ADOLESCENT OBESITY: IS IT BAD FOR THE BONES

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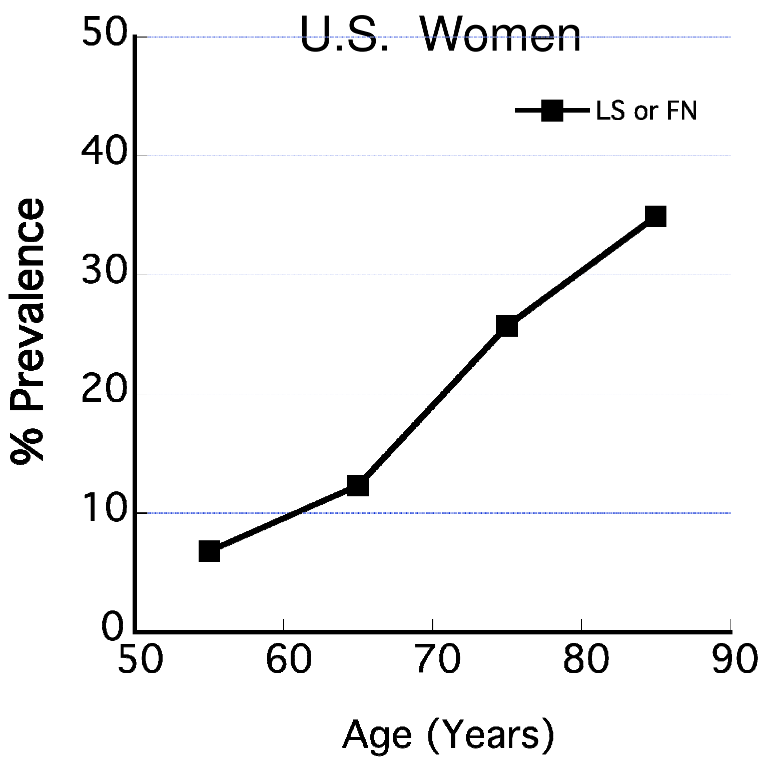
SCOPE OF THE PROBLEM - OBESITY

- An estimated 1.5 billion people were obese in the year 2008 worldwide (WHO 2011)
- In 2011-2014 the U.S. obesity prevalence was 36.5% of the adult population, and 20.5% of adolescents, 12-19y (Ogden et al NCHS Data Brief, no. 219, 2015)
- In 2012-13, prevalence of adult obesity in Argentina was 20.8%, and among adolescents, 13-15y, the prevalence was 5.9%, respectively (Galante et al. Rev Argent Cardiol 2016;84:126-132)

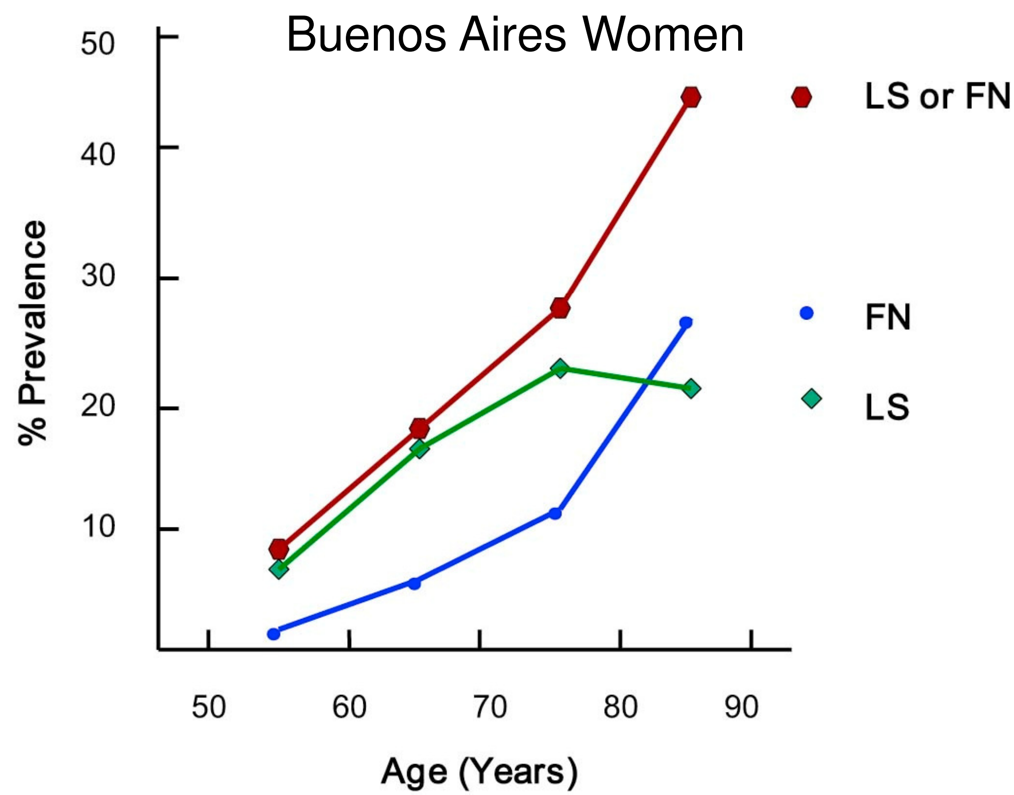
SCOPE OF THE PROBLEM - OSTEOPOROSIS

- Osteoporosis is a “silent disease”, compared to the high visibility of obesity.

PREVALENCE OF OSTEOPOROSIS IN WOMEN IN BUENOS AIRES AND THE U.S.



Wright et al. JBMR 29(11) 2520–26, 2014



Mautalen et al. J Clin Dens19 (4): 471-476, 2016

SCOPE OF THE PROBLEM

- Osteoporosis is a "silent disease", compared to the high visibility of obesity.
- Neither obesity nor osteoporosis is considered to be a part of normal aging
- Lifestyle/behavioral factors associated with obesity are risk factors for poor bone accretion
  - Low levels of physical activity
  - Poor diet quality: calcium intake, fruit and vegetable intake

POTENTIAL NEGATIVE EFFECTS OF OBESITY ON BONE ACCRETION?

- Complications of obesity present risk factors for bone accretion
  - Inflammation
  - Insulin resistance and other endocrine issues
  - Non-alcoholic fatty liver disease
  - Depression

POTENTIAL POSITIVE EFFECTS OF OBESITY ON BONE ACCRETION

- Earlier puberty and advanced skeletal maturation are common in obesity. These are associated with greater bone density

- Weight-bearing physical activity stimulates larger bone size in obese children because of their greater body weight

- Is larger bone size adequate to meet stresses of excess weight?

EVIDENCE FROM ADULTS

ASSOCIATION OF BMD AND BMI IN ADULTS

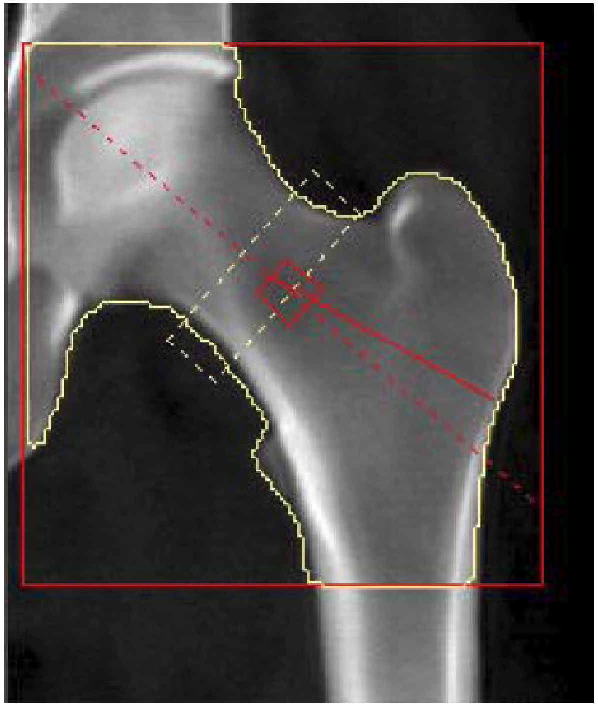
Associations of Body Mass Index With Incident Fractures and Hip Structural Parameters in a Large Canadian Cohort

Jian Shen, William D. Leslie, Carrie M. Nielson, Sumit R. Majumdar, Suzanne N. Morin, and Eric S. Orwoll (J Clin Endocrinol Metab 101: 476–484, 2016

- Dual energy x-ray absorptiometry measures of areal-BMD and bone strength
- Women (n=51,313) and men (n=4,689) aged 50 years or older in Canada with Health Service Records
- Assessed for incident major osteoporotic fractures (MOFs) over 6.2y in women and 4.7y in men)

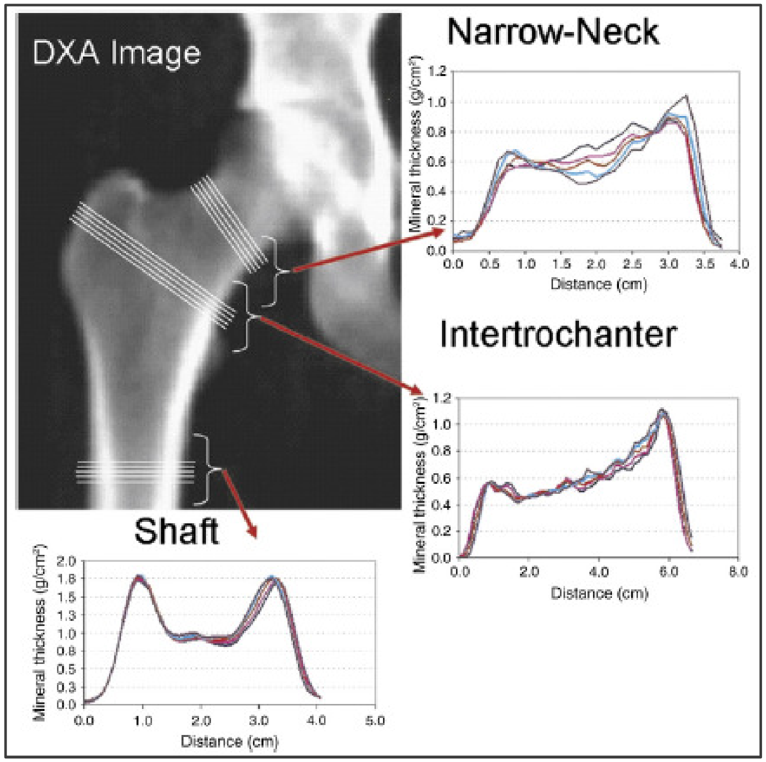
DXA MEASURES OF BONE DENSITY AND STRUCTURE - HIP

Hip Areal Bone Mineral Density



From Hologic website

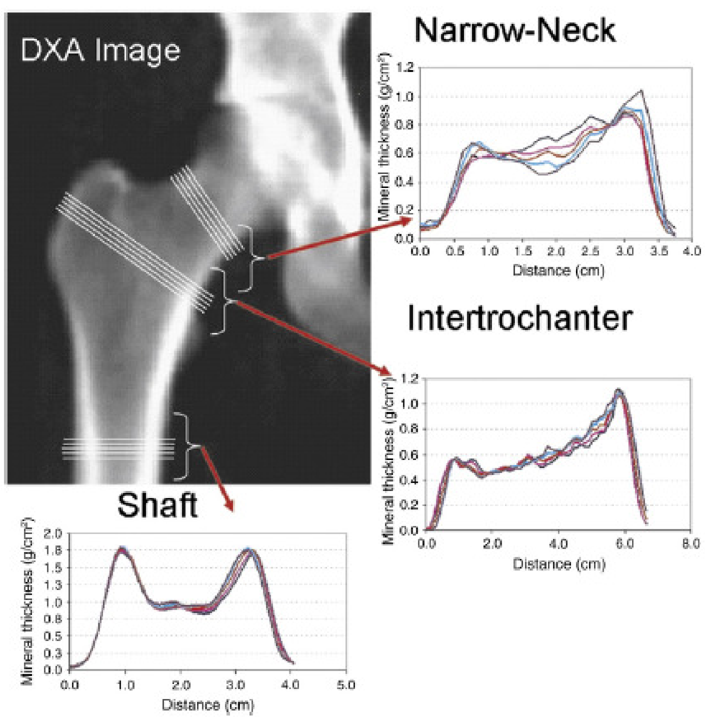
Hip Structural Analysis



From Al-Shaar Bone 56 (2013) 296–303

DXA MEASURES OF BONE DENSITY AND STRUCTURE - HIP

Hip Structural Analysis

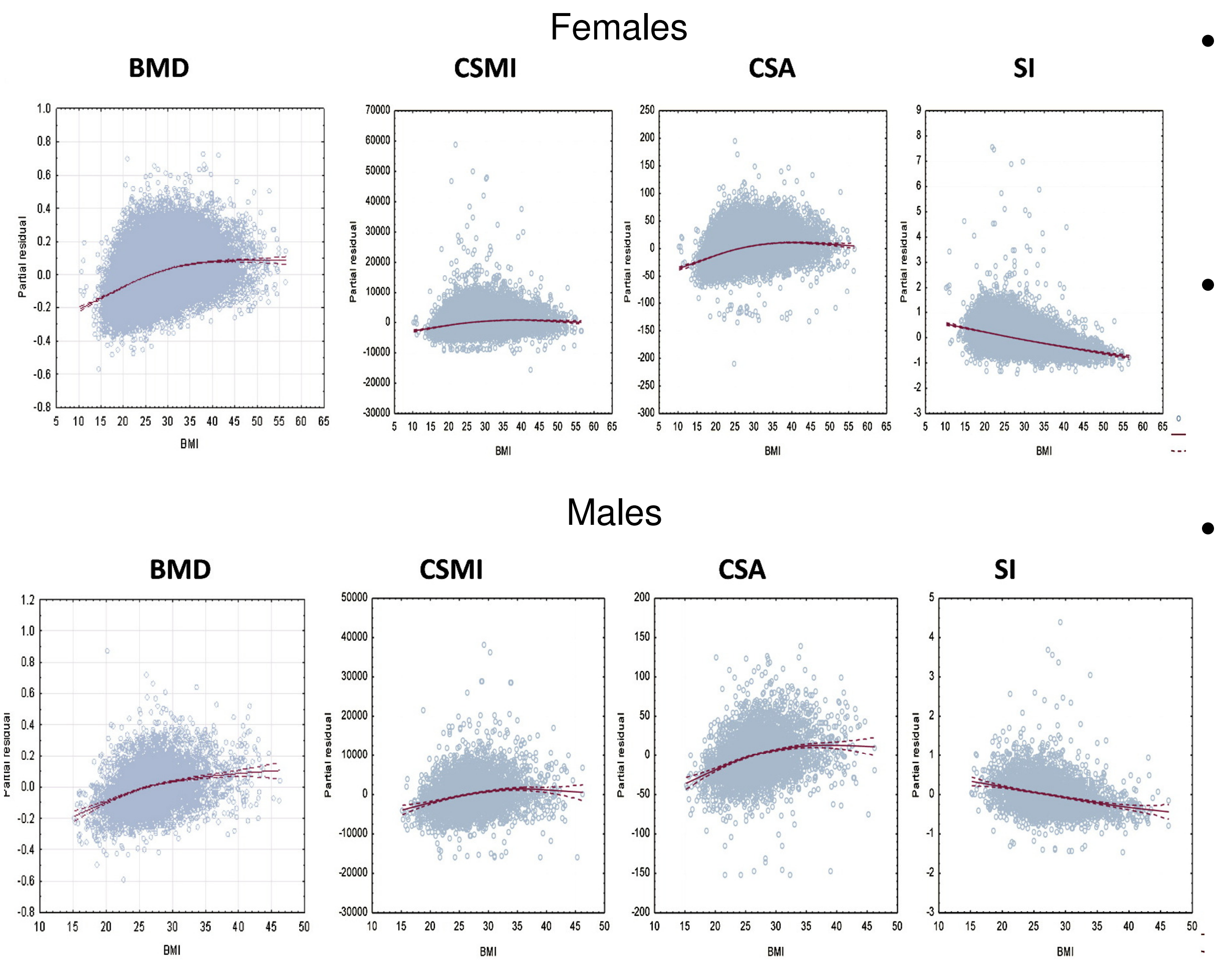


From Al-Shaar Bone 56 (2013) 296–303

Structural measures of femoral neck

- Cross-sectional area (CSA, mm^2)
- Cross-sectional moment of inertia (CSMI, mm^4):
  - measures resistance to bending
- Strength index (SI; unitless):
  - a ratio of estimated compressive yield strength of femoral neck to expected compressive stress of a fall on the greater trochanter adjusted for age, height, and weight

• ASSOCIATION OF BMI WITH FEMORAL NECK BMD AND STRUCTURAL STRENGTH



- BMI positively associated to BMD, cross-sectional moment of inertia, and cross-sectional area
- Relationship plateaus around BMI= 30 kg/m2, with little additional increment with further increases in BMI
- Increasing BMI was negatively associated with strength index

From: Shen et al. *J Clin Endo Metab* **2016,** 101, 476-484.

INCIDENT MAJOR OSTEOPOROTIC FRACTURES ARE LOWER IN OBESE ADULTS

Table 4. Crude Fracture Incidence Rates and Adjusted Hazard Ratios for Association of BMI With Incident Fractures Without and With BMD Adjustment in Women and Men

	Underweight < 18.5 kg/m²	**Normal 18.5–24.9 kg/m²**	**Overweight 25–29.9 kg/m²**	**Obese 1 30–34.9 kg/m²**	**Obese 2 ≥ 35 kg/m²**
Women					
Major osteoporotic fractures					
Fractures/person-years, n	147/6277	1665/129 241	1232/111 073	501/49 526	176/23 364
Crude incidence rate[a]	23.3	13.0	11.0	10.1	7.5
Base model[b]	1.59 (1.35–1.89)	1.0 (referent)	0.85 (0.79–0.91)	0.80 (0.72–0.88)	0.67 (0.57–0.79)
Base model + femoral neck BMD	1.18 (0.99–1.40)	1.0 (referent)	1.00 (0.93–1.08)	1.05 (0.95–1.16)	0.95 (0.81–1.12)
Hip fractures					
Fractures/person-years, n	67/6277	528/129 241	307/111 073	96/49 526	29/23 364
Crude incidence rate[a]	10.6	4.1	2.7	1.9	1.2
Base model[b]	1.67 (1.30–2.16)	1.0 (referent)	0.70 (0.61–0.80)	0.53 (0.42–0.66)	0.41 (0.28–0.60)
Base model + femoral neck BMD	1.04 (0.80–1.36)	1.0 (referent)	0.89 (0.77–1.02)	0.79 (0.63–0.99)	0.67 (0.46–0.98)

[a] Per 1000 person-years.

[b] Adjusted for age, prior fracture, parental hip fracture, chronic obstructive lung disease, recent glucocorticoid use, rheumatoid arthritis, alcohol abuse diagnosis, and osteoporosis treatment after BMD testing.

From Shen et al. *J Clin Endo Metab* **2016,** 101, 476-484.

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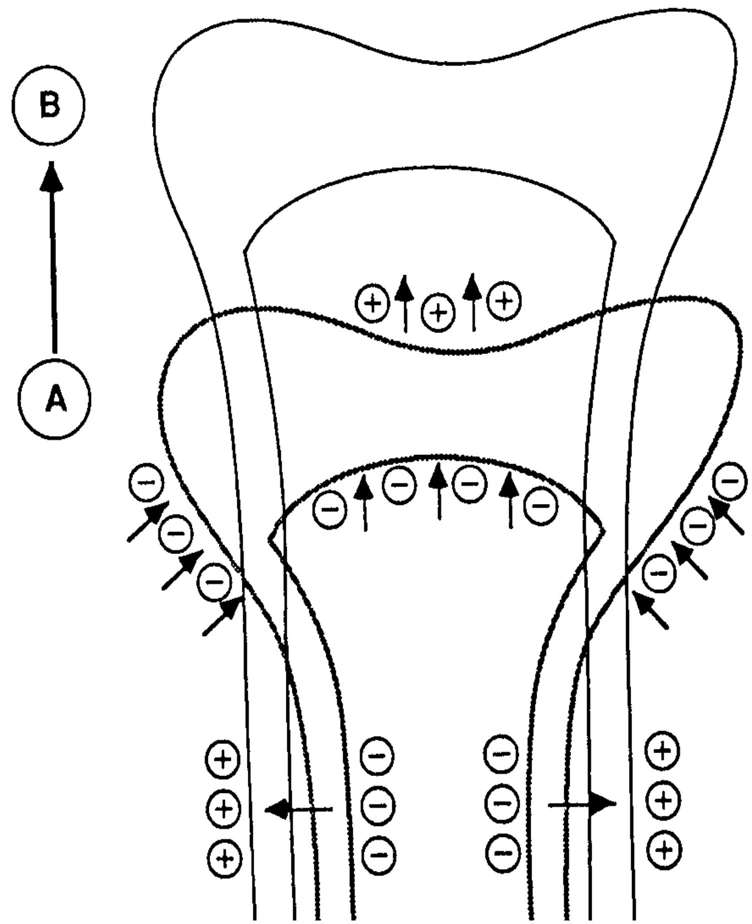
From Shen et al. *J Clin Endo Metab* **2016,** 101, 476-484.

WHY IS THIS A CONCERN FOR CHILDREN



FRACTURE INCIDENCE IN CHILDREN

- 30 to 50% of children have at least one fracture by the end of teenage years
- Fracture incidence similar to adults
  - estimated lifetime risk for fracture in U.K. at age 50: 53.2% women, 20.7% men (Van Staa et al. Bone 2001)

http://i.dailymail.co.uk/i/pix/2008/01_05/ChildBrokenArmREX_228x326.jpg

ISCD

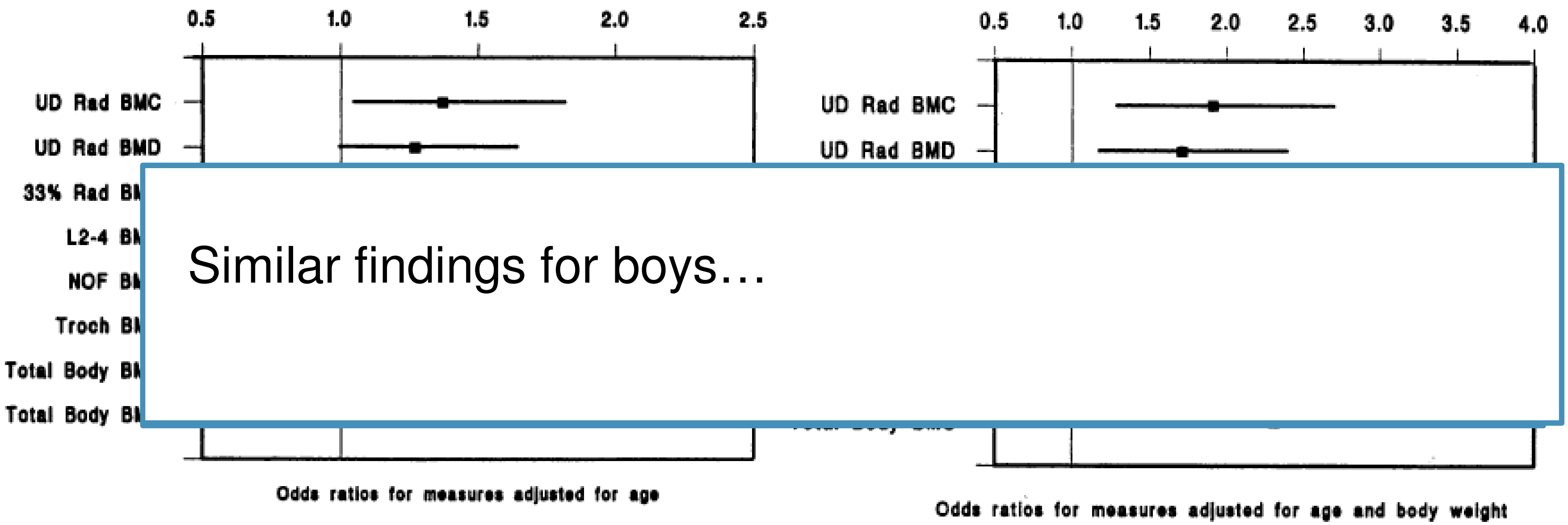
JOURNAL OF BONE AND MINERAL RESEARCH
Volume 13, Number 1, 1998
Blackwell Science, Inc.

Bone Mineral Density in Girls with Forearm Fractures

A. GOULDING, R. CANNAN, S.M. WILLIAMS, E.J. GOLD, R.W. TAYLOR, and N.J. LEWIS-BARNED

- 100 Caucasian girls, 3–15 y, with recent distal forearm fractures 2/1994 to 6/l995
- Each fracture case identified a friend to take part as a control; 100 age- and gender-matched controls enrolled
- DXA measures of BMC and aBMD at radius, spine, hip, and whole body and total body and lean tissue and fat mass

ODDS RATIO FOR FRACTURE: GOULDING ET AL. 1998



Similar findings for boys…

FIG. 1. Odds ratios with 95% confidence intervals derived from logistic regresssion of continuous data adjusted for age, or age and body weight, for a decrease of bone standard deviation from the control sample in each variable (ultradistal BMC in g/cm; BMD values all g/cm^2, total body mineral in kg).

DO OBESE CHILDREN WHO FRACTURE HAVE LOWER BONE DENSITY THAN OBESE CHILDREN WHO DON'T FRACTURE?

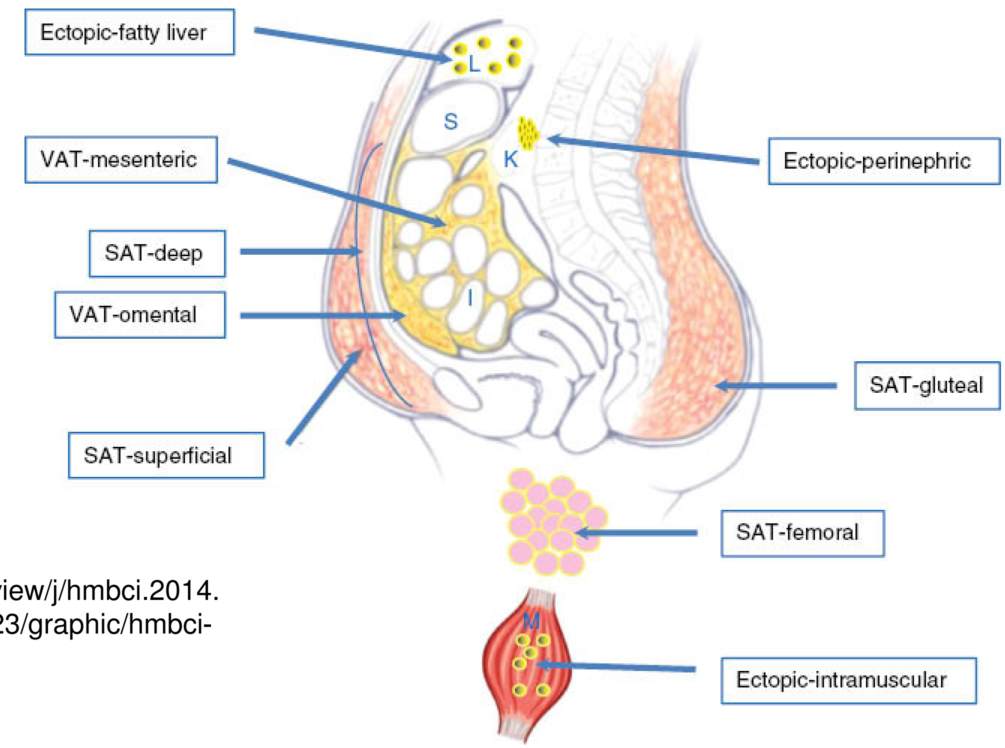
	Non-Obese			Obese			
	Group 1, no fracture (n=38)	Group 2, prior fracture (n=13)		Group 3, no fracture (n=39)	Group 4, prior fracture (n=13)		p Value
Total body adjusted for age							
BA	0 (1.00)	0.10 (0.71)		1.32 (0.95)*	0.82 (0.88)		<.0001
BMC	0 (1.00)	0.09 (0.68)		1.54 (0.92)*	0.84 (0.94)		<.0001
aBMD	0 (1.00)	0.00 (0.87)		1.50(1.00)*	0.62(1.01)		<.0001
Lumbar (L2–4) adjusted for age							
BA	0 (1.00)	0.56 (1.20)		1.49 (1.17)*	1.11 (1.01)		<.0001
BMC	0 (1.00)	0.04 (0.99)		1.32 (1.02)*	0.44 (0.95)		<.0001
aBMD	0 (1.00)	0.34 (0.80)		1.02 (1.01)*	0.14 (0.87)		<.0001

From Dimitri et al. JBMR 25 (3): 527-36, 2010

NOT ALL OBESE CHILDREN ARE ALIKE: EFFECTS OF BODY COMPOSITION

- Lean mass is a strong predictor of bone density in children; bones respond to the muscle forces to which they are exposed.
- Obese children have greater lean mass for their height compared to healthy weight children.
- Obese children tend to have earlier sexual and skeletal maturation, and earlier maturing children differ in body composition compared to same age peers.

NOT ALL FAT IS CREATED EQUAL



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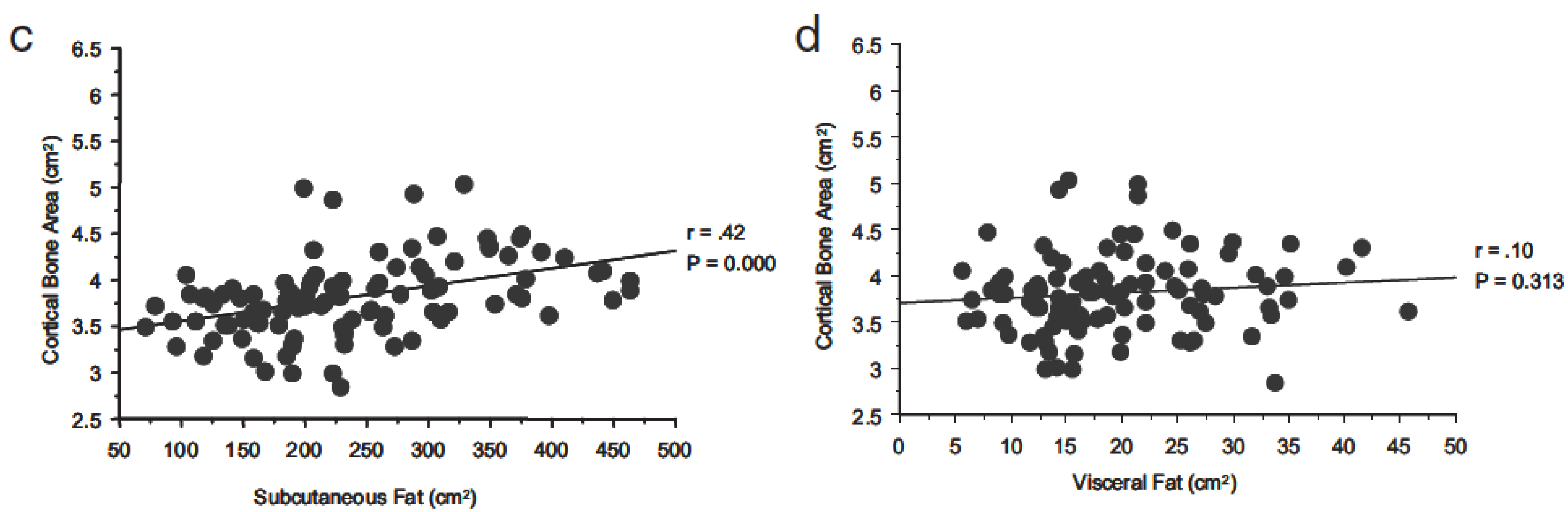
http://www.degruyter.com/view/j/hmbci.2014.19.issue-1/hmbci-2014-0023/graphic/hmbci-2014-0023_fig1.jpg

EFFECT OF VISCERAL ADIPOSE TISSUE ON BONE

- Gilsanz et al. J Clin Endocrinol Metab 94: 3387–3393, 2009
- Enrolled 100 females, 15 -25y, BMI 24.2±4.3 (16.8 –34.2)
- CT scans at umbilicus for measurement of fat depots, and midshaft of femur of bone dimensions: SAT but not VAT positively associated with bone strength



EFFECT OF VISCERAL ADIPOSE TISSUE ON BONE

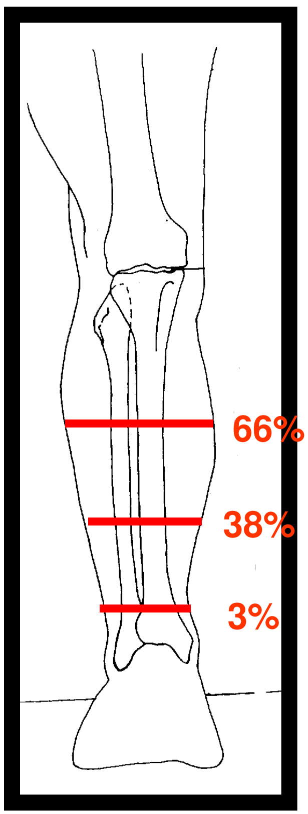
- Multivariate models showed that SAT was positively associated and VAT negatively associated with cortical bone structure of the femur

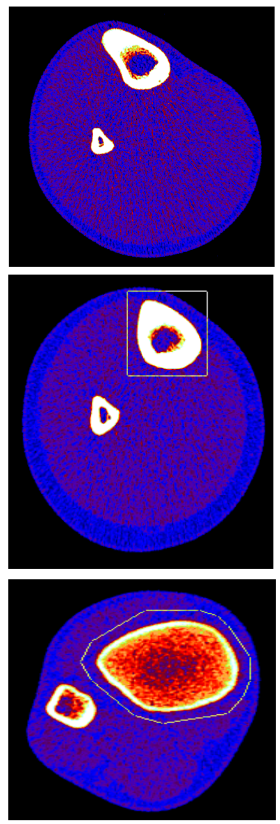
	Standardized coefficient	SE	*P* value	95% confidence interval
Femoral CSA (cm^2)				
Leg length (cm)	0.239	0.08	0.004	0.08 to 0.40
Thigh musculature (cm^2)	0.364	0.10	<0.001	0.17 to 0.56
Subcutaneous fat (cm^2)	0.437	0.13	<0.001	0.19 to 0.69
Visceral fat (cm^2)	−0.323	0.11	0.005	−0.54 to −0.10

BONE HEALTH OF OBESE ADOLESCENTS AND OBESITY RELATED COVARIATES

- Leonard et al. Bone 73: 69–76, 2015
- Examined the association between obesity and bone outcomes, independent of sexual and skeletal maturity, muscle area and strength, physical activity, calcium intake, biomarkers of inflammation, and vitamin D status
- Sample: 91 healthy obese (BMI>97th percentile, age >10 and <15 years of age) and 51 non-obese adolescents (BMI >5th and <85th percentiles, age >10 and <18 years)

Peripheral Quantitative CT





Muscle Cross Sectional Area

Cortical vBMD, dimensions and strength

Trabecular & Total vBMD

DESCRIPTIVE STATISTICS

	Obese (N = 91)	Non-Obese (N = 51)	p-value
Demographics			
Age, yr	12.2 (1.2)	14.5 (2.0)	<0.0001
Sex, n (%) female	59 (65%)	32 (63%)	0.8
Race, n (%) African American	56 (62%)	31 (61%)	0.9
Anthropometry and Maturation			
Height Z-score	1.00 (0.92)	0.40 (0.96)	<0.001
BMI Z-score	2.39 (0.22)	-0.01 (0.61)	<0.0001
Puberty, n Tanner 1 or 2 (%)	26 (30.2)	8 (15.7)	0.06
Advanced skeletal maturity, yr	1.5 (1.0)	0.2 (1.1)	<0.0001
Muscle Strength and Physical Activity			
Ankle Muscle strength Z-score	0.24 (0.09)	-0.51 (0.13)	<0.0001
Handgrip Z-score	-0.1 (1.10)	-0.28 (1.16)	0.19
Mod to vig physical activity, %	0.64 (0.28, 1.27)	1.19 (0.69, 1.97)	<0.01
Total physical activity, counts/minute	254 (185,363)	239 (182, 316)	0.5

Leonard et al. Bone 73 (2015) 69–76

	Obese (N = 91)	Non-Obese (N = 51)	p-value
pQCT Lower Leg Muscle and Fat Area			
Calf muscle area Z-score	1.19 (0.98)	-0.44 (0.88)	<0.0001
Calf subcutaneous fat area Z-score	2.06 (0.61)	-0.36 (0.81)	<0.0001

Leonard et al. Bone 73 (2015) 69–76

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Laboratory Parameters			
hsCRP, mg/L	2.05 (0.96, 4.01)	0.19 (0.11, 0.49)	<0.0001
25(OH) vitamin D, ng/mL	20.1 (9.9)	23.1 (10.3)	0.08

Leonard et al. Bone 73 (2015) 69–76

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25(OH) vitamin D, ng/mL	20.1 (9.9)	23.1 (10.3)	0.08
Tibia QCT Bone Outcomes			
Cortical section modulus Z-score	0.76 (0.75)	-0.31 (0.78)	<0.0001
Cortical periosteal circumference Z-score	0.78 (0.86)	-0.30 (0.80)	<0.0001
Trabecular volumetric BMD Z-score	0.51 (1.10)	0.17 (1.08)	0.08
Cortical volumetric BMD Z-score	-0.04 (1.00)	-0.04 (1.12)	0.7

Leonard et al. Bone 73 (2015) 69–76

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Trabecular volumetric BMD Z-score	0.51 (1.10)	0.17 (1.08)	0.08
Cortical volumetric BMD Z-score	-0.04 (1.00)	-0.04 (1.12)	0.7
Radius QCT Bone Outcomes			
Cortical section modulus Z-score	0.43 (1.36)	-0.02 (1.59)	0.08
Cortical periosteal circumference Z-score	0.40 (1.15)	-0.11 (1.29)	0.02
Trabecular volumetric BMD Z-score	0.29 (1.19)	0.10 (1.21)	0.4
Cortical volumetric BMD Z-score	0.02 (1.07)	0.16 (1.03)	0.5

Leonard et al. Bone 73 (2015) 69–76

BONE HEALTH OF OBESE ADOLESCENTS AND OBESITY RELATED COVARIATES

Full model adjusted for all variables considered to contribute significantly to the group difference for the difference in tibia cortical section modulus Z-score (SD) between obese and non-obese subjects.

Variable	β (95% CI)	p-value
Obese vs. non-obese	0.32 (−0.01 to 0.64)	0.06
Calf muscle area Z-score	0.35 (0.21 to 0.49)	<0.0001
Advanced skeletal maturity, per year	0.06 (−0.05 to 0.17)	0.3
Muscle strength Z-score	0.21 (0.05 to 0.36)	<0.01
Moderate to vigorous physical activity, per percent	0.21 (0.10 to 0.32)	<0.0001

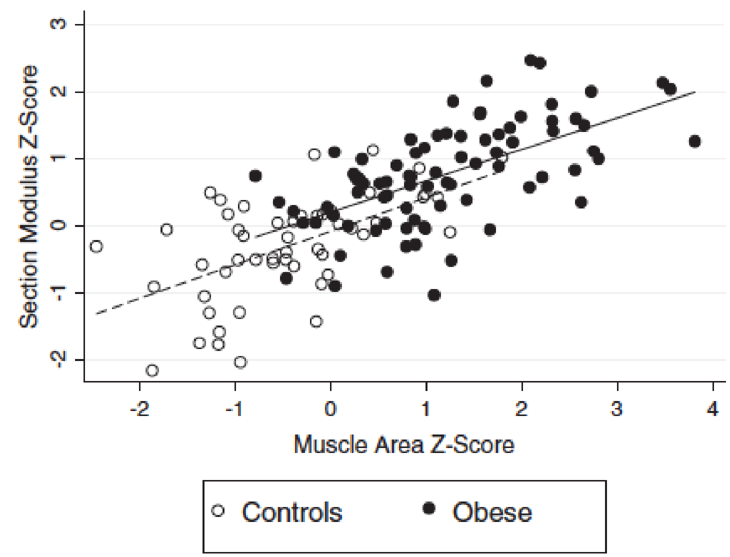

Fig. 2. Tibia cortical section modulus Z-score relative to muscle area Z-score in obese and non-obese control participants. This figure illustrates the markedly greater muscle area and section modulus Z-scores in the obese participants, and the positive association observed in both groups. Section modulus Z-score relative to muscle area Z-score was marginally greater in obese compared with non-obese participants ($p = 0.06$).

Differences between obese and healthy weight adolescents were attenuated after adjustment for independent effects of muscle area and strength, advanced skeletal maturity, and MVPA (fat measures were not significant)

CONCLUSIONS

- Obesity during adolescence results in larger bone size / thickness at weight-bearing sites, largely due to effects of lean body mass and muscle forces on bone as a consequence of weight-bearing activity
- Less benefit at lower weight-bearing sites such as the radius – may account for increased forearm fracture incidence
- Visceral adipose tissue has negative effects on bone accretion, but subcutaneous fat has positive effects on bone accretion

CONCLUSIONS

- A subset of obese children with low bone density relative to size may be more susceptible to fracture
- As excess weight gain progresses, does bone continue to adapt to greater load?
- Future studies should focus on identifying the subset of obese children at greatest risk for current and future fracture, and account for physiological, maturational and lifestyle factors associated with obesity

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  - Vicente Gilsanz, MD, PHD
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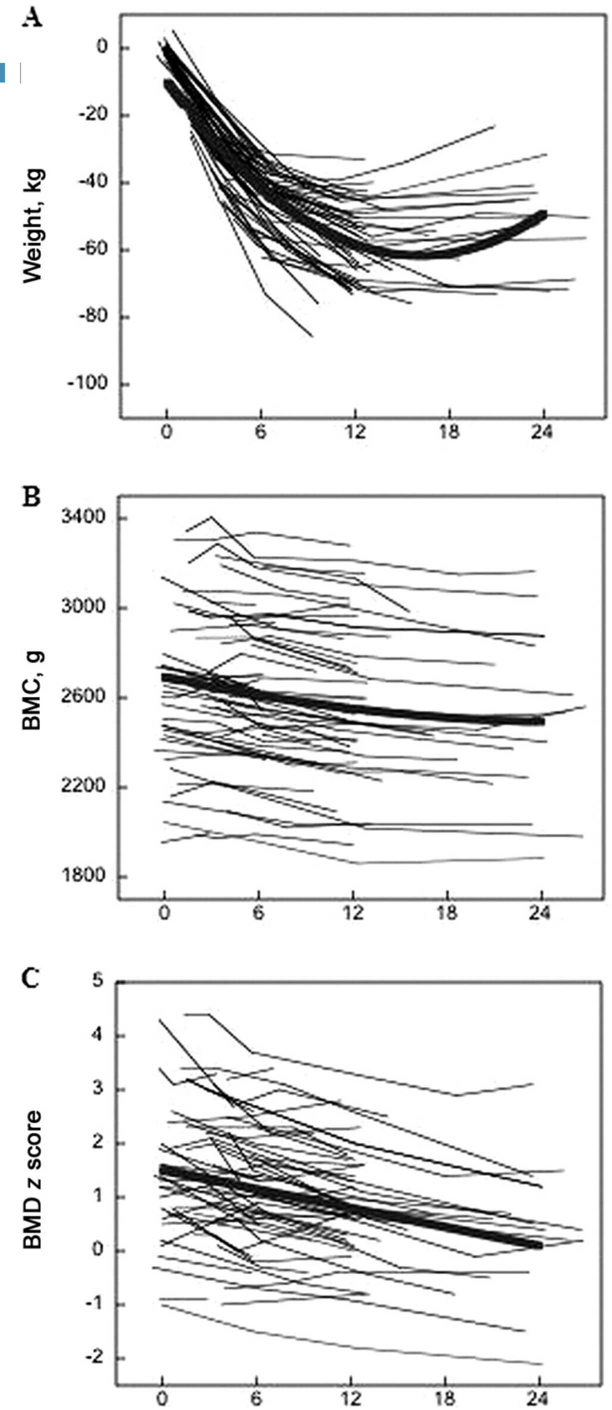
  - Shana McCormack, MD
  - Justine Shults, PhD

Weight (A), BMC (B), and BMD z score (C) over time after bariatric surgery.

From: Anne-Marie D. Kaulfers et al. Pediatrics 2011;127:e956-e961



NAFLD AND BMD IN CHILDREN

Pardee Et Al. Aliment Pharmacol Ther 2012; 35: 248–254

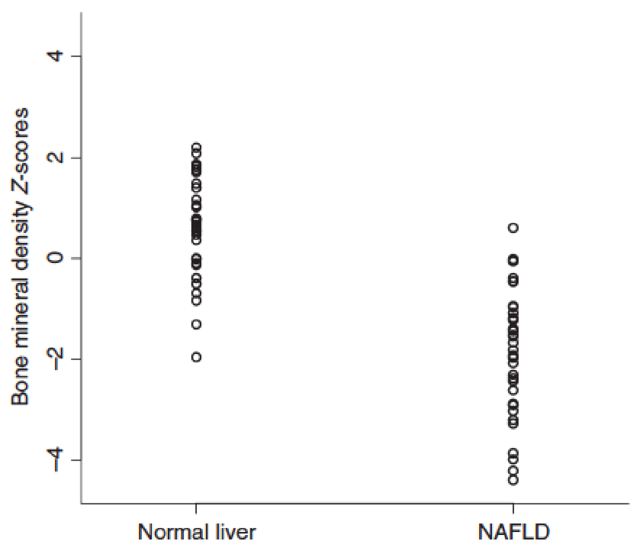


Figure 1 | Scatterplot of bone mineral density *Z*-scores for obese children with and without NAFLD. Children with NAFLD had significantly ($P < 0.0001$) lower BMD *Z*-scores than children without NAFLD.

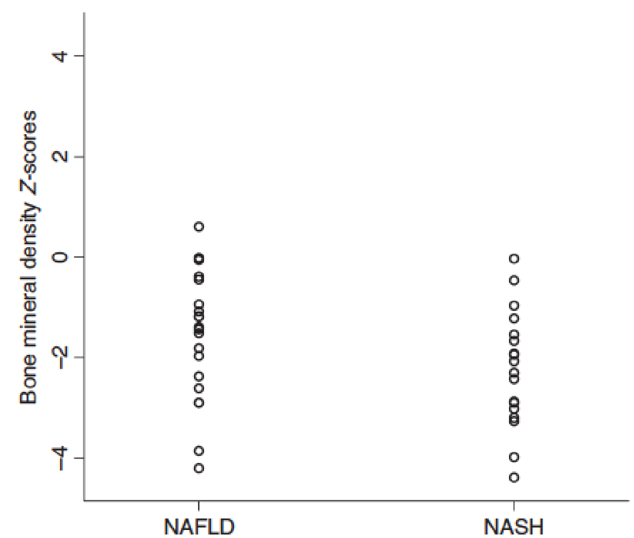
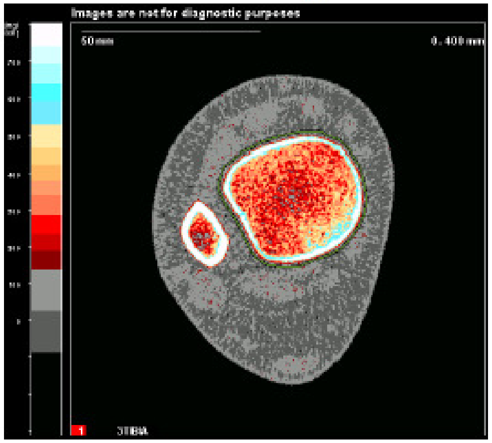


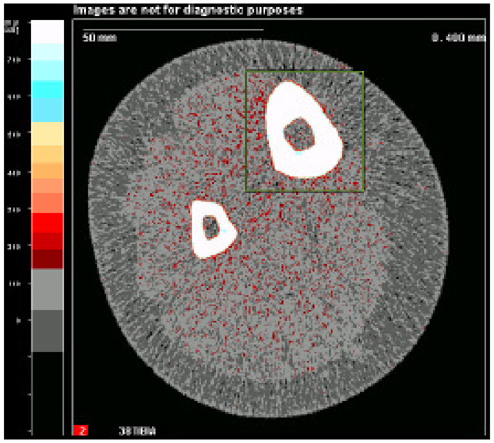
Figure 2 | Scatterplot of bone mineral density *Z*-scores for obese children NAFLD subdivided into those with and without NASH. Children with NASH had significantly ($P < 0.05$) lower BMD *Z*-scores than children with NAFLD who did not have NASH.

PQCT BONE DENSITY AND STRUCTURE IN HEALTHY WEIGHT VS OBESE YOUTH

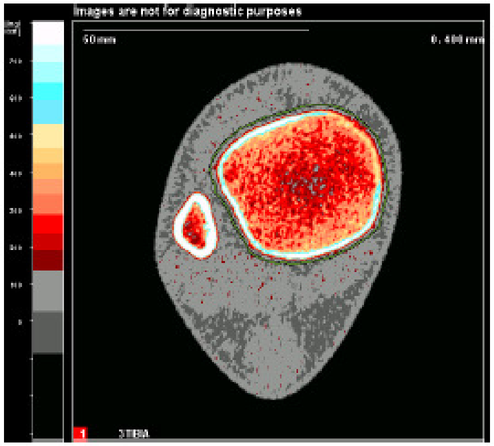
A. Obese 3% of Tibia Length



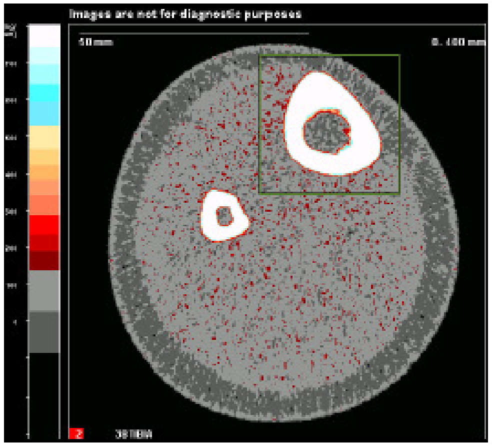
Obese 38% of Tibia Length



B. Healthy Weight 3% of Tibia Length



Healthy Weight 38% of Tibia Length



	3% Site		38% Site				66% Site (not shown)		
	Trabecular Density	Total Density	Cortical Area	Cortical Thickness	Periosteal Circ.	Endosteal Circ	Section Modulus	Muscle Area	Fat Area
Obese	313.2	383.6	336.5	6.8	71.0	28.4	27236	7743	5491
Lean	282.7	335.4	245.6	4.9	65.2	34.2	17744	5308	1371