Maternal Antenatal Vitamin D Status and Offspring Muscle Development: Findings From the Southampton Women's Survey

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Context: Maternal 25-hydroxyvitamin D [25(OH)D] status in pregnancy has been associated with offspring bone development and adiposity. Vitamin D has also been implicated in postnatal muscle function, but little is known about a role for antenatal 25(OH)D exposure in programming muscle development.

Objective: We investigated the associations between maternal plasma 25(OH)D status at 34 weeks of gestation and offspring lean mass and muscle strength at 4 years of age.

Design and Setting: We studied a prospective UK population–based mother-offspring cohort: the Southampton Women's Survey (SWS).

Participants: Initially, 12 583 nonpregnant women were recruited into the SWS, of whom 3159 had singleton pregnancies; 678 mother-child pairs were included in this analysis.

Main Outcomes Measured: At 4 years of age, offspring assessments included hand grip strength and whole-body dual-energy x-ray absorptiometry, yielding lean mass and percent lean mass. Physical activity was assessed by 7-day accelerometry in a subset of children (n = 326).

Results: The maternal serum 25(OH)D concentration in pregnancy was positively associated with offspring height-adjusted hand grip strength ($\beta = 0.10$ SD/SD, $P = .013$), which persisted after adjustment for maternal confounding factors, duration of breastfeeding, and child's physical activity at 4 years ($\beta = 0.13$ SD/SD, $P = .014$). Maternal 25(OH)D was also positively associated with offspring percent lean mass ($\beta = 0.11$ SD/SD, $P = .006$), but not total lean mass ($\beta = 0.06$ SD/SD, $P = .15$). However, this association did not persist after adjustment for confounding factors ($\beta = 0.09$ SD/SD, $P = .11$).

Conclusions: This observational study suggests that intrauterine exposure to 25(OH)D during late pregnancy might influence offspring muscle development through an effect primarily on muscle strength rather than on muscle mass. **(*J Clin Endocrinol Metab* 99: 330–337, 2014)**

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Abbreviations: DXA, dual-energy x-ray absorptiometry; MVPA, moderate to vigorous physical activity; 25(OH)D, 25-hydroxyvitamin D; SWS, Southampton Women's Survey; VDR, vitamin D receptor.

It is well established that vitamin D is important for muscle function in postnatal life. First, the vitamin D receptor (VDR) has been isolated in skeletal muscle (1), and polymorphisms in the VDR are related to differences in muscle strength (2). Second, severe vitamin D deficiency can present with a proximal myopathy, which improves with vitamin D supplementation (3, 4). Third, subclinical vitamin D insufficiency has been associated with reduced physical performance and muscle function in adolescent girls and older adults (5, 6), although trials of vitamin D supplementation have had inconsistent results with regard to improvements in muscle strength (7, 8).

In addition, evidence is accruing that maternal serum 25-hydroxyvitamin D [25(OH)D] concentrations during pregnancy might influence offspring body composition in childhood (9–12). Thus, in observational studies, maternal antenatal serum 25(OH)D concentrations have been associated positively with bone mass (11–13) and negatively with fat mass (9) in the offspring. Although there are scant data relating postnatal muscle development to intrauterine 25(OH)D exposure, birth weight, a marker of prenatal nutrition, has been associated with muscle mass and grip strength throughout the life course from childhood to older age (14–21), consistent with a potential role for early life influences in long-term muscle development. We therefore aimed, using a population-based mother-offspring cohort study (Southampton Women's Survey [SWS]), to test the hypothesis that maternal serum 25(OH)D concentrations during pregnancy are positively associated with markers of muscle size and strength in the offspring at 4 years of age.

Materials and Methods

The SWS

The SWS is a study of 12 583, initially nonpregnant, women aged 20 to 34 years, residing in the city of Southampton, United Kingdom (22). Assessments of lifestyle, diet, and anthropometry were performed at study entry (April 1998–December 2002), and, for women who became pregnant, again at 11 and 34 weeks of gestation.

The SWS was conducted according to the guidelines 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 participating women and by parents or guardians with parental responsibility on behalf of their children.

Maternal data

At the prepregnancy interview, details of maternal parity, highest educational attainment, and social class were obtained, and height and weight were measured. At 34 weeks of gestation, the women were reweighed, and triceps skinfold thickness was measured. Details of dietary supplements, smoking status, and walking speed were ascertained by direct interview.

Vitamin D analysis

At 34 weeks of gestation, a venous blood sample was obtained and an aliquot of maternal serum was frozen at −80°C. Serum 25(OH)D concentrations were analyzed by RIA (Diasorin). This assay measures both 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3. The assay met the requirements of the UK National Vitamin D External Quality Assurance Scheme, and intra- and interassay coefficients of variance were <10%.

Childhood assessment of body composition, hand grip strength, and habitual physical activity

There were 3159 singleton live births. The children were followed up at birth and during infancy. The duration of breastfeeding was determined from feeding histories obtained at 6 and 12 months of age. Consecutive subsets of children have been assessed postnatally; 900 children underwent dual-energy x-ray absorptiometry (DXA) measurements at the Osteoporosis Centre at Southampton General Hospital at 4 years of age.

At this visit, height was measured using a Leicester height measurer (Seca Ltd), and weight (in underpants only) was measured using calibrated digital scales (Seca Ltd). A whole-body DXA scan was obtained using a Hologic Discovery instrument (Hologic Inc) in pediatric scan mode (Apex 3.1 software), yielding fat mass, lean mass, and bone mineral content. Because children with greater adiposity also tend to have higher absolute lean mass (23), percent fat mass and percent lean mass were subsequently derived using a 3-compartment model (fat mass, lean mass, and bone mineral content) to provide an indication of a more favorable body composition. Furthermore, the variable lean mass adjusted for fat mass was generated to remove any effect of lean mass increasing with fat mass. The coefficient of variation for body composition analysis for the DXA instrument was 1.4% to 1.9%. The reliability of DXA in small subjects has been demonstrated previously (24, 25).

Grip strength was measured using a Jamar handgrip dynamometer (Promedics) with a standardized approach (26). The dynamometer was adjusted to fit the hand size of each individual, and 3 measurements for each hand were taken with the maximum from all 6 measurements being used in the analysis. Because of the learning and tiring effect in grip strength assessment, which can lead to some variability across measurements, and because we wanted to encourage children to get as high a score as possible (26), we opted to use the maximum of 6 measurements as our main outcome. Test-retest reliability has previously been demonstrated in this age group (27), and the coefficient of variation of the 6 measurements was 11%, which is similar to that in other studies (28). Additional sensitivity analyses were undertaken using average grip strength. Grip strength was adjusted for the child's height.

In a subset of children (n = 326), habitual physical activity was assessed using an Actiheart combined accelerometer and heart rate monitor (Cambridge Neurotechnology Ltd) worn continuously for 7 days except during bathing and swimming. The detailed methodology has been described previously (29). Moderate, vigorous, and very vigorous activity levels were grouped to give the primary exposure measure (moderate to vigorous physical activity [MVPA]).

Statistical analysis

Differences in demographic characteristics and body composition of the children by sex were explored using *t* tests and Mann-Whitney *U* tests for normally and nonnormally distributed variables, respectively. Owing to differences between boys and girls, the body composition variables were adjusted for the sex of the child. To allow for subsequent comparison of effect sizes in univariate and multivariable linear regression models, the exposures and outcomes [offspring body composition, physical activity, grip strength, and maternal late pregnancy 25(OH)D concentration] were standardized using a Fisher-Yates transformation to a normally distributed variable with a mean of 0 and an SD of 1. These analyses thus yielded standardized regression coefficients (SD per SD). In the first multivariable model (model 1), we included a number of child (sex, age, height, milk intake at 4 years, and duration of breastfeeding) and maternal (parity, late pregnancy walking speed, late pregnancy smoking status, triceps skinfold thickness at 34 weeks of gestation, age at delivery, and social class) factors. In addition, we explored whether use of maternal BMI (measured either prepregnancy or at 6 months postdelivery) as a measure of adiposity instead of late pregnancy triceps skinfold thickness in model 1 changed the associations. In further analyses, offspring time in MVPA was subsequently added (model 2), and we also determined whether inclusion of either season of maternal 25(OH)D measurement, birth, or 4-year assessment in the models would change the associations. Seasons were defined as winter (December–February), spring (March–May), summer (June–August), or autumn (September–November). All analysis was performed using Stata version 12.0 (StataCorp). A value of $P < .05$ was accepted as statistically significant, and, given the observational nature of the study together with the substantial collinearity among both predictors and outcomes, testing for multiple comparisons was felt to be inappropriate (30).

Results

Characteristics of the mothers and children

Data were available for 678 mother-offspring pairs who had maternal serum 25(OH)D status in late pregnancy and offspring body composition by DXA and grip strength measurement at 4 years. The characteristics of the mothers and children are presented in Tables 1 and 2, respectively.

The mothers included in this study were of similar age (mean ± SD) at delivery (30.7 ± 3.8 years vs 30.6 ± 3.9 years, $P = .69$) and parity (51.3% vs 51.0% nulliparous, $P = .88$) but had achieved a higher educational level (25% vs 21% had a higher degree, $P < .001$) than mothers in the SWS cohort whose children did not participate in this study. In addition, fewer mothers included in this study smoked in late pregnancy (9.9% vs 16.9%, $P = .001$).

The boys and girls were of similar age, height, and weight, but the girls had lower total and percent lean mass (both $P < .0001$) (Table 2). Although absolute grip strength was greater in the boys than in the girls (8.5 ± 1.7 kg vs 8.2 ± 1.7 kg, $P = .023$), after adjustment for child's height, this difference was attenuated and became statistically nonsignificant (8.5 ± 1.5 kg vs 8.3 ± 1.6 kg, $P = .072$). Physical activity indices were similar in boys and girls (Table 2).

Table 1. Characteristics of the Mothers

Maternal Characteristic	Value
No. of subjects	678
Age at delivery, y, mean ± SD	30.7 ± 3.8
Height, cm, mean ± SD	164.0 ± 6.5
BMI, kg/m^2, median (IQR)	
Prepregnancy	24.2 (22.2–27.3)
6 mo postdelivery	25.4 (22.9–29.1)
Triceps skinfold thickness in late pregnancy, mm, median (IQR)	20.8 (16.9–25.7)
Smoking in late pregnancy, % (n)	9.9 (67)
Primiparous, % (n)	51.3 (348)
Duration of breastfeeding, % (n)	
Never tried	13.6 (89)
<1 mo	21.0 (138)
1–3 mo	19.7 (129)
4–6 mo	20.3 (133)
7–11 mo	15.6 (102)
≥12 mo	9.9 (65)
Serum 25(OH)D at 34 wk of gestation, nmol/L, median (IQR)	61 (43–88)
Vitamin D intake at 34 wk of gestation, IU/d, median (IQR)	136 (100–178)
Taking 400 IU/d vitamin D supplement in late pregnancy, % (n)	9.2 (62)

Abbreviation: IQR, interquartile range.

Maternal 25(OH)D and offspring muscle mass and strength

A significant positive correlation was identified between maternal serum 25(OH)D concentration in late pregnancy and offspring height-adjusted grip strength at 4 years (β=0.10 SD/SD, $P = .013$; Figure 1), such that for every SD increase in maternal serum 25(OH)D, offspring height-adjusted grip strength increased by 0.15 kg (95% confidence interval, 0.03–0.27 kg). This association persisted after adjustment for confounding factors (model 1: $\beta = 0.08$ SD/SD, $P = .040$). Furthermore, in the 326 children who had physical activity monitoring, the child's mean daily time in MVPA was positively associated with height-adjusted hand grip strength ($\beta = 0.13$ SD/SD, $P = .011$), and inclusion of time in MVPA strengthened the association between maternal 25(OH)D and offspring grip strength (model 2: $\beta = 0.13$ SD/SD, $P = .014$) (Table 3). Although the associations between maternal 25(OH)D and offspring grip strength appeared somewhat more robust in the girls than in the boys (Table 3), the test for a statistical interaction between maternal serum 25(OH)D concentration and grip strength by child sex did not achieve statistical significance ($P = .30$).

Table 2. Characteristics of the Children

	Boys	Girls
No. of subjects	345	333
Age, y, median (IQR)	4.11 (4.08–4.16)	4.10 (4.07–4.15)
Height, cm, mean ± SD	104.6 ± 3.6	104.1 ± 4.1
Weight, kg, mean ± SD	17.5 ± 2.0	17.4 ± 2.3
Lean mass, kg, mean ± SD	12.4 ± 1.4	11.4 ± 1.4[a]
Fat mass, kg, median (IQR)	4.3 (3.8–4.9)	5.1 (4.4–5.9)[a]
Percent lean mass, %, mean ± SD	71.1 ± 3.9	66.0 ± 4.5[a]
Percent fat mass, %, mean ± SD	25.4 ± 4.0	30.5 ± 4.7[a]
Absolute grip strength, kg, mean ± SD	8.5 ± 1.7	8.2 ± 1.7[b]
Height-adjusted grip strength, kg, mean ± SD	8.5 ± 1.5	8.3 ± 1.6
Time spent in MVPA, min/d, median (IQR)	65.7 (44.8–90.3)	61.5 (45.2–82.7)

Abbreviation: IQR, interquartile range.

[a] $P < .0001$ compared with boys.

[b] $P < .05$.

Maternal serum 25(OH)D concentration in late pregnancy was positively associated with offspring percent lean mass ($\beta = 0.11$ SD/SD, $P = .006$) (Figure 1) and lean mass adjusted for fat mass ($\beta = 0.08$ SD/SD, $P = .035$) but not total lean mass ($\beta = 0.06$ SD/SD, $P = .15$). The associations with percent lean mass and lean mass adjusted for fat mass, however, were attenuated after the addition of potential confounding maternal and child factors (model 1) and just failed to achieve statistical significance ($\beta = 0.07$ SD/SD, $P = .062$ and $\beta = 0.05$ SD/SD, $P = .051$, respectively).

There was a high correlation between the maximum and the mean of six measurements in our cohort ($r = 0.94$, $P < .0001$). In further sensitivity analyses, we repeated the analysis using average grip strength instead of maximum grip strength, and the relationship with maternal 25(OH)D in late pregnancy was almost identical ($\beta = 0.10$ SD/SD, $P = .012$; model 1: $\beta = 0.08$ SD/SD, $P = .042$; model 2: $\beta = 0.12$, $P = .016$). The associations did not differ when maternal body mass index (BMI) was included in the multivariate models as a measure of adiposity instead of maternal triceps thickness in late pregnancy. Finally, the inclusion of either season of 25(OH)D measurement, season of birth, or season of 4-year assessment did not alter the relationships.

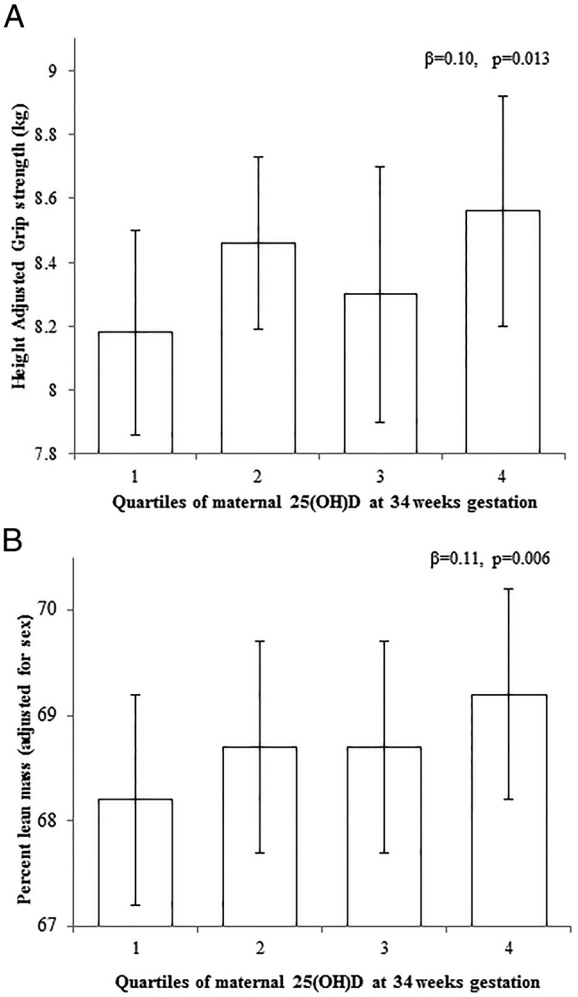

Figure 1. Offspring grip strength (A) and percent lean mass (B) at 4 years of age by quartiles of maternal serum 25(OH)D status at 34 weeks of gestation (means ± 95% CI).

Discussion

In this prospective mother-offspring study, we have identified a number of key associations between maternal serum 25(OH)D concentration in late pregnancy and offspring muscle development. Thus, maternal 25(OH)D status was positively associated with offspring grip strength at 4 years. This finding persisted after adjustment for a number of potential confounding factors relating to maternal/childhood lifestyle, body build, and physical activity. The weaker relationships between offspring muscle mass and maternal 25(OH)D status are consistent with the notion that the association between maternal vitamin D and offspring grip strength might be mediated via an effect on muscle function partly independently of an increase in muscle mass.

The strengths of this study are the detailed phenotyping of the mother-offspring pairs and its prospective design. Although the children included in this study were born to mothers who were slightly older and tended to be better

Table 3. Associations Between Maternal 25(OH)D in Pregnancy and Offspring Grip Strength and Muscle Mass at 4 Years of Age after Addition of Confounding Factors

	β Coefficient (95% Confidence Interval)		
	Unadjusted		
	All (n = 678)	Boys (n = 345)	Girls (n = 333)
Height-adjusted grip strength	0.096 (0.021 to 0.171)[a]	0.060 (−0.045 to 0.165)	0.135 (0.027 to 0.242)[a]
Percent lean mass	0.106 (0.031 to 0.1810[b]	0.097 (0.001 to 0.193)[a]	0.116 (−0.001 to 0.116)
Total lean mass	0.059 (−0.020 to 0.131)	0.119 (0.016 to 0.222)[a]	−0.011 (−0.122 to 0.100)
Lean mass adjusted for fat mass	0.081 (0.006 to 0.156)[a]	0.137 (0.034 to 0.240)[b]	0.022 (−0.088 to 0.133)

Results shown are for standardized variables (SD/SD). Model 1: child sex, age, height, current milk intake, duration of breastfeeding; maternal age and parity at delivery, maternal social class, smoking status, walking speed, and triceps skinfold thickness in late pregnancy. Model 2: model 1 + child's physical activity (minutes per day spent in MVPA) at 4 years of age.

[a] $P < .05$.

[b] $P < .01$.

educated than mothers of children not included, they do represent a wide range of maternal age and family backgrounds, and all comparisons were internal. However, there are a number of limitations to this study. First, although DXA is well validated in adults, there are some problems in children because of their smaller size and tendency to move. Body composition assessment of small subjects by DXA has been validated previously using biochemical assessment of carcass nitrogen content and lipid extraction to determine lean and fat mass, respectively, in piglets, which were sacrificed immediately after DXA scanning (24); we used specific pediatric software, and movement artifacts were minimal. The few scans with excess movement artifacts were excluded from the analysis. Second, measurement of grip strength in children is less straightforward than in adults, but the children were able to cooperate, and the validity and reproducibility of grip strength measurements in this age group has been demonstrated previously (27, 28). Indeed, the coefficient of variation across the 6 measurements was 11%, which is similar to that reported in other studies (28). Despite the greater precision of DXA, stronger relationships with 25(OH)D were identified with grip strength than with lean mass, suggesting that any noise introduced by random variation in the grip measurements did not prevent the detection of meaningful associations. Third, children may remove physical activity monitors, and we did not systematically record this. However, we accounted for nonwear time in the analysis of the accelerometer output. Finally, it is not possible in this observational study to determine whether the observed associations are causal.

There are few previous data relating maternal 25(OH)D concentrations during pregnancy to offspring muscle development. Findings from the Mysore Parthenon Study, a prospective mother-offspring birth cohort in India, demonstrated greater arm muscle area at 5 and 9 years in children born to vitamin D–replete [serum 25(OH)D > 50 nmol/L] compared with vitamin D–depleted [25(OH)D < 50 nmol/L] mothers (10). Consistent with these results, in the Avon Longitudinal Study of Parents and Children (ALSPAC), a positive association between maternal estimated UV-B exposure in the third trimester [a proxy for maternal 25(OH)D concentrations] and offspring lean mass determined by DXA at 9 years was observed (12). In contrast to our findings, in the Mysore study, no difference in grip strength was identified at 9 years of age between children born to mothers defined as vitamin D–deficient and –replete at 28 to 32 weeks of gestation (10). However, there are marked differences across these 3 populations in terms of exposure definition [maternal 25(OH)D concentration or sunlight exposure], 25(OH)D assay technique, confounding factors considered, and socioeconomic status, childhood body composition, 25(OH)D distribution, and age of the children studied, making direct comparison difficult. Furthermore, racial differences in vitamin D metabolism have been demonstrated (31) and increases in sex hormones at the inception of puberty, together with greater exposure to manual work, may have obscured any association between maternal pregnancy serum 25(OH)D concentration and offspring grip strength at 9 years in the Mysore study.

Taken together, the results of these previous studies are consistent with a positive association between maternal 25(OH)D concentration during pregnancy and offspring muscle development. However, our findings suggest that this relationship might be mediated partly via muscle function rather than purely by muscle size. Such a disparity between the influence of muscle size and strength has been observed in relation to outcomes such as disability and mortality in adult cohorts (32), and there is good evidence that vitamin D might influence muscle strength in postnatal life: The VDR has been isolated in skeletal muscle (1), and myopathy is a prominent feature of vitamin D deficiency in both infants and adults; histological studies have demonstrated atrophy of the type II muscle fibers in vitamin D–deficient subjects (33, 34). These fibers are

Table 3. Continued

β Coefficient (95% Confidence Interval)					
Model 1			Model 2		
All (n = 636)	Boys (n = 316)	Girls (n = 320)	All (n = 309)	Boys (n = 145)	Girls (n = 164)
0.083 (0.004 to 0.162)[a]	0.033 (−0.079 to 0.145)	0.142 (0.028 to 0.256)[a]	0.129 (0.027 to 0.231)[a]	0.085 (−0.073 to 0.243)	0.182 (0.044 to 0.320)[a]
0.074 (−0.004 to 0.151)	0.056 (−0.045 to 0.157)	0.085 (−0.035 to 0.204)	0.091 (−0.019 to 0.200)	0.090 (−0.060 to 0.239)	0.085 (−0.080 to 0.250)
0.036 (−0.012 to 0.083)	0.042 (−0.028 to 0.112)	0.026 (−0.040 to 0.092)	−0.003 (−0.069 to 0.064)	0.013 (−0.093 to 0.119)	−0.026 (−0.113 to 0.061)
0.053 (0.000 to 0.106)	0.053 (−0.021 to 0.128)	0.046 (−0.032 to 0.124)	0.025 (−0.050 to 0.100)	0.037 (−0.073 to 0.146)	0.004 (−0.101 to 0.110)

necessary for rapid bursts of speed and power and are therefore likely to be involved in the action required for grip strength assessment. Vitamin D supplementation may improve muscle strength, although the results of randomized controlled trials are inconsistent (7, 8). Importantly, IM fat accumulation appears to be inversely associated with 25(OH)D concentration independent of BMI and muscle area (35), and muscle adiposity is negatively related to muscle strength (36, 37). Anthropometric measures such as arm muscle area cannot distinguish lean mass from IM fat infiltration and hence might explain some of the observed discrepancy in associations between maternal 25(OH)D and offspring muscle strength compared with muscle mass. Given that fiber number is largely set in utero and muscle size increases by hypertrophy postnatally (38, 39), another possibility is that maternal 25(OH)D concentrations might in some way influence fiber number or motor unit size more than overall mass. Such effects, in the context of maternal undernutrition, have been demonstrated in animal models (40).

Clinically, these findings could have long-term health benefits. There is evidence for the tracking of muscle function and mass (41–46); Gabel et al (41) demonstrated significant tracking of muscle function over a 15-month period in preschool children, and others have shown tracking of muscle strength through childhood and into early adulthood (43). Indeed, our own studies of fetal and postnatal growth suggest that most children have settled onto a sustained growth trajectory by the age of 4 years (47). Muscle strength peaks in young adulthood before declining, and low grip strength in adulthood has been associated with poor health outcomes including diabetes, falls, fractures, and all-cause mortality (48, 49). Accordingly, we expect that the greater muscle strength identified at 4 years of age in children born to mothers with higher vitamin D levels would track into adulthood, and this method of increasing peak muscle mass might be one approach to addressing the increasing burden of sarcopenia. Previous research has demonstrated that for every SD reduction in grip strength in older women, the risk of incident falls and fractures during follow-up over the subsequent 3 to 9 years was increased by 33% and 25%, respectively (50). We observed a 0.25 SD difference in height-adjusted grip strength between the children in the lowest and highest quartiles of maternal vitamin D status; thus, if this difference were maintained into adulthood, it might translate into an 8% reduction in falls risk and a 6% decrease in fracture risk.

In summary, in this observational study, maternal serum 25(OH)D concentration in late pregnancy was associated positively with offspring hand grip strength at 4 years independent of child's height and a range of other maternal and childhood confounding factors. In contrast, a weaker positive nonsignificant association was observed with offspring percent lean mass, observations that would be consistent with maternal 25(OH)D status influencing muscle function more than muscle mass. These results suggest that vitamin D supplementation in pregnancy might lead to improved muscle development in the offspring. However, formal testing of this hypothesis in an interventional setting (51, 52) should be undertaken before the development of any clinical recommendations.

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