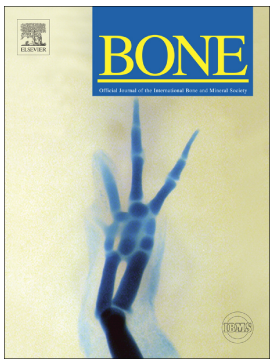

Cognitive function and skeletal size and mineral density at age 6–7 years: Findings from the Southampton women's survey

Rebecca J. Moon, Stefania D'Angelo, Sarah R. Crozier, Michelle Fernandes, Caroline Fall, Catharine R. Gale, Keith M. Godfrey, Justin H. Davies, Cyrus Cooper, Nicholas C. Harvey

PII: S8756-3282(24)00056-5

DOI: https://doi.org/10.1016/j.bone.2024.117067

Reference: BON 117067

To appear in: *Bone*

Received date: 11 December 2023

Revised date: 23 February 2024

Accepted date: 1 March 2024

Please cite this article as: R.J. Moon, S. D'Angelo, S.R. Crozier, et al., Cognitive function and skeletal size and mineral density at age 6–7 years: Findings from the Southampton women's survey, *Bone* (2023), https://doi.org/10.1016/j.bone.2024.117067

Cognitive function and skeletal size and mineral density at age 6-7 years: Findings from the Southampton Women's Survey

Rebecca J **Moon**[a,b], Stefania **D'Angelo**[a,c], Sarah R **Crozier**[a,d], Michelle **Fernandes**[a,e], Caroline **Fall**[a], Catharine R **Gale**[a], Keith M **Godfrey**[a,f], Justin H **Davies**[b,g], Cyrus **Cooper**[a,f,h], Nicholas C **Harvey**[a,f]

Affiliations:

a) MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD, UK

b) Paediatric Endocrinology, Southampton Children's Hospital, University Hospital Southampton NHS Foundation Trust, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD, UK

c) MRC Versus Arthritis Centre for Musculoskeletal Health and Work, MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK

d) NIHR Applied Research Collaboration Wessex, Southampton Science Park, Innovation Centre, 2 Venture Road, Chilworth, Southampton, SO16 7NP, UK

e) Department of Neonatal Medicine, Southampton Children's Hospital, University Hospital Southampton NHS Foundation Trust, Princess Anne Hospital, Tremona Road, Southampton, SO16 5YA, UK

f) NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton General Hospital, Tremona Road, Southampton, SO16 6YD, UK

g) Faculty of Medicine, University of Southampton, Southampton General Hospital, Tremona Road, Southampton, UK

h) NIHR Biomedical Research Centre, University of Oxford, UK

Corresponding Author:

Dr Rebecca Moon, rm@mrc.soton.ac.uk

MRC Lifecourse Epidemiology Centre, University of Southampton, Tremona Road, Southampton, SO16 6YD, UK

Competing Interests

RJM has received travel bursaries from Kyowa Kirin unrelated to this work. KMG has received reimbursement for speaking at conferences sponsored by companies selling nutritional products, and is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec, BenevolentAI Bio Ltd. and Danone, outside the submitted work. JHD has received travel bursaries from Novo Nordisk, SANDOZ and Pfizer unrelated to this work. CC reports personal fees from ABBH, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier and Takeda, outside the submitted work. NCH reports personal fees, consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Shire, UCB, Kyowa Kirin, Consilient Healthcare and Internis Pharma, outside the submitted work. SD, CG, MF and SRC declare no potential conflicts of interest.

Funding

This work was supported by grants from Medical Research Council (MRC) [MC_PC_21003; MC_PC_21001], British Heart Foundation, National Institute for Health and Care Research

(NIHR) Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, NIHR Oxford Biomedical Research Centre, University of Oxford. The work leading to these results was supported by the European Union's Seventh Framework Programme (FP7/2007–2013), projects EarlyNutrition, ODIN and LifeCycle under grant agreements numbers 289346, 613977 and 733206, and by the BBSRC (HDHL-Biomarkers, BB/P028179/1), as part of the ALPHABET project, supported by an award made through the ERA-Net on Biomarkers for Nutrition and Health (ERA HDHL), Horizon 2020 grant agreement number 696295. KMG is supported by the UK Medical Research Council (MC_UU_12011/4), the National Institute for Health Research (NIHR Senior Investigator (NF-SI-0515-10042) and NIHR Southampton Biomedical Research Centre (IS-BRC-1215-20004)), the European Union (Erasmus+ Programme ImpENSA 598488-EPP-1-2018-1-DE-EPPKA2-CBHE-JP), British Heart Foundation (RG/15/17/3174, SP/F/21/150013) and the US National Institute On Aging of the National Institutes of Health (Award No. U24AG047867). RJM is funded by Health Education England (HEE)/NIHR for this research project. MF is funded by the MRC via a MRC Post-Doctoral Clinical Research Training Fellowship.

Author contributions:

RJM: Conceptualization, formal analysis, writing – original draft. SD: data curation, formal analysis, writing – review & editing. SRC: data curation, formal analysis, writing – review & editing; MF: conceptualization, writing – review & editing; CF: conceptualization, investigation, methodology, writing – review & editing; CRG: conceptualization, investigation, methodology, data curation, writing – review & editing. KMG: conceptualization, funding acquisition, investigation, methodology, project administration, supervision, writing – review & editing. JHD: writing – review & editing. CC: conceptualization, funding acquisition,

investigation, methodology, project administration, supervision, writing – review & editing. NCH: conceptualization, funding acquisition, investigation, methodology, project administration, supervision, writing – review & editing

Abstract (297 words)

Introduction

Poor cognitive function and osteoporosis commonly co-exist in later life. In women, this is often attributed to post-menopausal estrogen loss. However, a common early life origin for these conditions and the associations between cognitive function and bone mineral density (BMD) in childhood have not previously been explored. We examined these relationships at age 6-7 years in the Southampton Women's Survey (SWS) mother-offspring cohort.

Methods

Child occipitofrontal circumference (OFC), a proxy for brain volume, intelligence quotient (IQ) [Wechsler Abbreviated Scale of Intelligence] and visual recognition and working memory [CANTAB® Delayed Matching to Sample (DMS) and Spatial Span Length (SSP), respectively] were assessed. Whole-body-less-head (WBLH) and lumbar spine dual-energy X-ray absorptiometry [Hologic Discovery] (DXA) were performed to measure bone area (BA), bone mineral content (BMC), BMD and bone mineral apparent density (BMAD). Linear regression was used to examine associations between age and sex standardized variables (β represent standard deviation (SD) difference per SD of cognitive function).

Results

DXA was performed in 1331 children (mean (SD) age 6.8 (0.33) years, 51.5% male), with OFC, IQ, DMS and SSP assessed in 1250, 551, 490 and 460, respectively. OFC (β=0.25 SD/SD, 95%CI 0.20,0.30), IQ (β=0.11 SD/SD, 95%CI 0.02,0.19), and DMS (β=0.11, SD/SD, 95%CI 0.01,0.20) were positively associated with WBLH BA, with similar associations for

lumbar spine BA. OFC and DMS were also positively associated with WBLH BMC, but only OFC was associated with BMD (WBLH: β=0.38 SD/SD, 95%CI 0.33,0.43; LS: β=0.19 SD/SD, 95%CI 0.13,0.24).

Conclusion

Childhood brain volume was positively associated with measures of skeletal size and BMD, whereas IQ and memory were associated only with skeletal size. These findings suggest that common early life determinants for skeletal growth and BMD and cognitive function should be explored to identify potential early-life approaches to preventing osteoporosis and cognitive decline.

Keywords: bone mineral density, cognition, height, intelligence quotient, occipitofrontal circumference

1. Introduction

Both cognitive decline and osteoporosis are major public health issues worldwide, and coexistence of these is common. Osteoporosis and associated fractures are particularly common in individuals with dementia and evidence suggests that sustaining a fracture accelerates cognitive decline [1]. Poorer mobility and diet may contribute to the increased risk of osteoporosis in those with dementia, but bone mineral density (BMD) has also been associated with cognitive function in adults without dementia [2, 3]. Furthermore bone loss has been shown to predict subsequent cognitive decline in a longitudinal study of older women [4], potentially suggesting a common pathway or origin.

Proposed mechanisms for the coexistence of bone loss and cognitive decline include lifetime estrogen exposure and/or post-menopausal lack of estrogen in women, common lifestyle risk factors such as smoking or nutrition, and chronic inflammation. Hormonal interaction between the brain and bone is also increasingly recognized. For example, in mouse models,

osteocalcin, an osteoblast-derived hormone that can cross the blood brain barrier, has a role in brain and cognitive development. *Osteocalcin* -/- mice have smaller brain volumes and a major deficit in learning and memory [5]. In contrast brain-derived neurotransmitters also appear to influence bone mass, for example serotonin, neuropeptide Y and the sympathetic and parasympathetic nervous systems [6].

Despite the increasing understanding of important interactions between the brain and bone and the observed relationships between cognition and bone health in later life, it has not been established if similar relationships between cognition and skeletal development exist in early life. We therefore assessed the relationships between measures of cognitive function, including intelligence quotient (IQ) and working memory, and occipitofrontal circumference (OFC), as a proxy for brain volume [7], with skeletal size and BMD at age 6-7 years.

2. Methods

2.1 The Southampton Women's Survey

The Southampton Women's Survey is a prospective pre-conception mother-offspring cohort study. Details of the study have been previously published [8]. Briefly, 12,583 non-pregnant women aged 20-34 years living in the city of Southampton, UK were recruited into the study during 1998-2002 and those that reported a pregnancy during the study period were invited to participate in pregnancy and offspring follow-up. Infant anthropometric data including birth weight, length and OFC were measured at birth by a trained research nurse.

The SWS was conducted according to the guidelines laid down in the Declaration of Helsinki, and the Southampton and South-West Hampshire Research Ethics Committee approved all procedures (06/Q1702/104). Written informed consent was obtained from all participants and by a parent or guardian with parental responsibility on behalf of their children.

2.2 Follow-up at 6-7 years of age

A subset of the children were invited to participate in assessments of bone health and/or cognition at ages 6-7 years. Anthropometric data was collected by trained research nurses. Height was measured with a Leicester height measurer (Seca Ltd, Birmingham, UK) to the nearest 0.1 cm with the head placed in the Frankfurt plane. Weight was measured in light clothing to the nearest 0.1 kg using electronic scales (Seca Ltd, Birmingham, UK). OFC was measured using a cloth tape to the nearest 0.1cm. Standard deviations scores (SDS) for age and sex were calculated using the British 1990 reference data [9, 10].

A whole-body dual-energy X-ray absorptiometry (DXA) scan was obtained using a Hologic Discovery Instrument (Hologic Inc., Bedford, MA, USA) to measure whole-body-less-head (WBLH) and lumbar spine bone area (BA), bone mineral content (BMC), BMD and bone mineral apparent density (BMAD). All scan images were reviewed and any with excessive movement or artefact were excluded. The DXA instrument underwent daily calibration using a spine phantom. The experimental coefficient of variation for this instrument when a spine phantom was repeatedly scanned in the same position 16 times, in a single session with no repositioning, was 0.68%.

A subset of the children had cognitive testing by a trained research nurse supervised by an educational psychologist during a home visit. The Wechsler Abbreviated Scale of Intelligence (WASI) was used to assess full-scale IQ as an estimate of overall cognitive ability [11]. Specific components of executive function were assessed using tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition, Cambridge, United Kingdom). Delayed Matching to Subject (DMS) and Spatial Span (SSP) are both tests of memory. DMS assesses forced choice recognition memory for novel non-verbalizable patterns, and tests both simultaneous and short-term visual memory. SSP assesses working memory capacity. We used the following outcomes: DMS total correct and SSP longest span length recalled. For both of these tests, a higher score indicates greater cognitive ability for the function assessed.

2.3 Statistical analysis

Data were included if the child had a DXA scan at age 6-7 years and OFC or cognitive testing data. All data were visually checked for normality of distribution. Mean (standard deviation) and median (interquartile range) were used to described normally distributed and non-normally distributed continuous variables, respectively; n (%) was used to describe categorical variables. T-tests, Mann-Whitney U-tests and chi-squared tests were used to compare normally, non-normally distributed and categorical variables, respectively.

Both cognitive function data and DXA outcomes were adjusted for age and sex at assessment using linear regression. All variables were standardized to allow comparison of regression coefficients. Linear regression was used to examine the associations between measures of cognitive function and OFC with DXA measures and height z-score. Linear regression was used to assess for evidence of a statistical interaction with child sex. All data were analysed using Stata 18.0 (Statacorp, Texas, USA).

3. Results

DXA assessment of WBLH and/or lumbar spine was available for 1331 children at age 6-7 years. The children who had DXA data tended to be born to mothers who were older at delivery, more highly educated and less likely to smoke in late pregnancy, and the children were on average heavier at birth and breastfed for longer than those for whom DXA data was not available (Supplementary Table 1). OFC measurement at 6-7 years and at birth were available for 1323 and 1280 of these children, respectively. 551, 490 and 460 of the children with DXA assessment completed the IQ, DMS and SSP testing, respectively (Figure 1). In comparison to those who had DXA but did not have cognitive function tests, the children who had their cognitive function tested were on average older, but of similar height, weight, and OFC z-scores, and DXA outcomes adjusted for age and sex (Supplementary Table 2).

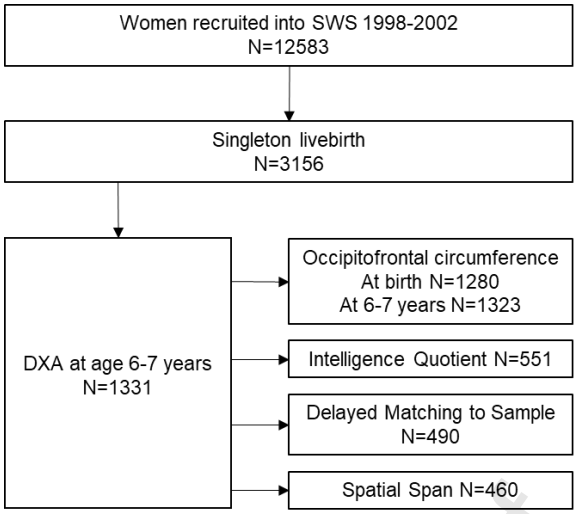

Figure 1: Participant flow in the study

The median interval between cognitive function testing and DXA was 45 days (IQR 20, 79). IQ, DMS (total correct) and SSP were similar between the boys and girls (Table 1). The boys were taller and had larger OFC than the girls, but z-scores for age and sex for these measures were similar (Table 1). The girls had greater bone area for WBLH, whereas boys had greater bone area for lumbar spine (Table 1). The boys had higher aBMD and BMAD for WBLH, whereas BMD and BMAD were higher in the girls at the lumbar spine (Table 1).

	Boys		Girls		p
	N		N		
Anthropometry					
Age (years)	684	6.69 (0.29)	644	6.69 (0.30)	0.74
Height (cm)	679	121.0 (5.1)	641	120.1 (5.4)	0.003
Height z-score	679	0.18 (0.94)	641	0.13 (1.00)	0.42
Weight (kg), median (IQR)	680	22.9 (21.0, 25.3)	638	22.9 (20.9, 25.7)	0.89
Weight z-score	680	0.23 (1.01)	638	0.26 (1.04)	0.66
OFC (cm)	681	52.7 (1.4)	642	52.0 (1.4)	<0.001
OFC z-score	681	-0.46 (0.90)	642	-0.38 (1.17)	0.18

Cognitive function					
Age (years)	282	6.94 (0.21)	273	6.93 (0.22)	0.72
Intelligence Quotient (IQ)	282	103 (15)	269	104 (15)	0.35
Delayed matching to sample (total correct)	252	9 (3)	238	9 (2)	0.61
Spatial span length	236	4 (1)	224	4 (1)	0.50
DXA					
Age (years)	685	6.83 (0.32)	646	6.84 (0.34)	0.58
Whole body less head					
Bone area (cm^2)	653	904.43 (62.91)	626	913.92 (64.80)	0.008
Bone mineral content (BMC) (g)	653	548.58 (74.70)	626	546.11 (77.11)	0.56
Bone Mineral density (BMD) (g/cm^2)	653	0.604 (0.047)	627	0.595 (0.050)	<0.001
Bone mineral apparent density (BMAD) (g/cm^3)	653	0.020 (0.001)	626	0.020 (0.001)	<0.001
Lumbar spine					
Bone area (cm^2)	673	34.88 (3.31)	635	32.98 (3.03)	<0.001
Bone mineral content (BMC) (g)	673	18.68 (2.83)	635	18.16 (2.79)	<0.001
Bone Mineral density (BMD) (g/cm^2)	673	0.535 (0.059)	635	0.550 (0.060)	<0.001
Bone mineral apparent density (BMAD) (g/cm^3)	635	0.181 (0.021)	595	0.191 (0.021)	<0.001

Table 1: Comparison of boys and girls included in the study

All shown as mean (SD), unless otherwise stated.

OFC z-score was very weakly associated with IQ (β=0.07 SD/SD, 95%CI -0.01, 0.15, p=0.11) but not with DMS (total correct) (β=0.01 SD/SD 95%CI -0.08, 0.09, p=0.91) or SSP (β=0.04 SD/SD, 95%CI -0.06, 0.13, p=0.44). However, cognitive function measures were positively associated (DMS-IQ β=0.18 SD/SD 95%CI 0.09, 0.27, p<0.001; SSP-IQ β=0.29 SD/SD, 95%CI 0.20, 0.38, p<0.001; SSP-DMS β=0.18 SD/SD, 95%CI 0.08, 0.27, p<0.001).

3.1 Occipitofrontal circumference and skeletal size and BMD

OFC z-score at age 6-7 years was strongly associated with bone area, BMC, BMD and BMAD for WBLH and lumbar spine (Figure 2; Supplementary Table 3). OFC z-score was also associated with height at age 6-7 years, with an association of similar magnitude to those observed with bone outcomes (β=0.37 SD/SD, 95%CI 0.32, 0.42, p<0.001; Figure 2). There was no interaction with the child's sex; associations stratified by sex are shown in Supplementary Table 3.

1280 of the children also had OFC measured at birth. Similar, but weaker, associations were observed between OFC at birth and DXA measures at 6-7 years apart for with lumbar spine BMD and BMAD (Figure 2; Supplementary Table 3).

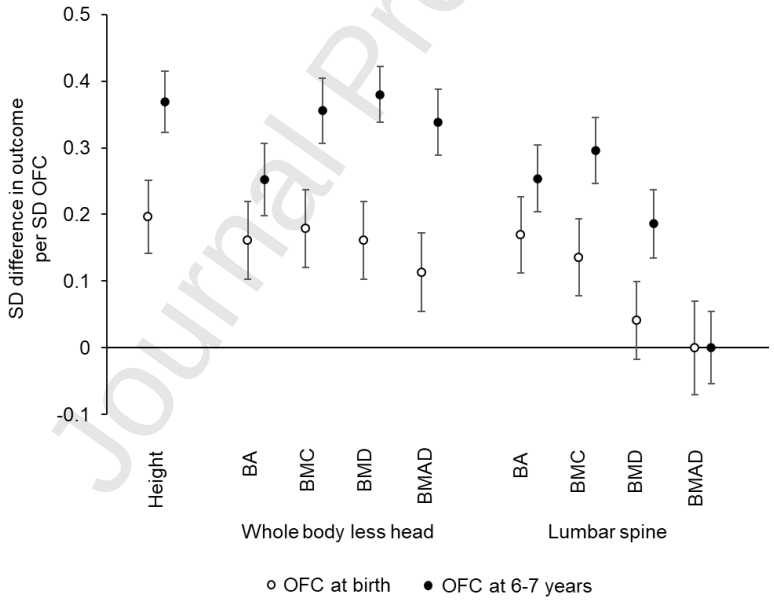

Figure 2: Associations between occipitofrontal circumference (OFC) at birth and at 6-7 years with measures of skeletal size and bone mineral density at 6-7 years.

Markers represent β (SD difference in outcome per SD OFC) and 95% CI. BA, bone area; BMC, bone mineral content; BMD, bone mineral density (BMD); BMAD bone mineral apparent density

3.2 IQ

IQ was associated with measures of skeletal size including height (β=0.16 SD/SD, 95%CI 0.08, 0.24, p<0.001), WBLH bone area (β=0.11 SD/SD, 95%CI 0.02, 0.19, p=0.01) and lumbar spine bone area (β=0.15 SD/SD, 95%CI 0.06, 0.23, p=0.001) (Figure 3A). A positive association was also observed between IQ and BMC at the lumbar spine (β=0.09 SD/SD, 95%CI 0.01, 0.18, p=0.03), with a similar, but weaker, association for WBLH BMC (β=0.07 SD/SD, 95%CI -0.01, 0.16, p=0.09). There were no clear associations between IQ and BMD or BMAD for WBLH nor lumbar spine (Figure 3A). There were no statistical interactions with the child's sex (Supplementary Table 4).

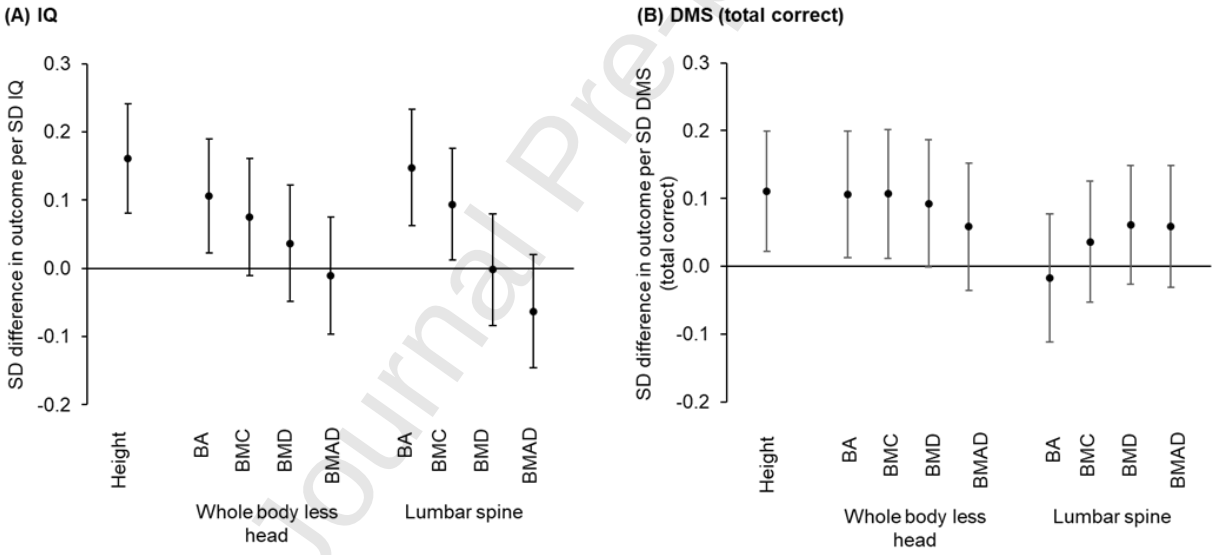

Figure 3: Associations between intelligence quotient (IQ) and Delayed Matching to Sample (DMS) (total correct) with measures of skeletal size and bone mineral density at 6-7 years.

Markers represent β (SD difference in outcome per SD IQ or DMS) and 95% CI. BA, bone area; BMC, bone mineral content; BMD, bone mineral density (BMD); BMAD bone mineral apparent density

3.3 Tests of memory

DMS (total correct) was similarly positively associated with height (β=0.11 SD/SD, 95%CI 0.02, 0.20, p=0.02) and WBLH bone area (β=0.11 SD/SD, 95%CI 0.01, 0.20, p=0.03) but not bone area at the lumbar spine (Figure 3B). DMS (total correct) was also positively associated with WBLH BMC (β=0.11 SD/SD, 95%CI 0.01, 0.20, p=0.03) with a similar association for BMD (β=0.09 SD/SD, 95%CI -0.00, 0.19, p=0.05). Associations at the lumbar spine were weaker (Figure 3B). These associations were similar in analyses stratified by sex (Supplementary Table 4). There were no associations between SSP and height or DXA outcomes (Supplementary Table 4).

4. Discussion

In this prospective mother-offspring cohort study, OFC, IQ and memory were all positively associated with skeletal size. Additionally, OFC was associated with measures of bone mineralisation. In a subset of the cohort, an association between visuospatial memory and WBLH BMD was observed, but relationships between IQ and BMD were not clearly apparent. These findings did not differ by sex.

OFC has been considered a proxy marker of brain size in otherwise healthy individuals, more accurately so in younger children than adolescents and adults [7]. In previous studies, absolute head circumference, growth in OFC during early childhood and MRI derived brain volume have been shown to correlate with IQ in children and young adults [12-14], and one study suggested OFC in early childhood correlates with IQ in adulthood [15]. However this relationship is not consistently reported [16], as in our cohort. Indeed, our findings suggest that the associations of brain volume (as determined by OFC in children at age 6-7 years) with bone size and density are stronger than the relationships of the functional cognitive

measures with bone size and density. Positive relationships between cognitive function and height have also previously been recognized [17, 18], and indeed WBLH bone area and BMC measured on DXA is partly a function of height, which could account for the relationships observed in our cohort.

To our knowledge, there are scant data relating OFC, other measures of brain size or cognitive function to BMD in children. Interestingly, OFC was associated with WBLH BMD and BMAD, but relationships between IQ and BMD/BMAD were not observed. This may partly reflect the smaller subset of children for whom IQ assessment was completed. In contrast, the relationships between visuospatial memory, assessed by DMS, and WBLH BMC and BMD were stronger than with IQ in this group of children. This is similar to findings in later life. For example, Loskutova et al demonstrated that early cognitive dysfunction, particularly in memory, was associated with lower BMD after adjustment for traditional risk factors [19]. In the Framingham Offspring Cohort, verbal memory was positively associated with BMD in women and visual memory with BMD in men at mean ages of 65 and 66 years, respectively [2], and in the NHANES III cross-sectional survey, verbal memory impairment prevalence decreased as femoral neck BMD quintile increased in both men and women [20]. In our cohort, there were no associations observed between either skeletal size or mineralization and working memory assessed using spatial span length. However, this test may have a lower ability to discriminate between individuals as all test values were integers between 2 and 7.

The relationship between cognitive function and BMD in later life has typically been attributed to common multifactorial risk factors for both outcomes over the life course, including diet and estrogen exposure. Our finding that OFC, and to a lesser extent visuospatial memory, are associated with WBLH BMD in early childhood would suggest that a common factor(s) far earlier in development may also be important. Indeed, OFC at birth was also positively associated with skeletal size and BMD, suggesting exposures during fetal life or shared genetic causes [21] may also be important. Lawlor et al previously

demonstrated a number of factors to be associated with childhood IQ, including maternal IQ, parity, maternal age and social class [22]. Many of these have also been associated with neonatal and childhood bone geometry and BMD [23, 24]. Epigenetic programming in early life may be important to both bone and cognitive outcomes [25-27]. Alternatively, hormonal interaction between the brain and bone could underlie the observed associations. Osteocalcin derived from osteoblasts has a role in brain volume, cognitive function and cerebral gene upregulation in the mouse model [5, 28]; it could be a mechanism through which skeletal size is linked to head circumference and brain volume, but care should be taken when translating this finding to humans [29].

Other hormones also have positive effects on both cognitive function and growth. Serum insulin-like growth factor-1 (IGF-1), which mediates the actions of growth hormone, has been positively associated with IQ and cognitive function in healthy children [30], children with growth hormone deficiency [31] and older adults [32], and the IGF-1 receptor is expressed widely throughout the brain where it is thought to have important roles in early brain development [33]. Exogenous growth hormone replacement in both adults and children with confirmed growth hormone deficiency has also been shown to have small but positive effects on IQ and memory [34-36]. Vitamin D status, particularly during early development, might also be an important mediator of both skeletal health and cognitive function. Pregnancy vitamin D supplementation increases offspring BMD in intervention studies [37-39] although the effects on offspring height and bone area are less consistent. In observational studies, maternal 25-hydroxyvitamin D status during pregnancy has been associated with offspring IQ in some but not all studies [40-42], although, to our knowledge, this has not been explored in intervention studies.

The strength of this study is in the detailed phenotyping of a population mother-offspring cohort, including the gold standard DXA for assessment of bone mineral density, and measures of both IQ and memory. There are several limitations to this study, including a limited assessment of cognitive function. This included only IQ and assessments of

visuospatial and working memory. Furthermore, this study was undertaken in a cohort of children living in a high-income country who, on average, were well-nourished considering the mean weight z-score for age and sex using population data was above zero (mean for our study population of 0.23 for boys and 0.26 for girls) and of slightly above average intelligence (mean IQ of 103 and 104 for boys and girls, respectively). They were predominantly of White ethnicity, reflecting the local population from which the cohort were recruited, and the children for whom cognitive function data was available were not fully representative of the original birth cohort. They weretypically born to older and more well-educated mothers, fewer smoked in pregnancy and the infants were on average heavier at birth and breastfed for longer. Our findings may not therefore be generalizable to other ethnic groups or populations in which malnutrition and/or stunting is highly prevalent. Nonetheless, whilst poor cognitive outcomes have been associated with stunting in lower-middle income countries [43], these findings also highlight that relationships between skeletal size and cognitive function exist in children in high income countries. One child in the analysed dataset had epilepsy and an OFC within the normal range; cognitive testing was not performed with this child, but their OFC data was included. There were no other children with known significant neurological impairment or disorders associated with micro- or macrocephaly.

Importantly, in this observational work, a causal relationship between brain size or function and skeletal growth cannot be determined and indeed a causal relationship between the two outcomes may not exist. The observed relationships may result from a common cause such as a positive effect of early life nutrition on both brain development and skeletal growth. Future work should attempt to elucidate potential early life factors that might be important to allow consideration of approaches to optimise both skeletal health and cognitive function.

5. Conclusion

In conclusion, childhood OFC and visual-spatial working memory were positively associated with measures of skeletal size and BMD, whereas IQ was associated only with skeletal size in a smaller cohort of children. These findings suggest the potential for common novel approaches to improving bone and cognitive health at the population level through early life interventions.

6. Table Legend

Table 1: Comparison of boys and girls included in the study.

7. Figure Legends

Figure 1: Participant flow in the study

Figure 2: Associations between occipitofrontal circumference (OFC) at birth and at 6-7 years with measures of skeletal size and bone mineral density at 6-7 years.

Markers represent β (SD difference in outcome per SD OFC) and 95% CI. BA, bone area; BMC, bone mineral content; BMD, bone mineral density (BMD); BMAD bone mineral apparent density

Figure 3: Associations between intelligence quotient (IQ) and Delayed Matching to Sample (DMS) (total correct) with measures of skeletal size and bone mineral density at 6-7 years.

Markers represent β (SD difference in outcome per SD IQ or DMS) and 95% CI. BA, bone area; BMC, bone mineral content; BMD, bone mineral density (BMD); BMAD bone mineral apparent density

8. References

1. Min D, Lee HS, Shin M. Consequences of fall-induced hip fractures on cognitive function, physical activity, and mortality: Korean longitudinal study of aging 2006-2016. *Injury* 2021;52(4):933-40.

2. Stefanidou M, O'Donnell A, Himali JJ, DeCarli C, Satizabal C, Beiser AS, et al. Bone Mineral Density Measurements and Association With Brain Structure and Cognitive Function: The Framingham Offspring Cohort. *Alzheimer Disease & Associated Disorders* 2021;35(4):291-7.
3. Kang HG, Park HY, Ryu HU, Suk SH. Bone mineral loss and cognitive impairment: The PRESENT project. *Medicine (Baltimore)* 2018;97(41):e12755.
4. Lui LY, Stone K, Cauley JA, Hillier T, Yaffe K. Bone loss predicts subsequent cognitive decline in older women: the study of osteoporotic fractures. *J Am Geriatr Soc* 2003;51(1):38-43.
5. Obri A, Khrimian L, Karsenty G, Oury F. Osteocalcin in the brain: from embryonic development to age-related decline in cognition. *Nat Rev Endocrinol* 2018;14(3):174-82.
6. Chamouni A, Schreiweis C, Oury F. Bone, brain & beyond. *Rev Endocr Metab Disord* 2015;16(2):99-113.
7. Bartholomeusz HH, Courchesne E, Karns CM. Relationship between head circumference and brain volume in healthy normal toddlers, children, and adults. *Neuropediatrics* 2002;33(5):239-41.
8. Inskip HM, Godfrey KM, Robinson SM, Law CM, Barker DJ, Cooper C. Cohort profile: The Southampton Women's Survey. *Int J Epidemiol* 2006;35(1):42-8.
9. Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. *Arch Dis Child* 1995;73(1):25-9.
10. Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA. Cross sectional stature and weight reference curves for the UK, 1990. *Arch Dis Child* 1995;73(1):17-24.
11. Wechsler D. Wechsler Abbreviated Scale of Intelligence 2nd edition. Bloomington, MN: Pearson; 2011.
12. Kirkegaard H, Möller S, Wu C, Häggström J, Olsen SF, Olsen J, et al. Associations of birth size, infancy, and childhood growth with intelligence quotient at 5 years of age: a Danish cohort study. *Am J Clin Nutr* 2020;112(1):96-105.
13. Beck IH, Bilenberg N, Davidsen KA, Rasmussen AA, Boye H, Jensen TK. Prenatal and early childhood predictors of intelligence quotient (IQ) in 7-year-old Danish children from the Odense Child Cohort. *Scand J Public Health* 2023;51(6):862-73.
14. Flensborg-Madsen T, Falgreen Eriksen HL, Mortensen EL. Early life predictors of intelligence in young adulthood and middle age. *PLoS One* 2020;15(1):e0228144.
15. Jaekel J, Sorg C, Baeuml J, Bartmann P, Wolke D. Head Growth and Intelligence from Birth to Adulthood in Very Preterm and Term Born Individuals. *J Int Neuropsychol Soc* 2019;25(1):48-56.
16. Gale CR, O'Callaghan FJ, Bredow M, Martyn CN. The influence of head growth in fetal life, infancy, and childhood on intelligence at the ages of 4 and 8 years. *Pediatrics* 2006;118(4):1486-92.
17. Gale C. Commentary: Height and intelligence. *International Journal of Epidemiology* 2005;34(3):678-9.
18. Luo L, Xie F, Wang Y, Qin LQ, Yin JY, Wan Z. Taller adult height is associated with better performance of cognitive trajectories in Chinese over 45 years old: Evidence from the China Health and Retirement Longitudinal Study. *Geriatr Gerontol Int* 2021;21(8):732-40.
19. Loskutova N, Honea RA, Vidoni ED, Brooks WM, Burns JM. Bone density and brain atrophy in early Alzheimer's disease. *J Alzheimers Dis* 2009;18(4):777-85.
20. Zhang Y, Seshadri S, Ellison RC, Heeren T, Felson DT. Bone Mineral Density and Verbal Memory Impairment: Third National Health and Nutrition Examination Survey. *American Journal of Epidemiology* 2001;154(9):795-802.
21. Guo B, Wang C, Zhu Y, Liu Z, Long H, Ruan Z, et al. Causal associations of brain structure with bone mineral density: a large-scale genetic correlation study. *Bone Res* 2023;11(1):37.
22. Lawlor DA, Batty GD, Morton SM, Deary IJ, Macintyre S, Ronalds G, et al. Early life predictors of childhood intelligence: evidence from the Aberdeen children of the 1950s study. *J Epidemiol Community Health* 2005;59(8):656-63.
23. Harvey NC, Javaid MK, Arden NK, Poole JR, Crozier SR, Robinson SM, et al. Maternal predictors of neonatal bone size and geometry: the Southampton Women's Survey. *J Dev Orig Health Dis* 2010;1(1):35-41.

24. Cole ZA, Gale CR, Javaid MK, Robinson SM, Law C, Boucher BJ, et al. Maternal dietary patterns during pregnancy and childhood bone mass: a longitudinal study. *J Bone Miner Res* 2009;24(4):663-8.
25. Reichenberg A, Mill J, MacCabe JH. Epigenetics, genomic mutations and cognitive function. *Cogn Neuropsychiatry* 2009;14(4-5):377-90.
26. Curtis EM, Fuggle NR, Cooper C, Harvey NC. Epigenetic regulation of bone mass. *Best Pract Res Clin Endocrinol Metab* 2022;36(2):101612.
27. Lillycrop KA, Costello PM, Teh AL, Murray RJ, Clarke-Harris R, Barton SJ, et al. Association between perinatal methylation of the neuronal differentiation regulator HES1 and later childhood neurocognitive function and behaviour. *Int J Epidemiol* 2015;44(4):1263-76.
28. Danilo Correa Pinto J, Delgado IC, Yang H, Clemenceau A, Corvelo A, Narzisi G, et al. Osteocalcin of maternal and embryonic origins synergize to establish homeostasis in offspring. *bioRxiv* 2023:2023.08.11.552969.
29. Manolagas SC. Osteocalcin promotes bone mineralization but is not a hormone. *PLOS Genetics* 2020;16(6):e1008714.
30. Gunnell D, Miller LL, Rogers I, Holly JM. Association of insulin-like growth factor I and insulin-like growth factor-binding protein-3 with intelligence quotient among 8- to 9-year-old children in the Avon Longitudinal Study of Parents and Children. *Pediatrics* 2005;116(5):e681-6.
31. Zhou Z, Luo Y, Gao X, Zhu Y, Bai X, Yang H, et al. Alterations in brain structure and function associated with pediatric growth hormone deficiency: A multi-modal magnetic resonance imaging study. *Front Neurosci* 2022;16:1043857.
32. Landi F, Capoluongo E, Russo A, Onder G, Cesari M, Lulli P, et al. Free insulin-like growth factor-I and cognitive function in older persons living in community. *Growth Horm IGF Res* 2007;17(1):58-66.
33. Wrigley S, Arafa D, Tropea D. Insulin-Like Growth Factor 1: At the Crossroads of Brain Development and Aging. *Front Cell Neurosci* 2017;11:14.
34. Chaplin JE, Kriström B, Jonsson B, Tuvemo T, Albertsson-Wikland K. Growth Hormone Treatment Improves Cognitive Function in Short Children with Growth Hormone Deficiency. *Hormone Research in Paediatrics* 2015;83(6):390-9.
35. Maric NP, Doknic M, Pavlovic D, Pekic S, Stojanovic M, Jasovic-Gasic M, et al. Psychiatric and neuropsychological changes in growth hormone-deficient patients after traumatic brain injury in response to growth hormone therapy. *Journal of Endocrinological Investigation* 2010;33(11):770-5.
36. Sathiavageeswaran M, Burman P, Lawrence D, Harris AG, Falleti MG, Maruff P, et al. Effects of GH on cognitive function in elderly patients with adult-onset GH deficiency: a placebo-controlled 12-month study. *European Journal of Endocrinology* 2007;156(4):439-47.
37. Curtis EM, Moon RJ, D'Angelo S, Crozier SR, Bishop NJ, Gopal-Kothandapani JS, et al. Pregnancy Vitamin D Supplementation and Childhood Bone Mass at Age 4 Years: Findings From the Maternal Vitamin D Osteoporosis Study (MAVIDOS) Randomized Controlled Trial. *JBMR Plus* 2022;n/a(n/a):e10651.
38. Brustad N, Garland J, Thorsen J, Sevelsted A, Krakauer M, Vinding RK, et al. Effect of High-Dose vs Standard-Dose Vitamin D Supplementation in Pregnancy on Bone Mineralization in Offspring Until Age 6 Years: A Prespecified Secondary Analysis of a Double-Blinded, Randomized Clinical Trial. *JAMA Pediatr* 2020;174(5):419-27.
39. Moon RJ, Green HD, D'Angelo S, Godfrey KM, Davies JH, Curtis EM, et al. The effect of pregnancy vitamin D supplementation on offspring bone mineral density in childhood: a systematic review and meta-analysis. *Osteoporos Int* 2023;34(7):1269-79.
40. Cantio E, Bilenberg N, Nørgaard SM, Beck IH, Möller S, Cantio C, et al. Vitamin D status in pregnancy and childhood associates with intelligence quotient at age 7 years: An Odense child cohort study. *Aust N Z J Psychiatry* 2023;57(7):1062-72.

41. Melough MM, Murphy LE, Graff JC, Derefinko KJ, LeWinn KZ, Bush NR, et al. Maternal Plasma 25-Hydroxyvitamin D during Gestation Is Positively Associated with Neurocognitive Development in Offspring at Age 4-6 Years. *J Nutr* 2021;151(1):132-9.
42. Veena SR, Krishnaveni GV, Srinivasan K, Thajna KP, Hegde BG, Gale CR, et al. Association between maternal vitamin D status during pregnancy and offspring cognitive function during childhood and adolescence. *Asia Pac J Clin Nutr* 2017;26(3):438-49.
43. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. Developmental potential in the first 5 years for children in developing countries. *The Lancet* 2007;369(9555):60-70.

Highlights

- We explored the associations between cognitive function and BMD in children.
- Head circumference, IQ and working memory were associated with skeletal size.
- Only head circumference, and not IQ or memory, was associated with BMD.
- Common determinants for skeletal growth and cognitive function should be explored.