

TABLES

Table 1. Puberty Measures, DXA ~~Percent%~~ Body Fat and Bone Mass Measurements, and MRI Breast Tissue Composition of the Participants; [ALSPAC study, 1991-2014](#)

Variable		N	Mean/%	SD	Median	IQR
Puberty variables						
Age at menarche (years)		469	12.7	1.0	12.7	1.3
Age at thelarche (years) <sup>a</sup>		486	10.4	1.4	10.2	2.1
Age at breast development completion (years) <sup>a</sup>		451	13.1	1.6	12.7	1.5
Breast development duration (years) <sup>a</sup>		426	2.9	1.4	2.7	1.7
DXA measures <sup>b</sup>						
Age at DXA measures (years)	9 years	449	9.8	0.3	9.8	0.3
	11 years	461	11.7	0.2	11.8	0.3
	13.5 years	443	13.8	0.2	13.9	0.3
	15.5 years	423	15.4	0.2	15.5	0.3
DXA body fat mass (%)	9 years	447	26.0	8.2	25.3	11.3
	11 years	460	27.2	8.2	26.7	11.4
	13.5 years	443	28.2	8.0	27.9	11.9
	15.5 years	428	30.0	7.8	29.1	11.5
DXA body bone mass (%)	9 years	447	3.5	0.4	3.6	0.5
	11 years	460	3.7	0.4	3.7	0.6
	13.5 years	443	4.0	0.4	4.0	0.6
	15.5 years	428	4.2	0.4	4.2	0.5
Participants characteristics at MRI examination						
Age (months)		491	257.9	11.0	259.0	14.0
Menstrual phase <sup>c</sup>	Follicular	70	14			
	Luteal	50	10			
	Hormone contraceptive	339	70			
	Irregular period	28	6			
MRI breast measures <sup>d</sup>						
Left-right average breast volume (cm <sup>3</sup> )		490	647.2	461.1	507.8	469.2
Left-right average breast fat volume (cm <sup>3</sup> )		490	406.3	349.5	292.2	327.9
Left-right average breast water volume (cm <sup>3</sup> )		490	240.9	131.2	209.8	172.4
Left-right average breast <del>% percent</del> water ( <del>%)</del>		491	41.8	10.3	41.7	16.0

DXA: dual-energy X-ray absorptiometry; IQR: inter-quartile range; MRI: magnetic resonance imaging; N: number of participants; SD: standard deviation

<sup>a</sup> Age at thelarche and age at breast development completion estimated as described in the Methods section. Breast development duration estimated as age at breast development completion minus age at thelarche.

<sup>b</sup> DXA percent% body bone and fat masses estimated as described in the Methods section.

<sup>c</sup> Estimated for women who were not taking hormone contraception at the time of the MRI by calculating the number of days since last menstrual period (date of MRI – start of last menstrual period). Luteal phase (day 14-17 to 28-31), follicular phase (day 0 to 14-17) and 'irregular period' (32+ days) were defined using self-reported average length of menstrual cycle.

<sup>d</sup> Sections of the breast missing in the MRI images for one participant. Hence, percent% water could be estimated from the available MRI images, but not absolute volumetric measures (i.e. breast, fat and water volumes).

Table 2. Mutually-Adjusted Associations of MRI Breast Volume and **Percent%** Water with Observed Measures of Height, Weight and DXA **Percent%** Body Fat and Bone Masses, and Markers of Pubertal Development; [ALSPAC study, 1991-2014](#)

Variable <sup>a</sup>	MRI Breast Volume						MRI <b>Percent%</b> Water					
	Model 1 (N=287)		Model 2 (N=261)		Model 3 (N=244)		Model 1 (N=287)		Model 2 (N=261)		Model 3 (N=244)	
	RC <sup>b</sup>	95% CI <sup>b</sup>	RC <sup>b</sup>	95% CI <sup>b</sup>	RC <sup>b</sup>	95% CI <sup>b</sup>	RC <sup>b</sup>	95% CI <sup>b</sup>	RC <sup>b</sup>	95% CI <sup>b</sup>	RC <sup>b</sup>	95% CI <sup>b</sup>
Birth length	1.00	0.93, 1.08	1.05	0.97, 1.14	1.02	0.95, 1.10	1.01	0.98, 1.05	0.99	0.96, 1.02	1.00	0.97, 1.03
Pre-pubertal height growth <sup>c</sup>	0.86	0.74, 1.00*	0.88	0.75, 1.03	0.93	0.78, 1.11	1.12	1.04, 1.20*	0.95	0.90, 1.01	0.93	0.87, 1.00
Pubertal height growth <sup>d</sup>	0.84	0.75, 0.94*	0.90	0.81, 1.01	0.89	0.78, 1.01	1.07	1.02, 1.14*	1.07	1.03, 1.12*	1.07	1.02, 1.13*
Birth weight	0.99	0.92, 1.06	0.98	0.91, 1.05	1.00	0.93, 1.07	1.03	1.00, 1.07	1.03	1.00, 1.06	1.03	1.00, 1.06*
Pre-pubertal weight growth <sup>e</sup>	1.22	1.13, 1.32*	1.21	1.07, 1.37*	1.15	1.02, 1.30*	0.87	0.84, 0.90*	1.05	1.00, 1.10	1.05	1.00, 1.11
Pubertal weight growth <sup>f</sup>	1.78	1.68, 1.89*	1.67	1.56, 1.80*	1.70	1.58, 1.82*	0.84	0.82, 0.87*	0.86	0.84, 0.89*	0.86	0.84, 0.89*
Age at menarche	1.04	0.97, 1.12			1.05	0.97, 1.14	1.00	0.97, 1.04			1.00	0.97, 1.03
Age at thelarche <sup>g</sup>	1.01	0.87, 1.16			1.04	0.88, 1.22	1.06	0.99, 1.14			1.02	0.96, 1.09
Age at breast completion <sup>g</sup>	0.88	0.83, 0.93*			0.88	0.83, 0.94*	1.00	0.97, 1.02			1.01	0.98, 1.03
DXA body fat mass (%) <sup>h</sup>												
9 years			1.11	1.00, 1.23	1.13	1.02, 1.25*			0.86	0.83, 0.90*	0.86	0.83, 0.90*
9 – 11 years			1.04	0.96, 1.13	1.03	0.96, 1.11			0.94	0.92, 0.97*	0.95	0.92, 0.98*
11 – 13.5 years			1.07	0.99, 1.15	1.08	1.00, 1.16			0.96	0.93, 0.98*	0.96	0.93, 0.99*
13.5 – 15.5 years			0.98	0.92, 1.04	0.98	0.93, 1.04			0.99	0.96, 1.01	0.99	0.97, 1.02

Variable <sup>a</sup>	MRI Breast Volume						MRI <del>Percent%</del> Water					
	Model 1 (N=287)		Model 2 (N=261)		Model 3 (N=244)		Model 1 (N=287)		Model 2 (N=261)		Model 3 (N=244)	
	RC <sup>b</sup>	95% CI <sup>b</sup>	RC <sup>b</sup>	95% CI <sup>b</sup>	RC <sup>b</sup>	95% CI <sup>b</sup>	RC <sup>b</sup>	95% CI <sup>b</sup>	RC <sup>b</sup>	95% CI <sup>b</sup>	RC <sup>b</sup>	95% CI <sup>b</sup>
DXA body bone mass (%) <sup>h</sup>												
9 years			1.01	0.94, 1.09	1.02	0.95, 1.09			1.03	1.00, 1.06*	1.03	1.00, 1.06*
9 – 11 years			0.96	0.90, 1.02	0.96	0.90, 1.03			1.01	0.99, 1.04	1.02	0.99, 1.04
11 – 13.5 years			0.93	0.86, 1.00	0.96	0.88, 1.03			0.97	0.95, 1.00	0.98	0.95, 1.01
13.5 – 15.5 years			0.91	0.86, 0.97*	0.91	0.86, 0.97*			1.01	0.98, 1.03	1.01	0.99, 1.04

CI: confidence interval; DXA: dual-energy X-ray absorptiometry; MRI: magnetic resonance imaging; RC: relative change per one standard deviation increment in the exposure variable of interest; \*  $P < 0.05$

<sup>a</sup> All growth variables, and growth differences across ages, were standardised (see Methods section).

<sup>b</sup> MRI breast measures were log transformed. Exponentiated estimated regression parameters are presented; 95% CI were calculated by exponentiating the original 95% CIs. RC estimates adjusted for age and menstrual phase at MRI examination and all the other variables included in the model.

Model 1 includes all the height/weight growth trajectory variables and the pubertal development variables;

Model 2 includes all the height/weight growth trajectory variables and the DXA measures; ~~and~~

Model 3 includes - all the height/weight growth trajectory variables, the pubertal development variables, and the DXA measures.

<sup>c</sup> Pre-pubertal height growth calculated as 'height at age of thelarche' – 'height at age 7 ( $\pm 1$ ) years'.

<sup>d</sup> Pubertal height growth calculated as 'height at age 21 years' – 'height at age of thelarche'.

<sup>e</sup> Pre-pubertal weight growth calculated as 'weight at age of thelarche' – 'weight at age 7 ( $\pm 1$ ) years'.

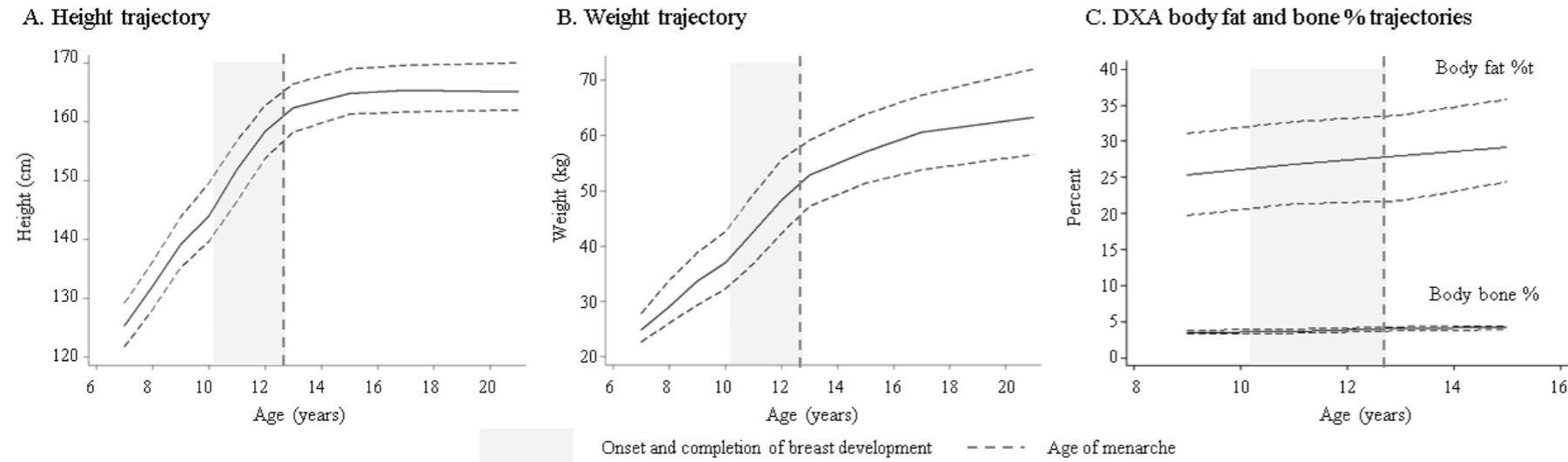
<sup>f</sup> Pubertal weight growth calculated as 'weight at age 21 years' – 'weight at age of thelarche'

<sup>g</sup> Age at thelarche and age at breast development completion estimated as described in the Methods section.

<sup>h</sup> DXA ~~percent%~~ body bone and fat masses estimated as described in the Methods section. These models include the relevant DXA measurements taken at age 9 years and their changes between ages 9 to 11 years, 11 to 13.5 years, and 13.5 to 15.5 years.

## FIGURES

Figure 1. Average (and Interquartile Range) Height, Weight and DXA Percent% Body Fat and Bone Mass Trajectories of the Participants from Age 7 to 21 Years, and Timing of Pubertal Development; ALSPAC study, 1991-2014

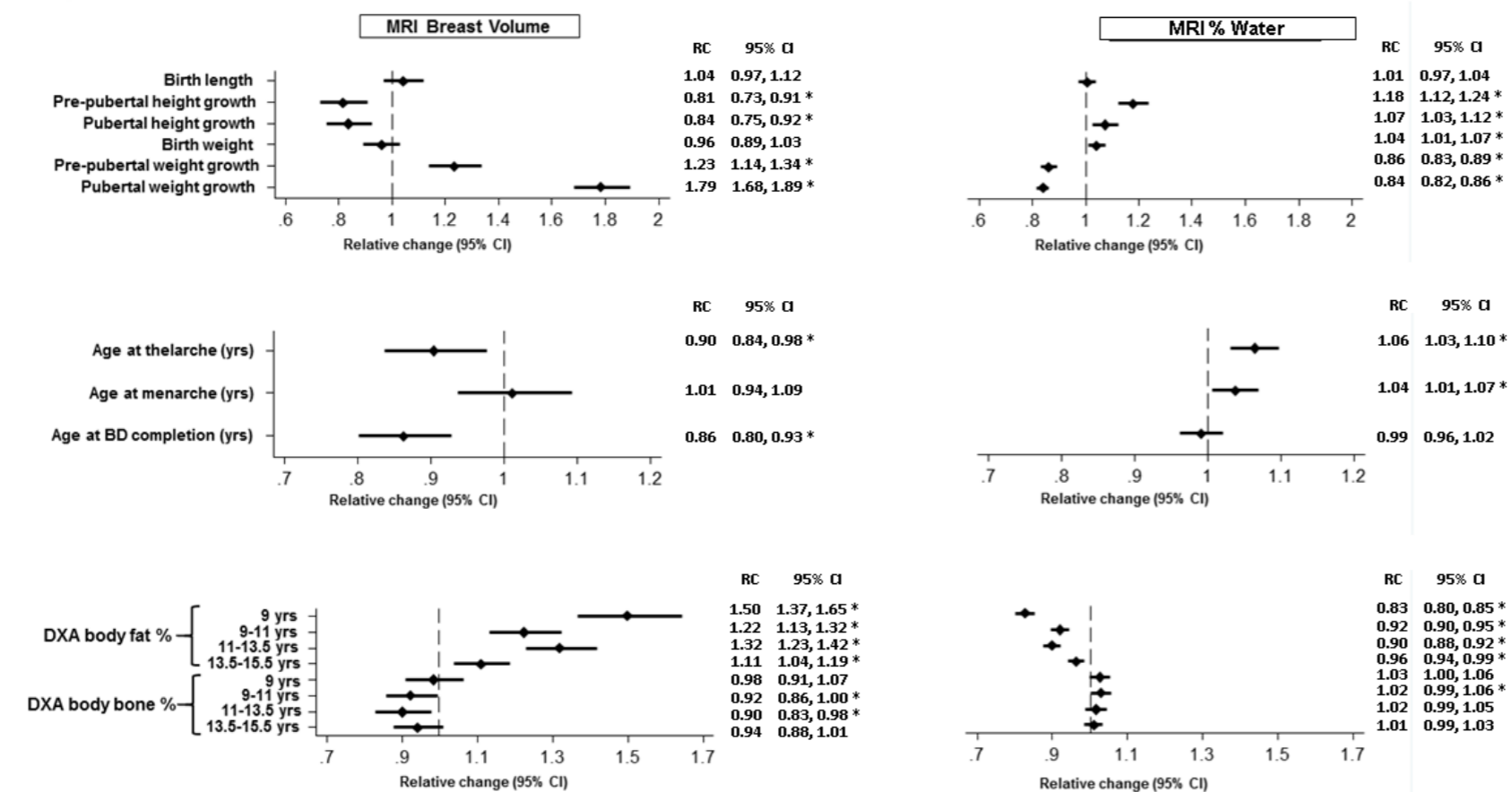


DXA: dual-energy X-ray absorptiometry; IQR: inter-quartile range

Solid horizontal lines represent the (smoothed) median height, weight, and DXA percent% body fat and bone masses; dashed horizontal lines represent the (smoothed) 25<sup>th</sup> and 75<sup>th</sup> centiles of their distributions. The dashed vertical line represents the median age at menarche. Median ages at thelarche (i.e. onset of breast development) and median age at breast development completion estimated as described in the Methods section.

Figure 2. Associations of MRI Breast Measures with Observed Measures of Height and Weight, Pubertal Development and DXA

Percent% Body Fat and Bone Masses; [ALSPAC study, 1991-2014](#)

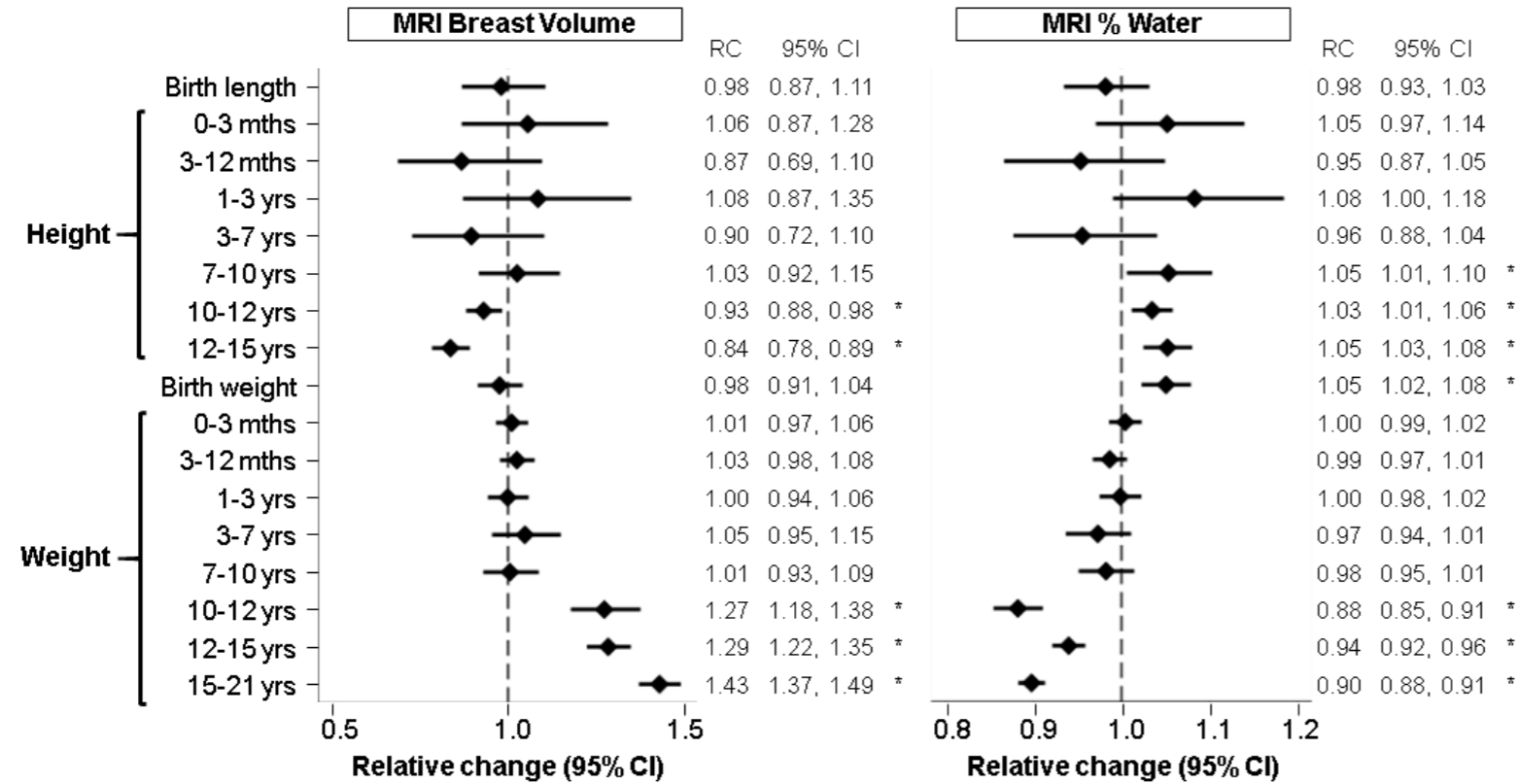


CI: confidence interval; DXA: dual-energy X-ray absorptiometry; MRI: magnetic resonance imaging; RC: relative change per one standard deviation increment in the exposure variable of interest; \*  $P < 0.05$

MRI breast measures were log transformed. Exponentiated estimated regression parameters are presented; 95% CI were calculated by exponentiating the original 95% CIs. All growth variables, and growth differences across ages, were standardised (see Methods section). RC estimates adjusted for age and menstrual phase at MRI examination and all the other variables in the same category, i.e. height/weight growth trajectories, pubertal development or DXA measures. Pre-pubertal and pubertal height/weight growth estimated as defined in the Methods section and in the footnotes c) to f) of Table 2.

Figure 3. Mutually-Adjusted Associations of MRI Breast Measures with Height and Weight Velocity Trajectories; [ALSPAC study](#),

[1991-2014](#)





CI: confidence interval; DXA: dual-energy X-ray absorptiometry; MRI: magnetic resonance imaging; RC: relative change per one standard deviation increment in the exposure variable of interest; \*  $P < 0.05$

Height and weight growth measures from birth to age 10 years were derived using linear spline multilevel modelling of height and weight (16). From age 10 years, standardised growth measures were calculated from a piecewise mixed effect model with knots at age 10, 12 and 15 years (see Methods section and Appendices 1 and 2).

MRI breast measures were log transformed. Exponentiated estimated regression parameters are presented; 95% CI were calculated by exponentiating the original 95% CIs (see Methods section). All growth measures, and all growth differences, were standardised. RC estimates were adjusted for age and menstrual phase at MRI examination and all the other variables listed in the graph.

