P=0·056). We found no consistent association between bone mineral density and smoking in women.

When the men were divided into four groups with various levels of the sum parameter of smoking there was a trend to lower bone mineral density values (adjusted for age, weight, and exercise) at the higher levels of the smoking index (table IV). At the femoral neck this nearly reached significance (P=0·054, analysis of covariance), the bone mineral densities

(adjusted for age, weight, and exercise) being 1·022 (0·127) and 0·923 (0·128) g/cm² (percentage difference −9·7%) for the groups with the lowest and highest smoking indices.

DEPENDENCE OF BONE MINERAL DENSITY ON CALCIUM INTAKE

There was no consistent association between mean calcium intake and weight adjusted bone mineral density at the lumbar spine. At the femoral neck all correlations in the four age cohorts were positive in women. When the data for all women were combined the relation between mean calcium intake and bone mineral density for adjusted weight was significant (r=0·17, 0·01 to 0·32, $P<0·05$). Femoral bone mineral density (adjusted for age, weight, and exercise) increased from 0·919 (0·098) g/cm² in the group consuming less than 800 mg of calcium daily to 0·962 (0·099) g/cm² in those consuming 800-1200 mg (percentage difference 4·7%) but rose no further at higher intakes (P=0·089, analysis of covariance; table V). When the women were divided into two groups instead of three the femoral bone mineral densities for those with mean daily intake less or more than 800 mg were 0·919 (0·098) and 0·964 (0·098) g/cm² (P=0·028, analysis of covariance).

STEPWISE MULTIPLE LINEAR REGRESSION ANALYSIS

Relative importance of the predictor variables (age, weight, exercise, smoking, and calcium intake) to bone mineral status at each site was determined by stepwise multiple linear regression analysis. Body weight, brand of densitometer, scan area, and interaction of densitometer brand with body weight (brand × weight) and with scan area (brand × area) were first forced into the model. For bone mineral density at the femoral neck, weight, exercise, age, and smoking were independent predictors for men, whereas weight, exercise, and age were for women (table VI). These predictors together explained 38% of the variance in bone mineral density in women and 46% in men (table VI). At the lumbar spine, weight, smoking, and exercise were predictors for men, explaining 51% of the variance, but only weight for women. Calcium intake was an independent predictor of femoral bone mineral density in women only when the analysis was performed without the above mentioned forced variables.

TABLE IV—*Mean (SD) bone mineral density (g/cm²) at lumbar spine and hip at various levels of smoking index (see text). Both non-adjusted and adjusted (for age, weight, and exercise) values are given*

Site of measurement	Smoking index 0 (47 women, 64 men)	1 (67 women, 45 men)	2 (25 women, 20 men)	3 (9 women, 9 men)
Non-adjusted L2-L4:				
Women	1·045 (0·130)	1·069 (0·111)	1·026 (0·102)	1·054 (0·097)
Men*	1·138 (0·121)	1·107 (0·133)	1·055 (0·155)	1·032 (0·099)
Non-adjusted hip:				
Women	0·912 (0·114)	0·939 (0·117)	0·902 (0·104)	0·907 (0·159)
Men†	1·061 (0·156)	1·032 (0·131)	0·976 (0·170)	0·919 (0·143)
Adjusted L2-L4:				
Women	1·077 (0·107)	1·082 (0·108)	1·059 (0·109)	1·047 (0·109)
Men	1·108 (0·124)	1·060 (0·123)	1·034 (0·124)	1·029 (0·125)
Adjusted hip:				
Women	0·956 (0·100)	0·958 (0·101)	0·959 (0·102)	0·914 (0·102)
Men‡	1·022 (0·127)	0·963 (0·126)	0·940 (0·126)	0·923 (0·128)

*P=0·057, †P=0·036, analysis of variance, ‡P=0·054, analysis of covariance.

TABLE V—*Mean (SD) bone mineral density (g/cm²) at hip adjusted for age, weight, and exercise with various mean daily calcium intakes*

Sex	Daily calcium intake (mg) <800	800-1200	>1200
Women*	0·919 (0·098) n=30	0·962 (0·099) n=65	0·966 (0·098) n=41
Men	0·963 (0·132) n=5	0·970 (0·133) n=27	0·976 (0·131) n=71

*P=0·089, analysis of covariance.

TABLE VI—*Stepwise regression analysis on bone mineral density at lumbar spine and hip. Body weight, brand of densitometer, scan area, and interaction of densitometer brand with body weight (brand × weight) and with scan area (brand × area) were first forced into model (primary steps)*

Detail	L2-L4 Step	L2-L4 r	L2-L4 r^2	Hip Step	Hip r	Hip r^2
			Women			
Primary steps		0·62	0·39		0·50	0·25
Step 1				Exercise	0·59	0·35
Step 2				Age	0·62	0·38
			Men			
Primary steps		0·66	0·44		0·49	0·24
Step 1	Smoking	0·70	0·49	Exercise	0·62	0·38
Step 2	Exercise	0·72	0·51	Age	0·66	0·43
Step 3				Smoking	0·68	0·46

Discussion

In this study of the lifestyle of 264 young adults exercise as measured over the past 10 years emerged as the most important determinant of bone mineral density. It significantly contributed to bone mineral density of the femoral neck in both sexes and to that of lumbar bone in men. Smoking as measured over the same period had a negative effect in men, and calcium intake beneficially affected bone mineral density of the femoral neck in women.

In contrast with many previous retrospective studies[3 5-7] the value of the present investigation rests on its prospective structure; data on lifestyle of the participants were collected over 10 years before any measurements of bone mineral density. The fact that the original study was planned for other purposes resulted, however, in some weaknesses in our investigation. The questions regarding exercise and smoking were qualitative rather than quantitative so it was not possible to draw any conclusions about the quality or frequency of physical activity most beneficial for bone and about the number of cigarettes daily which prove deleterious. The quite low participation rate of 51% is explained by the long duration of the original study and by the fact that when grown up several subjects had changed their place of residence. As the non-participants were less active than the participants with a higher participation rate the relation between bone mineral density and exercise may have been even stronger than found.

PEAK BONE MASS

We chose for measurements of bone mineral density subjects who in 1991 were 20 to 29 years old since we deemed them to best represent peak bone mass. The generally accepted notion, based on cross sectional data, has been that in both men and women bone mass continues to accumulate substantially at all skeletal sites until the fourth decade.[15] In adolescent and adult women, however, bone mineral density of the trabecular vertebrae measured by quantitative computed tomography reached its peak near the end of the second decade, at the time of cessation of longitudinal growth.[16] In another study peak bone mass was achieved for the lumbar spine and femoral neck in women as early as 14 to 15 years and in men at 17 to 18.[17] In fact femoral neck bone mineral density at age 17 to 18 was 105% and 107% of the mean values recorded in 20 to 35 year old women and men.[17] This accords well with our finding on the declining femoral neck bone mineral density from age 20 to 29.

Like us, Bonjour *et al* did not find any age dependence in either sex for lumbar spine bone mineral density from 18 to 35 years of age.[17] Recently, however, Recker *et al* pointed out in a longitudinal prospective study of 156 healthy college aged women that gain in bone mass occurs during the third decade of life; this was true for the forearm and the lumbar

spine as well as for the total body bone mass.[18] Differences between these studies in timing of peak bone mass may well be due to the lifestyle factors that we studied and perhaps due to some others—for example, alcohol consumption.

LIFESTYLE FACTORS AND PEAK BONE MASS

After adjustment of bone mineral density values for weight and age, regular exercise (two or more 30 minute sessions weekly) still seemed to be an important determinant of peak bone mass in the femoral neck for both sexes and in the lumbar spine for men. Bone mineral density correlated highly significantly with the index of physical activity, the highest values being clustered in the top groups for physical activity; and in stepwise regression analysis exercise also emerged as an independent predictor of bone mass.

These findings are in keeping with those in the study by Slemenda *et al* of 118 children aged 5-14 who showed consistent, positive associations between bone mineral density in the radius, spine, and hip and most physical activities.[9] As in our study the relation was weaker for the lumbar spine than for the femoral neck.[9] In a study of 84 children and adolescents aged 6 to 19 years significantly higher femoral neck bone mineral densities were found in subjects who were physically active.[19]

Smoking had a deleterious effect in men with inverse correlations between smoking and bone mineral density and clustering of the lowest bone mineral densities in groups of subjects with the highest scores on the smoking index. Although smoking and exercise were inversely correlated, smoking was an independent predictor of bone mass in men. Similar results were not seen in women, probably because our smoking index did not take into account the number of cigarettes smoked daily; women achieved high index values despite less smoking than men. Previous studies of the effect of smoking in respective age groups are not available.

Calcium intake contributed only modestly to femoral neck bone mineral density in our women and its significance disappeared after adjustments for scan area and brand of densitometer. That no effect was observed for men was possibly because of their high mean calcium intake of 1400 mg daily. This apparently exceeded the intake threshold—that is, the calcium intake below which skeletal accumulation of calcium varies with intake and above which it remains constant.[20] In women femoral neck bone mineral density seemed to stop increasing when mean calcium intake exceeded 1200 mg daily. Originating from adolescent and young adult women, this finding supports the recent revision of recommended dietary allowances for the United States, in which recommended intake of 1200 mg for adolescents was extended up to age 24.[21]

Most convincingly the role of calcium intake as a determinant of peak bone mass has been pointed out by interventional studies. Among 22 pairs of prepubertal identical twins a rise in mean calcium intake from 900 mg to 1600 mg augmented increases in bone mineral density at radial sites, in the lumbar spine, and also at two of three femoral sites measured.[10] Furthermore, Matkovic *et al* reported a positive trend in bone growth at radial sites and in the lumbar spine by calcium supplementation in pubertal girls.[8]

When we combined the age cohorts the correlation coefficients between separate lifestyle factors and bone mineral density reached values up to 0·36, which may seem quite low. Given errors in estimation of lifestyle factors, especially of calcium intake,[22] and the fact that up to 80% of the variation in bone mineral density may be explained by genetic factors,[2] such r values are at least as high as expected. It has been estimated that if both bone mineral density and calcium intake have been determined precisely, calcium intake would exhibit a population level value for r of only 0·224.[23] Compatible with strong genetic influence,[2] after primary steps in multiple regression analysis lifestyle factors added r^2 values with a percentage of 7-22. All possible factors, including weight and age, explained up to 51% of the variation in bone mineral density.

Our results suggest that getting regular exercise, avoiding smoking, and optimising calcium intake are all important in the acquisition of maximum peak bone mass. The advantage gained may persist throughout adult life.

Clinical implications

- Peak bone mass in young adults is a major determinant of bone mass later in life and consequently also a determinant of risk of osteoporosis
- Both genetic and environmental factors determine peak bone mass
- Bone mineral density at the femoral neck was 7·6% to 10·5% higher in subjects with most regular exercise compared with those with least exercise
- In men regular smoking reduced femoral neck bone mineral density by 9·7% as compared with non-smokers
- In women consumption of calcium 800-1200 mg daily increased bone mineral density at the femoral neck by 4·7% compared with those who consumed less

This study was supported by a grant from the Academy of Finland, Helsinki.

Appendix

The following people and study centres participated in the cardiovascular risk in young Finns study.

Principal investigators: Hans K Åkerblom, Children's Hospital, II department of paediatrics, University of Helsinki; Matti Uhari, department of paediatrics, University of Oulu; Jorma Viikari, department of medicine, University of Turku.

Local investigators: Matti Dahl, department of paediatrics, University of Turku; Erkki Pesonen, first department of paediatrics, University of Helsinki; Matti Pietikäinen, department of paediatrics, University of Kuopio; Matti Salo, department of paediatrics, University of Tampere.

Other special investigators: Arpo Aromaa, Social Insurance Institution, Helsinki; Lasse Kannas, department of health sciences, University of Jyväskylä; Liisa Keltikangas-Järvinen, department of psychology, University of Helsinki; Vesa Kuusela, Statistical Central Bureau, Helsinki; Kalevi Pyörälä, department of medicine, University of Kuopio; Tapani Rönnemaa, department of medicine, University of Turku; Leena Räsänen, department of applied chemistry and microbiology, Division of Nutrition, University of Helsinki; Seppo Sarna, department of public health, University of Helsinki; Asko Seppänen, Rehabilitation Research Centre of the Social Insurance Institution, Turku; and Risto Telama, department of physical education, University of Jyväskylä, Finland.

1 Hui SL, Slemenda CW, Johnston CC Jr. The contribution of bone loss to postmenopausal osteoporosis. *Osteoporosis International* 1990;1:30-4.
2 Slemenda CW, Christian JC, Williams CJ, Norton JA, Johnston CC Jr. Genetic determinants of bone mass in adult women: a reevaluation of the twin model and the potential importance of gene interaction on heritability estimates. *J Bone Miner Res* 1991;6:561-7.
3 Sandler RB, Slemenda CW, LaPorte RE, Cauley JA, Schramm MM, Barresi ML, *et al.* Postmenopausal bone density and milk consumption in childhood and adolescence. *Am J Clin Nutr* 1985;42:270-4.
4 Sowers MF, Wallace RB, Lemke JH. Correlates of forearm bone mass among women during maximal bone mineralization. *Prev Med* 1985;14:585-96.

5 Angus RM, Sambrook PN, Pocock NA, Eisman JA. Dietary intake and bone mineral density. *Bone Miner* 1988;4:265-77.
6 Cauley JA, Gutai JP, Kuller LH, LeDonne D, Sandler RB, Sashin D, *et al.* Endogenous estrogen levels and calcium intakes in postmenopausal women. Relationships with cortical bone measures. *JAMA* 1988;260:3150-5.
7 Picard D, Ste-Marie LG, Coutu D, Carrier L, Chartrand R, Lepage R, *et al.* Premenopausal bone mineral content relates to height, weight and calcium intake during early adulthood. *Bone Miner* 1988;4:299-309.
8 Matkovic V, Fontana D, Tominac C, Goel P, Chesnut III CH. Factors that influence peak bone mass formation: a study of calcium balance and the inheritance of bone mass in adolescent females. *Am J Clin Nutr* 1990;52: 878-88.
9 Slemenda CW, Miller JZ, Hui SL, Reister TK, Johnston CC Jr. Role of physical activity in the development of skeletal mass in children. *J Bone Miner Res* 1991;6:1227-33.
10 Johnston CC Jr, Miller JZ, Slemenda CW, Reister TK, Hui S, Christian JC, *et al.* Calcium supplementation and increases in bone mineral density in children. *N Engl J Med* 1992;327:82-7.
11 Vainio P, Ahonen E, Leinonen K, Sievänen H, Koski E. Comparison of instruments for dual-energy x-ray bone mineral densitometry. *Nucl Med Commun* 1992;13:252-5.
12 Telama R, Viikari J, Välimäki I, Siren-Tiusanen H, Åkerblom HK, Uhari M, *et al.* Atherosclerosis precursors in Finnish children and adolescents. X. Leisure-time physical activity. *Acta Paediatr Scand* 1985;318(suppl):169-80.
13 Byckling T, Sauri T. Atherosclerosis precursors in Finnish children and adolescents. XII. Smoking behaviour and its determinants in 12-18 year old subjects. *Acta Paediatr Scand* 1985;318(suppl):195-203.
14 Räsänen L, Laitinen S, Stirkkinen R, Kimppa S, Viikari J, Uhari M, *et al.* Composition of the diet of young Finns in 1986. *Ann Med* 1991;23:73-80.
15 Parfitt AM. Bone remodelling: relationship to the amount and structure of bone, and the pathogenesis and prevention of fractures. In: Riggs BL, Melton III LJ, eds. *Osteoporosis, etiology, diagnosis, and management.* New York: Raven Press, 1988.
16 Gilsanz V, Gibbens DT, Carlson M, Boechat MI, Cann CE, Schulz EE, *et al.* Peak trabecular vertebral density: a comparison of adolscent and adult females. *Calcif Tissue Int* 1988;43:260-2.
17 Bonjour J-P, Theintz G, Buchs B, Slosman D, Rizzoli R. Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. *J Clin Endocrinol Metab* 1991;73:555-63.
18 Recker RR, Davies KM, Hinders SM, Heaney RP, Stegman MR, Kimmel DB. Bone gain in young adult women. *JAMA* 1992;268:2403-8.
19 Kröger H, Kotaniemi A, Vainio P, Alhava E. Bone densitometry of the spine and femur in children by dual-energy x-ray absorptiometry. *Bone Miner* 1992;17:75-85.
20 Matkovic V, Heaney RP. Calcium balance during human growth: evidence for threshold behaviour. *Am J Clin Nutr* 1992;55:992-6.
21 National Research Council. *Recommended dietary allowances.* 10th ed. Washington DC; National Academy Press, 1989.
22 Heaney RP, Davies M, Recker RR, Packard PT. Long-term consistency of nutrient intakes in humans. *J Nutr* 1990;120:869-75.
23 Avioli LV, Heaney RP. Calcium intake and bone health. *Calcif Tissue Int* 1991;48:221-3.

(Accepted 20 April 1994)

Reliability of ultrasonography in identification of reflux nephropathy in children

Eira Stokland, Mikael Hellström, Sverker Hansson, Ulf Jodal, Anders Odén, Bo Jacobsson

Abstract

***Objective*—To assess the ability of ultrasonography to identify reflux nephropathy in children after urinary tract infection.**

***Design*—Ten experienced radiologists performed a total of 240 ultrasonographic examinations of kidneys in a one day study. The examiners were unaware of the results of previous radiological and clinical examinations and of the proportions of normal and abnormal kidneys. Urography was used as method of reference, supported by static renal scintigraphy (dimercaptosuccinic acid labelled with technetium-99m) in half of the cases.**

***Setting*—Outpatient radiology department.**

***Subjects*—25 children aged 2-16 years (20 kidneys with and 30 kidneys without renal scarring).**

***Main outcome measures*—Renal scarring. Overall size and length of kidneys. Sensitivity and specificity including receiver operator characteristics and variation between observers.**

***Results*—With renal scarring as the diagnostic criterion and including cases classified as abnormal, probably abnormal, and uncertain the sensitivity of ultrasonography was 54% (specificity 80%). Addition of reduced renal size as a diagnostic criterion increased the sensitivity to 64% (specificity 79%). There were, however, wide variations between observers, with sensitivity ranging between 40% and 90% (specificity 94% to 65%).**

***Conclusions*—Because of its low sensitivity and specificity and poor agreement between observers, ultrasonography cannot be generally recommended for the detection of reflux nephropathy after urinary tract infection in children.**

Department of Paediatric Radiology, East Hospital, S-416 85 Gothenburg, Sweden
Eira Stokland, *consultant radiologist*
Bo Jacobsson, *senior lecturer*

Department of Radiology, Sahlgrenska Hospital, Gothenburg, Sweden
Mikael Hellström, *senior lecturer*

Department of Paediatrics, East Hospital, Gothenburg, Sweden
Sverker Hansson, *consultant paediatrician*
Ulf Jodal, *senior lecturer*
Anders Odén, *medical statistician*

Correspondence to:
Dr Stokland.

BMJ 1994;309:235-9

Introduction

Urinary tract infection is one of the most common bacterial infections in children. At 7 years of age 135 (7·9%) of 1719 girls and 31 (1·7%) of 1834 boys had had symptomatic urinary tract infection, verified by bacterial culture.[1] As a consequence of renal infection in childhood 10-20% of children develop scarring or reflux nephropathy,[2] which is the term often used for the permanent renal damage associated with infection.

Once renal scarring has developed and is recognised several diagnostic and preventive measures need to be instituted. As scarring is commonly associated with reflux additional radiological studies are indicated to detect reflux, which may require an operation or treatment with long term prophylactic antibiotics. Scarring also indicates follow up renal imaging studies to detect progression. Recurrent attacks of pyelonephritis require early treatment to avoid progressive or new renal scarring. Furthermore, patients with scarring will need long term follow up of blood pressure and renal function[3] as well as increased attention during pregnancy to detect toxaemia.

There are various patterns of reflux nephropathy, including classical focal scars and generalised decrease of renal size or growth retardation.[4] For the detection of reflux nephropathy urography has traditionally been used. Recently static renal scintigraphy (dimercaptosuccinic acid labelled with technetium-99m) has also been used to identify changes in acute pyelonephritis[5,6] and permanent renal scarring.[7-9]

Ultrasonography is commonly used in the primary investigation of children with urinary tract infection because of its ability to detect major malformations and dilatation of the urinary tract[10-12] and because of its widespread availability, relatively low cost, and absence of side effects. There is, however, disagreement about its usefulness in detecting reflux nephropathy. Some authors consider ultrasonography sufficient,[13-15] and a recently published textbook states that ultrasonography can be used to recognise easily the patterns of reflux nephropathy.[16] Other authors find it necessary to add urography or renal scintigraphy.[9,17,18]

Ultrasonography differs from other radiological techniques in that interpretation is done "live"—that is, the diagnosis is based on the examiner's impressions on the monitor while the patient is examined. Although film documentation is usually done by the examiner, this is of limited or no diagnostic value to others, and second opinions on ultrasonography films are of little help in most cases. The outcome is thus strongly related to the skill of the examiner, which must be considered in the evaluation of the efficacy of ultrasonography in a clinical test.

Although the shortcomings of ultrasonography in