

*Original Research Article***Cow Milk Consumption, Insulin-Like Growth Factor-I, and Human Biology: A Life History Approach**

ANDREA S. WILEY\*

*Human Biology Program and Department of Anthropology, Indiana University, Bloomington, Indiana 47405*

**Objective:** To assess the life history consequences of cow milk consumption at different stages in early life (prenatal to adolescence), especially with regard to linear growth and age at menarche and the role of insulin-like growth factor I (IGF-I) in mediating a relationship among milk, growth and development, and long-term biological outcomes.

**Methods:** United States National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2004 and review of existing literature.

**Results:** The literature tends to support milk's role in enhancing growth early in life (prior to age 5 years), but there is less support for this relationship during middle childhood. Milk has been associated with early menarche and with acceleration of linear growth in adolescence. NHANES data show a positive relationship between milk intake and linear growth in early childhood and adolescence, but not middle childhood, a period of relatively slow growth. IGF-I is a candidate bioactive molecule linking milk consumption to more rapid growth and development, although the mechanism by which it may exert such effects is unknown.

**Conclusions:** Routine milk consumption is an evolutionarily novel dietary behavior that has the potential to alter human life history parameters, especially vis-à-vis linear growth, which in turn may have negative long-term biological consequences. *Am. J. Hum. Biol.* 24:130–138, 2012. © 2011 Wiley Periodicals, Inc.

Cow's milk consumption is an increasingly common aspect of human dietary behavior, especially that of children. Although historically routine consumption of dairy products had a geographically limited distribution, milk consumption has become widespread among children throughout the globe, a process that has been supported, in part, by promotion of milk in school feeding programs (Wiley, 2007, 2011a). Besides milk being a routine component of children's diets, its consumption has also become normative. That is, there are widespread messages that children should drink milk and/or that milk is essential for adequate growth and development (cf. National Institute of Child Health & Human Development, n.d.). However, from an evolutionary perspective, it is important to keep in mind that: (1) consumption of cow's milk is a novel behavior, ranging from 8,000 ya to only a few years or decades depending on the population; (2) there is well-documented genetic variability across human populations with respect to the ability to digest milk sugar (lactose) postweaning; and (3) milk produced for infants of one species supports the growth and development needs of infants of that species. Thus, cross-species milk consumption and ingestion beyond the typical weaning period may trigger unanticipated life history consequences.

Although the impact of any given food on postneonatal child growth and development is likely to be negligible (absent any major intolerance or metabolic complications), there are reasons to believe that milk may be an exception. First, unlike all other foods in the human diet that come from some form of predation, milk is the only mammalian food that is produced to be consumed by the same species. Of course, it is produced for consumption only by individuals during one life history stage: infancy. After an infant is weaned, it does not consume milk again, and for the vast majority of mammalian species,

the ability to digest lactose diminishes with weaning. Each species' milk is tailored with an array of bioactive molecules (e.g., growth hormones and immune proteins) and nutrients that shape the early developmental trajectory of nursing infants, who accrue body size (weight and linear dimensions) while various organ systems mature. Most nonhuman milk consumed by humans comes from cows, as this animal is used extensively in commercial production (United States Department of Agriculture, 2008), and hence in this article, I will restrict the analysis to cow milk. There is geographic variation in the use of other milks, however. In South Asia, for example, milk more often comes from water buffalo, whereas in the Middle East it may come from camels. Goat and sheep milk is consumed in the Mediterranean area, with local pockets of its consumption throughout the world. Whether these milks are associated with different life history effects than cow milk has yet to be ascertained.

Cow milk consumption among humans presents an unusual life history situation. First, this milk is from a species with very different life history characteristics. Cows, for example, grow rapidly in skeletal size and body weight, gaining 0.7–0.8 kg/day throughout lactation in the first year of life (Marlowe and Gaines, 1958; Reynolds et al., 1978), compared with breastfed human infants, who gain about 0.02 kg/day (World Health Organization, 2007). From a nutrient perspective, although cow and human milk are calorically similar, cow's milk has about three times as much protein, four times as much calcium,

\*Correspondence to: Andrea S. Wiley, Human Biology Program and Department of Anthropology, Indiana University, 130 Student Building, Bloomington, IN 47405. E-mail: wileya@indiana.edu

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and overall more minerals (except iron) than human milk (Patton, 2004). Thus, there may be elements in cow milk that could contribute to accelerated growth. Second, cow milk is widely consumed by children well after the weaning period and by many adults as well, resulting in a misalignment of the normal timing of milk consumption and the life history period during which it is actually being consumed. In some populations, this has been facilitated by selection for genes that regulate lactase, the enzyme responsible for lactose digestion in the small intestine. Among populations of European descent as well as those with pastoralist histories in Central and South Asia and East and West Africa, alleles associated with continual lactase production are common, releasing the age constraint on milk consumption (Enattah et al., 2002, 2008; Ingram et al., 2007, 2009; Romero et al., 2011; Tishkoff et al., 2007). However, as noted, a pattern of milk consumption well beyond the time of weaning is increasingly common across the world's populations, including those with low frequencies of genes for lactase persistence (Wiley, 2007, 2011a).

So, the question arises as to whether drinking cow milk accelerates linear growth and maturation or contributes to individuals attaining larger sizes in adulthood. Or, given that milk drinking is associated with an early life stage characterized by exclusive somatic investment, does it elongate this phase of the life history, contributing to protracted expression of juvenile characteristics (e.g., a longer growth period)? In this article, I will focus on the life history consequences of cow milk consumption among children from the prenatal period through adolescence, highlighting the ways in which it has been associated with alterations in growth and development, particularly height at different times during this period and age at menarche. I will draw on existing published studies as well as a new analysis of the United States National Health and Nutrition Examination Survey (NHANES) 1999–2004, for children 2–17 years of age. Details about this data set can be found elsewhere (Wiley, 2010, 2011b), and basic descriptors of the samples used here can be found in Table 1. Because milk is transformed mostly through fermentation or fractionalization into dairy products, and its qualities are significantly altered as a result, it is important to differentiate milk consumption from overall dairy intake. This review will focus on milk exclusively, and not dairy products more broadly, with recognition that fluid milk, in the form in which it is most commonly consumed, is already transformed frequently through pasteurization, homogenization, and fortification (most often with Vitamin D and Vitamin A for fat-reduced milk).

As trajectories of linear growth and reproductive maturation impact adult biological function, early life milk consumption has the potential to affect later life physiology, and there may be critical periods during which milk might have such effects. For example, if milk consumption contributes to greater height, the latter is associated with a greater risk of cancer in adulthood (Green et al., 2011; Gunnell et al., 2001), and prepubertal childhood growth velocity has also been linked to later risk of breast cancer (Berkey et al., 1999). Early menarche is a well-known risk factor for breast cancer (Petridou et al., 1996) and cardiovascular disease (Lakshman et al., 2009). In the Boyd Orr cohort from the United Kingdom, overall household dairy intake and milk intake when children were 4–11 years of

TABLE 1. Sample characteristics, 2–17 year olds, NHANES 1999–2004

Age group	N	White (%)	Mexican American (%)	Black (%)	Birth weight (g)	Height percentile	Milk (g/day)	Total (kcal)	Total protein (g)	Total calcium (mg)	% Drinking milk daily	% Never drinking milk
24–59 months	1,529	69	16	16	3,319	0.48 (0.46, 0.50)	201 (183, 219)	1,598 (1,558, 1,637)	54 (52, 55)	892 (852, 933)	89	1.6
5–11 years	1,822	72	13	15	3,344	0.59 (0.57, 0.61)	176 (165, 187)	1,958 (1,884, 2,032)	64 (62, 67)	915 (879, 951)	87	1.4
12–17 years	1,778	72	12	16	–	0.58 (0.55, 0.61)	191 (170, 212)	2,226 (2,131, 2,321)	76 (72, 79)	1,000 (925, 1,075)	78	1.9

age were associated with a dose-dependent increased risk of colorectal cancer, but not other cancers, after controlling for several potential confounders (van der Pols et al., 2007). Furthermore, given that growth velocity varies by age during childhood and adolescence (Bogin, 1999), milk consumption during different developmental windows needs to be considered, as milk might alter growth trajectories at some points but not others and the timing of milk consumption may be an important determinant of longer-term outcomes.

Historically, growth standards have been based on children in the U.S. where milk drinking is the norm, and thus it is unclear what “normal” child growth would look like in the absence of milk consumption. In recognition of the different growth patterns of infants fed breastmilk versus infant formula, the new World Health Organization growth standards up to age 5 years were based on healthy breastfed children from six countries (U.S., Norway, Oman, India, Ghana, and Brazil), but no consideration was given to whether they consumed cow milk before or after weaning (de Onis et al., 2004). Furthermore, comparisons of children who are milk drinkers and those who are nonmilk drinkers in Western countries are complicated by the fact that the latter often suffer from dairy allergies or other conditions and treatments (e.g., steroid usage) that negatively impact growth (cf. Black et al., 2002). As a result, it is difficult to ascertain how milk consumption might alter our evolved pattern of growth and development. Existing data available to assess the relationship between milk consumption and growth come from milk supplementation studies as well as cross-sectional studies in which milk consumption varies among individuals.

When considering how milk might influence growth and development it is wise to keep in mind that milk is—like other foods—primarily a source of energy. If milk has “special” effects on growth, it is important to distinguish these from its contribution to energy or overall macronutrient budgets, and relatively few studies reporting results of milk’s association with height control for these. Calcium has received a lot of attention as the milk component most likely to impact growth (National Institute of Child Health & Human Development, n.d.). Because it is a major component of skeletal tissue, and cow milk is particularly rich in this nutrient, it long has been assumed that this would be the nutrient responsible for any relationship between milk and growth (Patton, 2004; Takahashi, 1966). However, calcium supplementation studies in Europe (Bonjour et al., 1997, 2001), The Gambia (Dibba et al., 2000), and Hong Kong (Lee et al., 1994, 1995) have found no statistically significant relationship between calcium and growth in height, regardless of whether calcium is supplied as a mineral supplement or as a milk derivative. Children supplemented with calcium did not grow more in height than did those in the control groups.

The other component that has received more recent attention is insulin-like growth factor I (IGF-I), part of the protein fraction in milk. IGF-I has mitogenic properties, inducing cell division and proliferation, and preventing apoptosis. It is both found in milk and produced endogenously in the liver and other tissues such as bone, where it is the most abundant growth factor. Hepatic and tissue production of IGF-I is stimulated by pituitary growth hormone, insulin, and is also influenced by diet and nutritional status. Given that IGF-I is produced by the neonate and is active in many tissues, it is not entirely clear what

function the IGF-I in milk has; it may support the growth and development of the neonatal gastrointestinal tract or enhance lactase activity, but evidence is equivocal as to whether it is absorbed intact and thus able to exert systemic effects (Burrin, 1997).

Despite a threefold difference in total protein, cow milk does not contain more IGF-I than human milk, and bovine and human IGF-I are molecularly identical (Campana and Baumrucker, 1995; Koldovsky and Strbak, 1995). Circulating IGF-I levels rise after milk consumption (Holmes et al., 2002), and children who drink more milk, but not those who consume higher amounts of other forms of animal protein, have higher circulating IGF-I levels (Cadogan et al., 1997; Hoppe et al., 2004a,b; Qin et al., 2009; Zhu et al., 2006). Debate continues over whether the rise in serum levels is due to the IGF-I in milk or whether milk stimulates endogenous production through a process that has yet to be described (Holmes et al., 2002; Juskevich and Guyer, 1990; Rich-Edwards et al., 2007). It appears that the casein portion of milk protein, rather than whey protein, is most closely related to rises in circulating IGF-I after milk consumption (Hoppe et al., 2009). Interestingly, diets high in milk and dairy products in childhood are associated with lower IGF-I in adulthood, suggesting that the short- and long-term effects of milk intake may vary by life history stage (Ben-Shlomo et al., 2005; Martin et al., 2007). Furthermore, as there are periods of rapid and slow growth, there may be critical periods during which milk may raise IGF-I levels and contribute to growth, and these feed back over the long term to reduce IGF-I production via pituitary secretion of growth hormone (Martin et al., 2011). In any event, while current attention is focused on IGF-I, given milk’s complexity and its role in mammalian life history, it likely interacts with several other milk components, including calcium, and individual genotypes to affect growth and development.

## MILK CONSUMPTION AND GROWTH AT DIFFERENT LIFE HISTORY STAGES

### *Prenatal*

Pregnant women are advised to increase their intake of high-quality foods, and milk products are especially recommended to provide essential nutrients to meet fetal needs for growth (Institute of Medicine, 1992; National Institute of Nutrition, 2006). Thus, milk consumption should be positively associated with measures of fetal growth. Several studies have shown that maternal milk intake is positively related to birth weight (Heppe et al., 2011; Ludvigsson and Ludvigsson, 2004; Mannion et al., 2006; Olsen et al., 2007; Rao et al., 2009; Xue et al., 2008). The studies varied in how milk consumption was assessed: some reported on average milk intake during pregnancy (Ludvigsson and Ludvigsson, 2004; Mannion et al., 2006; Xue et al., 2008), while others specified consumption in the first and second (Rao et al. 2009) or second and third trimesters (Olsen et al., 2007). Milk intake has also been found to be positively related to birth length (Olsen et al., 2007; Rao et al., 2009 [rural sample only]), but other studies either did not measure these (Ludvigsson and Ludvigsson, 2004; Xue et al., 2008) or found no associations with neonatal size beyond birth weight (Heppe et al., 2011; Mannion et al., 2006). Greater maternal milk intake has been found to be associated with

TABLE 2. Milk intake, height percentiles, and coefficients for milk intake quartiles, adjusted for ethnic group, birth weight, energy, protein and calcium, children age 24–59 months and 5–11 years, NHANES 1999–2004

	Milk intake quartiles			
	QI	QII	QIII	QIV <sup>a</sup>
Children 24–59 months				
Average milk intake (g)	0	105 (101, 108)	204 (199, 208)	502 (468, 536)
Height percentile	0.47 (0.42, 0.53) <sup>†</sup>	0.44 (0.40, 0.48) <sup>‡</sup>	0.47 (0.43, 0.51) <sup>†</sup>	0.55 (0.51, 0.58)
Adjusted for total kcal	0.072 (–0.13, –0.02) <sup>†</sup>	0.090 (–0.15, –0.03) <sup>†</sup>	–0.065 (–0.12, –0.01) <sup>‡</sup>	
Adjusted for kcal, protein, calcium	–0.055 (–0.11, 0.00) <sup>*</sup>	0.077 (–0.14, –0.01) <sup>*</sup>	–0.057 (–0.11, 0.00) <sup>*</sup>	
Children 5–11 years				
Average milk intake (g)	4 (3, 6)	150 (146, 155)	237 (235, 239)	358 (342, 374)
Height percentile	0.57 (0.53, 0.61) <sup>*</sup>	0.59 (0.55, 0.62)	0.57 (0.52, 0.62) <sup>**</sup>	0.63 (0.59, 0.66)
Adjusted for total kcal	–0.025 (–0.08, 0.03)	0.001 (–0.05, 0.05)	–0.026 (–0.08, 0.03)	
Adjusted for kcal, protein, calcium	0.00 (–0.06, 0.06)	0.015 (–0.04, 0.07)	–0.018 (–0.07, 0.04)	

<sup>a</sup>Reference category.<sup>\*</sup>*P* < 0.05.<sup>\*\*</sup>*P* < 0.06.<sup>†</sup>*P* < 0.01.<sup>‡</sup>*P* < 0.001.

greater placental weight (Godfrey et al., 1996 [assessed as dairy protein in last trimester]; Olsen et al., 2007) after controlling for a variety of confounders.

Ascertaining the pathway by which maternal milk intake might contribute to fetal growth is complicated by the fact that maternal IGF-I does not cross the placenta (Caufriez et al., 1993). Therefore, any relationship between maternal IGF-I and fetal growth likely occurs only through alterations in placental function (Hills et al., 1996). Maternal IGF-I has been positively correlated with birth weight in some studies (Boyne et al., 2003) but not in others (Holmes et al., 1998; Orbak et al., 2001; Pathmaperum et al., 2007), and also positively correlated with placental weight (Boyne et al., 2003). To my knowledge, there have been no published studies of maternal milk intake during pregnancy in relation to maternal IGF-I levels and neonatal outcomes. Prenatal supplementation with milk, combined with additional milk over the first 5 years of life, has been shown to have a negative relationship with adult IGF-I levels in the next generation (Ben-Shlomo et al., 2005), although the study was not able to disentangle differential associations between the prenatal and postnatal supplementation.

#### Infancy (0–1 year)

Cow milk is not generally recommended for infants below 1 year of age. This is in part due to the potential allergenicity of cow milk proteins, but mainly because cow milk is relatively low in iron, which is also poorly absorbed, and children consuming substantial quantities of cow milk have a high frequency of iron deficiency anemia (Michaelsen et al., 2007; Ziegler, 2007). However, countries vary in their recommendations; in the U.S. cow milk is not recommended until 1 year of age, whereas in Canada it may be introduced as early as 9 months, with the proviso that the infant is consuming other iron-rich foods (Michaelsen et al., 2007). Despite these recommendations, many infants are given cow milk well before the recommended age. Across European countries, by 9 months 18% were receiving cow milk as their only milk source, whereas 33% had received some (Freeman et al., 2000). By 12 months, 31% were consuming cow milk as their primary milk, and 50% were receiving some. In the National Health and Examination Survey, a representative sample of U.S. children in 1999–2004, 32% of pre-

school age children (24–59 months) had been drinking milk daily before their first birthday; 53% started daily milk consumption at or close to their first birthday.

Infant formula is more commonly given to infants who are not being breastfed, or whose nursing is being supplemented. Most formula is based on cow milk, although the protein content is greatly reduced compared with plain cow milk and more closely aligned with that of breastmilk. No difference has been found in the growth of infants fed either whole milk or infant formula at 9 and 12 months (Larnkjaer et al., 2009). However, some studies show that formula-fed infants grow faster and to heavier weights and greater lengths than breastfed infants (Agostoni et al., 1999; Chellakooty et al., 2006; Michaelsen et al., 1994; Ong et al., 2002) whereas others show no difference in weight or length, especially after the first 3–6 months of life (Dewey et al., 1995). Formula-fed infants have higher levels of IGF-I than breastfed infants (Chellakooty et al., 2006; Ong et al., 2002), but this discrepancy may be even stronger for infants consuming whole cow milk. Among older infants, IGF-I was increased among boys (but not girls) drinking whole milk compared with those consuming infant formula (Larnkjaer et al., 2009).

#### Preschool age children (~24–59 months)

There are relatively few studies of growth in relation to milk consumption among young children, yet children in this age group continue to grow very rapidly, and are within the range of ages that evolutionarily would have included nursing. Thus, milk (albeit human rather than cow milk) would have continued to exert biological effects on their growth. The relative dearth of studies may be due to the fact that milk drinking is so common among this age group, particularly in European-derived populations among whom most studies have been conducted. Evidence suggests that children who do consume more cow milk during this period are taller than those who drink less (Hoppe et al., 2004b; Wiley, 2009). Among 24–59 month olds in NHANES 1999–2004 (over 76% of whom drank milk in the past 24 h and 89% reported daily milk consumption over the past 30 days), children in the highest quartile of milk intake (average = 502 g milk in 24-h recall [over two cups]) had greater height percentiles than those in each lower quartile (see Table 2). Controlling for ethnicity, birth weight, and energy intake, or these plus

calcium and protein intake did not change this outcome (Table 2). Whether a child had been fed milk before 1 year had no relationship to height in this sample. Children who reported never drinking milk or who had drunk no milk in the past 24 h were not different from those who consumed it more frequently or all of those who had drunk at least some milk in the past 24 h. In contrast, a New Zealand study of somewhat older children (3–10 year olds), those who avoided cow milk were shorter ( $-0.65$  z-score,  $P < 0.01$ ) than those who consumed milk (Black et al., 2002), although they did not control for differences in energy intake. Half of the children who avoided milk had some form of intolerance including cow milk allergy, and most reported other atopic issues as well. Hoppe et al. (2004b) also found positive correlations among height, milk consumption, and IGF-I in 2.5-year-old Danish children, and milk was a significant predictor of both height (each 100 g increment of milk intake = 0.5 cm greater height) and IGF-I in multivariate regression models.

#### *Prepubertal children (5–11 years)*

Much more work exists on milk consumption and height among this age group, in part because several studies have been based on school milk interventions, but relatively few have controlled for overall energy intake. This age group corresponds to what Bogin has called the human “childhood” and juvenile life stages (Bogin, 1999), occurring after the child is weaned, but still reliant on adult provisioning. It is also a relatively quiescent period for growth, with low linear growth velocity compared with both infancy and subsequent adolescence. Two intervention studies stand out for their high quality and control of caloric intake. First, a school milk study from the 1920s in the United Kingdom provided children in urban, working class areas age 6, 9, and 13 years with 3/4, 1, and 1 pint of whole or nonfat milk, respectively, a biscuit of caloric value equal to that of the skim milk, or no supplement (Leighton and Clark, 1929). After 7 months of supplementation on school days, the milk-supplemented groups had grown 0.26–0.28 in. (0.7 cm) more than those getting biscuits or no supplement, a pattern that was consistent across the three age groups. There was no difference in growth between the control and biscuit groups or between the whole and nonfat milk groups, indicating that greater caloric intake was not the driving factor behind greater growth in the milk supplement groups (although it is assumed that the children’s diet was not otherwise altered by the provisioning). Although these increments are modest, this study replicated the results of a similar study conducted in the previous year (Orr, 1928), and collectively they suggested that there might be some “special” growth-promoting components of milk. A more recent, similar structured study in Kenya did not support this conclusion, however (Grillenberger et al., 2003). Seven-year-old children were given 1050 kJ supplements of either milk, meat, oil, or no additional food for 2 years, but there were no differences in growth in height among the four groups. After dividing the sample into those who were stunted at baseline (height-for-age z-scores  $\leq -1.4$ ), and those who were not, stunted children who received milk grew more than the control group, but not more than the meat or energy-supplemented group (Grillenberger et al., 2003).

There have been several other supplementation and observational studies among children in this age group

that vary in their results, with some showing positive associations between milk and height (Baker et al., 1980; Chen, 1989; Du et al., 2004; Lampl et al., 1978; Okada, 2004; Takahashi, 1984), and others showing no such relationships (Chan et al., 1995; Cook et al., 1979; Rogers et al., 2006; Rona and Chinn, 1989; Wiley, 2005). Importantly, none of those showing positive associations controlled for energy or macronutrient intake. Analysis of 1999–2004 NHANES data indicated that while children in the highest quartile of milk intake were taller than those in the lowest (63rd vs. 57th percentile,  $P < 0.05$ , average intake 348 g vs. 5 g on average, see Table 2), milk consumption had no relationship to height in this age group after controlling for energy, or energy, protein, and calcium intake. There were no differences in height between those who drank milk daily versus less-than-daily or reported never drinking milk versus those who drank it at least occasionally (based on the 30-day frequency), or between who drank no milk in the past 24 h and those who drank at least some.

#### *Adolescents (12–17 years)*

Among adolescents, there are likewise variable results. Two supplementation studies show no impact of milk on height (Cadogan et al., 1997; Merrilees et al., 2000, although the girls in this study were 15–16 years old and hence had likely ceased growing in stature). Cadogan et al. (1997) reported no difference in growth in height among 12-year-old girls in England who consumed an average of 300 ml more milk over an 18-month period but did find that IGF-I levels increased in the girls consuming more milk (35% vs. 25% increase,  $P < 0.02$ ). Others studies do find a positive relationship between milk consumption and height. The older children in UK studies from the 1920s (age 13) grew more when supplemented with milk (Leighton and Clark, 1929; Orr, 1928). Berkey et al. (2009) found that while at age 11 there was a 1 cm difference in height between U.S. girls who drank less than 1 serving of milk per day and those who drank 3+, there was a 2.5 cm difference in their adult height, indicating a more steep growth trajectory in adolescence for girls consuming 3+ servings of milk per day.

Wiley (2005) found that reported 30-day frequency of milk intake and milk intake from the 24-h recall (milk kcal/total kcal) were significant predictors of height in this age group after controlling for energy intake, with those consuming milk daily being 9-mm taller on average than those who reported never consuming milk. In the 1999–2004 NHANES sample, one-third of 12–17 year olds drank no milk, and thus milk tertiles rather than milk quartiles were used. A significant positive association was found between milk intake from the 24-h recall and height, and those in the mid-tertile of milk intake were shorter than those in the top tertile (Table 3). These relationships weakened somewhat after adjusting for energy ( $P < 0.06$ ), and also protein ( $P < 0.07$ ) and calcium. Unfortunately, since less than 3% of U.S. adolescents reported drinking 3+ servings of milk per day, this sample could not be compared directly with that of Berkey et al. (2009).

#### *Age at menarche*

Milk supplementation studies designed to assess effects on bone mineralization among perimenarcheal girls have

TABLE 3. Milk intake, height percentiles, and coefficients for milk intake quartiles, adjusted for ethnic group and household income, 12–17 year olds in NHANES 1999–2004

	Milk intake tertiles		
	I	II	III <sup>a</sup>
Average milk intake (g)	0	178	420
Height percentile	0.58 (0.54, 0.61)	0.55 (0.50, 0.60) <sup>*</sup>	0.60 (0.56, 0.64)
Height percentile coeff., adj. for total kcal	–0.026 (–0.07, 0.02)	–0.044 (–0.09, 0.00) <sup>**</sup>	
Height percentile coeff., adj. for total kcal, protein	–0.24 (–0.07, 0.02)	–0.042 (–0.09, 0.00) <sup>††</sup>	
Height percentile coeff., adj. for kcal, protein, calcium	0.00 (–0.04, 0.04)	–0.031 (–0.08, 0.02) <sup>‡‡</sup>	

<sup>a</sup>Reference category.<sup>\*</sup> $P < 0.05$ .<sup>\*\*</sup> $P < 0.06$ .<sup>††</sup> $P < 0.07$ .<sup>‡‡</sup> $P < 0.20$ .

generally not found effects on age at menarche (Cadogan et al., 1997; Du et al., 2004). Chinese girls receiving milk supplements over 2 years were not more likely to reach menarche (48.3 vs. 40.1%;  $P = 0.09$ ), and there were no significant differences in age at menarche between supplementation and control groups 3 years after the supplementation ended, when over 97% of study participants had reached menarche (Zhu et al., 2006). In a recent report on 1999–2004 NHANES data, Wiley (2011b) found a negative relationship between quantity of milk consumed in the past 24 h and risk of early menarche for girls age 9–12 years. Girls in the second tertile of milk intake had a lower risk of early menarche than those in the highest tertile. This association was strengthened after controlling for height as well as total calcium and dairy fat; thus, milk's relationship to early menarche is not mediated by associations between milk consumption and childhood height or calcium or dairy fat.

## DISCUSSION AND CONCLUSIONS

This review shows that individuals who consume cow milk during childhood may experience life history changes, here assessed as accelerated growth in height-for-age, larger adult body size, and possibly earlier sexual maturation for girls. However, the corpus of study results is variable, with stronger evidence in favor of positive effects in early life and adolescence, and weaker evidence for primary school age children. Young children are still within the nursing phase and thus have evolved to expect milk during this time. Their physiologies may be more susceptible to modulation by milk, although in this case, milk comes from another species with a more rapid growth pattern during nursing. It is also worth noting that despite their smaller size, 2- to 5-year-old children in NHANES drank more milk than both school-age children and adolescents (see Table 1), and milk makes up a larger proportion of their caloric intake. Older infants (9 months to 1 year) who consume cow milk have been shown to grow more rapidly than those consuming lower protein infant formula and have higher IGF-I levels, (Larnkjaer et al., 2009), as do 2 year olds who consume more milk (Hoppe et al., 2004b). Unfortunately, there are no studies comparing growth or IGF-I levels in young children who consume cow milk to those who continue to nurse to see if there are meaningful differences.

IGF-I levels peak during adolescence (Juul et al., 1994), corresponding to a rapid rate of growth. As milk consump-

tion results in increased serum levels of IGF-I and IGF-I levels are already high during this time, milk may be able to have its most potent effects on growth then. In addition, if earlier milk consumption has the capacity to increase the likelihood of early menarche, postpubertal linear growth is likely to be advanced (at least among girls; there are scant data on boys). In contrast to younger children, whose rapid growth would have been supported in part by milk, the consumption of this fluid is truly an evolutionary anomaly for adolescents, and biological consequences both in the short term (e.g., growth, maturation) and in the long term (risk of various cancers) may be more evident.

As most existing studies are either based on cross-sectional associations or milk supplementation lasting 2 years at most, the life history consequences of continual milk consumption are not known with any certainty. Collaborators at KEM Hospital in Pune, India and I are currently conducting a cohort study of a sample of children from both rural and urban areas in and around Pune. In this study, mothers were recruited during early pregnancy, and their diet and anthropometric characteristics were assessed each trimester. At birth, we have cord IGF-I levels and anthropometry, followed by anthropometric and dietary assessments at 3, 6, 12, and 24 months. At 24 months, blood samples were also collected, and IGF-I levels were measured. Children in the study are now 5–6 years old and have been followed up with specific questions about milk and dairy consumption, overall diet and activity, as well as anthropometry and IGF-I. We intend to follow this cohort as it moves through growth and development and into adulthood and will have a broader life course perspective on the consequences of milk consumption from the prenatal period through childhood and adolescence. India is the largest milk-producing country in the world, and a high cultural value is placed on milk (and height), yet overall consumption of milk is low. Thus, this study will provide an ideal comparative sample for investigating links between milk consumption and child growth in a context in which both overall caloric intake and milk intake is relatively low, in contrast to existing studies conducted in nutritionally replete northern European populations, where baseline milk and macronutrient intake is high. India is also notable as a country in which the majority of milk consumed is from water buffalo rather than cows, and we can distinguish the impact of cow versus water buffalo milk on growth. Preliminary analysis of the Pune data suggests that for the prenatal period, maternal milk consumption was not associated with greater neona-

tal size, or umbilical cord IGF-I, and that there was no variation by type of milk consumed (Lubree et al., 2010).

This review demonstrates the importance of considering milk as an unusual food with bioactive properties but also as one that also contains nutrients that are not unique to this food. Studies that fail to control for energy intake, or protein and calcium, may find associations between milk and growth that are not due to “special” qualities of milk but which are attributable to nutrients that are accessible through other foods. In the NHANES data, controlling for energy removed the relationship between milk intake and height among school age children, but not younger children, and weakened somewhat the significant relationship among adolescents. Further control of calcium removed any association among adolescents, suggesting that milk’s calcium is critical to its impact on skeletal growth, which is not surprising given calcium’s role in bone biology. At present, it is difficult to ascertain the contribution—if any—of IGF-I in milk; while overall protein or milk protein itself can be controlled for, only a small fraction of milk protein is made of IGF-I and whether it survives digestion is not known.

In sum, the biological sequelae of routine consumption of cow milk are still not well-understood, but a life history approach is a fruitful way to evaluate them. Evolutionarily, milk consumption typified a distinct mammalian life history phase, corresponding to rapid growth and development, whereas currently there is widespread intake of milk of a different species, and for periods of time well beyond the typical age at weaning. Thus, there are reasons to believe that the human life history could be altered as a consequence of this dietary behavior. If milk does accelerate growth or result in larger adult size, the effects are not necessarily positive, as early puberty, rapid growth in childhood, and increases in height are associated with increased risk of chronic diseases. However, as the existing research on IGF-I suggests, early upregulation of IGF-I by milk may be followed by its downregulation in adulthood (Ben-Shlomo et al., 2005; Martin et al., 2007), which may reduce the risk of diseases related to unregulated cell proliferation. Thus, the timing, duration, and amount of cow milk consumed, and its relationship to other dietary patterns may be critical to the overall life history consequences of this food in the human diet.

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