weight we observed among infants born with a vitamin D deficiency.[1] Proving a relationship between maternal exposure to sunshine, infant vitamin D status and infant size at birth is difficult because of the high cost of analyzing circulating 25-hydroxyvitamin D levels in a large cohort, quantifying skin exposure to ultraviolet B light and endogenous synthesis of vitamin D, and assessing the confounder, dietary vitamin D intake.

Other seasonally varying factors such as temperature are linked to size at birth.[2] It is important to point out that the 299-g difference in birth weight between the infants with deficient and adequate vitamin D status in our study is 10 times greater than the weight difference that would be expected because of seasonal effects alone in industrialized countries.[2] In the Winnipeg cohort, vitamin D status was highest in infants born in the summer (although season did not contribute to the regression analysis for bone mineral content in our study), but body weight did not follow the same pattern (Fig. 1).

It is possible that the infants born with vitamin D deficiency might have had a higher birth weight because of maternal exposure to sunshine in the first trimester.[2] The spring-born infants (n = 14) tended to weigh the most (difference of 244 g, p = 0.08, t test). These infants would have been conceived in the peak period of sunshine and warm temperatures in Winnipeg. Whether vitamin D status at the time of conception is behind these differences is unclear. In addition, melatonin should be included in future research on the relationships among seasonality, vitamin D, growth and bone mass.[3]

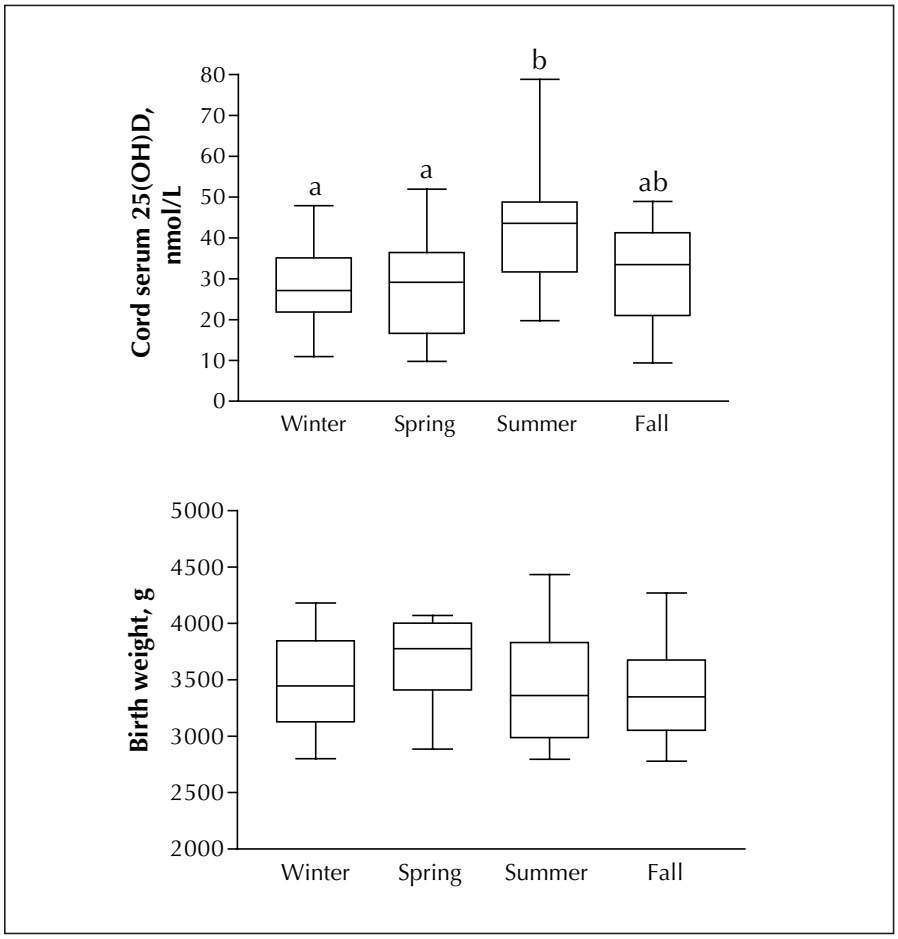

Fig. 1: Infant vitamin D status (above) and weight at birth (below) categorized by season. Seasons are defined as winter: January through March (n = 14); spring: April through June (n = 14); summer: July through September (n = 12); fall: October through December (n = 10). Differences among groups were tested using ANOVA with Tukey's multiple comparison test. Bars with different letters indicate differences between groups ($p < 0.05$). (There were significant differences between the summer months and those in winter and spring. There were no significant differences between the fall months and the rest of the year.)

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Nonalcoholic fatty liver disease

Leon Adams and associates[1] rightly state that obesity is associated with nonalcoholic fatty liver disease (NAFLD). In particular, visceral adiposity is highly correlated with NAFLD, whereas the correlation with subcutaneous obesity is weaker.[2]

Intra-abdominal fat delivers fatty acids directly into the portal vein, promoting insulin resistance.[2] Patients with truncal obesity have very low levels of adiponectin and high levels of tumour necrosis factor-α (TNF-α).[3] Secretion of TNF-α from adipose tissue is strongly associated with obesity-related insulin resistance, which suggests that TNF-α may function in a paracrine fashion in adipose tissue; in contrast, expression of adiponectin from adipose tissue is associated with higher degrees of insulin sensitivity and lower TNF-α expression.[4] In addition, TNF-α has

been shown to decrease levels of adiponectin.[5] Thus, a combination of increased TNF-α and decreased adiponectin leads to severe insulin resistance, which in turn leads to NAFLD. Various treatments for NAFLD (e.g., weight loss or use of drugs such as thiazolidinediones) serve to increase adiponectin levels.[5,6]

Adams and associates,[1] in their discussion of the inflammatory and fibrotic mediators of NAFLD, suggest that adiponectin promotes liver fibrosis in NAFLD, but the evidence indicates that the opposite is true. Some clarification seems warranted.

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Leon Adams and associates[1] provide an excellent and up-to-date review of NAFLD in adults,[1] but they do not discuss the condition in children. Childhood NAFLD has been reported globally since our first large clinical series from the Hospital for Sick Children in Toronto was published in 2000.[2] In part this recent reporting reflects the increasing prevalence of obesity in childhood.[3,4] NAFLD is typically diagnosed in children 12–14 years old, but serious liver disease associated with NAFLD has been reported in children as young as 5 years of age.[5,6]

In adults NAFLD must be differentiated from alcoholic liver disease, but in children NAFLD must be distinguished from various rare metabolic disorders that cause fatty liver (such as Wilson disease). The typical child suffers from overnutrition, is asymptomatic or has vague abdominal pain, and may have abnormal results on liver biochemistry testing. As in adults, an important feature of childhood NAFLD is hyperinsulinemia associated with relative insulin resistance, as shown by clinical studies using the homeostasis model of insulin resistance.[5] Whether oxidative damage to the liver is prominent in childhood NAFLD is now being investigated.

NAFLD in adults can progress to cirrhosis with chronic liver failure requiring liver transplantation or to hepatocellular carcinoma, but the long-term outcome for children with NAFLD is unknown. Cirrhosis has been reported in a few children.[6] Although simple steatosis (hepatic fat accumulation without inflammation and fibrosis) carries a benign prognosis in adults, the long-term outcome for children with simple steatosis is uncertain. Current treatment strategies in NAFLD are aimed at eliminating or reducing the risk factors associated with NAFLD: they involve weight loss and increased physical activity. Few pediatric data are available regarding pharmacologic interventions such as vitamin E, ursodiol and metformin.[7-9] Well-designed prospective studies in children are urgently needed to determine the best overall medical management.

Childhood NAFLD may be the hepatic manifestation of the metabolic dysregulation leading to type 2 diabetes, hypertension and cardiovascular disease. Given that childhood NAFLD is highly prevalent — estimated at 3% to 10% of obese children — we need to intervene now so as to avoid cirrhosis, as well as these other diseases, in the current generation of children.

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