Letter to the Editor

Michael Biggs*

Revisiting the effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria

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To the Editors,

I write to respond to Joseph, Ting, and Butler's recent article, describing the effect of administering gonadotropin-releasing hormone analogue (GnRHa) to suppress puberty in adolescents diagnosed with gender dysphoria [1]. The mean of the patients' bone mineral density (BMD)—relative to the norm for their sex and age—declined significantly over 2 years. What really matters is the lower tail of the distribution, but this information was omitted by Joseph et al. This letter analyses individual data on 24 patients from Joseph et al.'s sample of 31 [2]. It finds that after 2 years of GnRHa, up to a third of patients had abnormally low bone density, in the lowest 2.3% of the distribution for their sex and age. A few patients recorded extremely low values, in the lowest 0.13% of the distribution. This finding undermines Joseph et al.'s conclusions.

The Dutch pioneers of this experimental treatment for gender dysphoria warned that patients could 'end with a decreased bone density, which is associated with a high risk of osteoporosis' [3]. The effects on bone density have been described by four Dutch studies [4–7], besides Joseph et al. BMD is measured by a dual energy X-ray absorptiometry (DXA) scan over the spine (lumbar) and the hip (femoral neck). The absolute value of BMD is standardized as a Z-score, expressing this individual's BMD relative to the population of the same sex and age. BMD can be adjusted for height to derive the volumetric bone mineral apparent density (BMAD), which is likewise standardized as a Z-score.

A Z-score below −2 is considered low; it indicates bone density in the lowest 2.3% of the population of the same sex and age [8]. Joseph et al. argue that 'this is not the sole definition of low bone mass in children, nor is this criterion a recognized predictor of later fracture risk'. But this threshold was prominent in the experiment which introduced puberty suppression for gender dysphoria to Britain. The original experimental protocol (co-authored by Butler) in 2010 excluded any child with a spine or hip BMD Z-score below −2. In 2012, however, this exclusion criterion was relaxed 'in exceptional circumstances'—if clinicians 'feel that on the balance of risks, pubertal suppression is an appropriate option despite risks of osteoporosis in later adult life' and patients 'understand the risks of GnRH analogue treatment for bone density (i.e., risks of later osteoporosis)' [9].

Information on the lower tail of the distribution of Z-scores—below −2—is omitted by Joseph et al. and by three out of four Dutch studies. Describing distributions by mean (and standard deviation) is not sufficient when clinical concern focuses on very low values. This will be illustrated for patients experiencing 2 years of puberty suppression. Joseph et al.'s sample after 24 months on GnRHa comprised 31 patients. Data on 24 of these patients —or at least patients from the same clinic at University College London Hospital—have recently been released, though sex is unavailable [2]. These patients were enrolled in the British experiment which recruited patients from 2011 to 2015. The Stata do file to replicate the analysis is posted at https://doi.org/10.7910/DVN/FSOMME.

Table 1 shows mean Z-scores for Joseph et al.'s three measures of BMD, at baseline and at 24 months (the hip measure is missing for three patients). The 2011–15 sample is naturally similar to Joseph et al.'s. The decline in the mean of all three scores is statistically significant in both samples ($p \leq 0.004$ in every paired t-test).

Using data from the 2011–15 sample, Figure 1 depicts the distributions of Z-scores at 24 months, along with the

*Corresponding author: Michael Biggs, Department of Sociology, University of Oxford, 42 Park End Street, Oxford OX1 1JD, UK, Phone: +44 (0)1865 286 174, E-mail: michael.biggs@sociology.ox.ac.uk

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Table 1: Bone density in adolescents undergoing puberty suppression.

	Hip BMD		Spine BMD		Spine BMAD	
	Joseph et al.	2011–15	Joseph et al.	2011–15	Joseph et al.	2011–15
Mean Z-score at baseline	−0.58	−0.55	−0.44	−0.34	−0.09	−0.46
Mean Z-score at 24 months	−1.40	−1.45	−1.64	−1.46	−0.71	−1.28
Change in Z-score	−0.82	−0.90	−1.20	−1.12	−0.62	−0.81
p-value (two-tailed)	0.000	0.000	0.000	0.000	0.000	0.004
n	31	21	31	24	31	24

BMD, bone mineral density; BMAD, bone mineral apparent density.

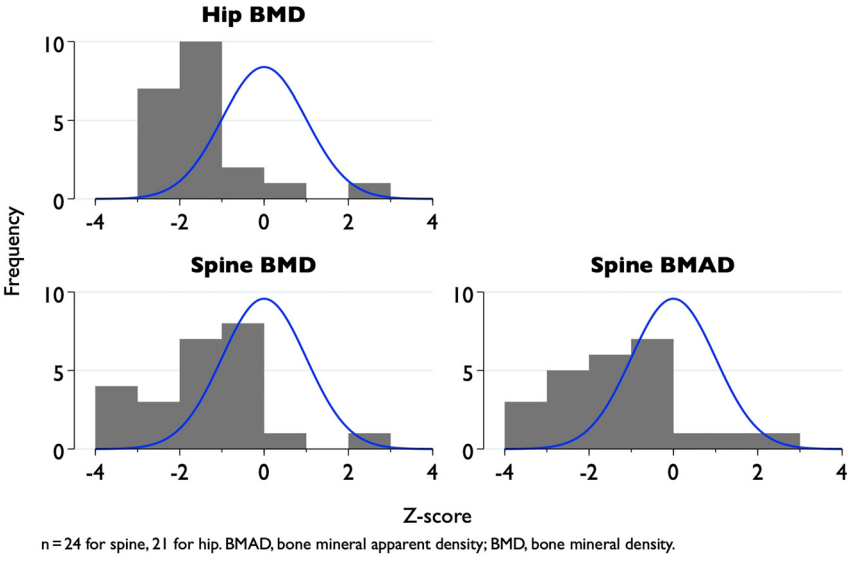

Figure 1: Bone density after 24 months of puberty suppression.

Normal distribution to compare with the population of the same sex and age. For hip BMD, a third of patients had a low Z-score, below −2. For spine BMD, more than a quarter of patients had low Z-scores. The lower tail extended far beyond. Indeed, four patients had Z-scores below −3, putting them in the bottom 0.13% of the population. Adjusting for height, by computing spine BMAD, does not shrink the lower tail.

Given that puberty suppression left up to a third of patients with abnormally low bone density, Joseph et al.'s recommendations are surprisingly complacent. One is to reduce DXA monitoring which 'can have significant financial implications for healthcare providers'. Another is to change the computation of Z-scores; 'reference ranges may need to be re-defined for this select patient cohort'. Rather than altering a measure that provides inconvenient findings, practitioners of puberty suppression must record fractures as adverse events. One British patient who started GnRHa at age 12 then experienced four broken bones by the age of 16 [10]. This history, if it were combined with BMD Z-scores below −2, would meet the diagnostic criteria for paediatric osteoporosis [11]. Whether this case is exceptional is unknown because clinicians have failed to collect relevant data.

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