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Comment on "Epigenetic Reduction in Invariant NKT Cells following In Utero Vitamin D Deficiency in Mice"

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Letters to the Editor

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Comment on "Epigenetic Reduction in Invariant NKT Cells following In Utero Vitamin D Deficiency in Mice"

We read with interest the recent study showing that gestational vitamin D deficiency significantly reduces the number of invariant NKT cells in mice and that later supplementation was not able to correct this. The authors conclude that low vitamin D levels in utero may result in long-term epigenetic changes affecting thymic output (1).

Invariant NKT cells are known to play an important role in the immune system and have been implicated in the pathogenesis of autoimmune disorders such as multiple sclerosis (MS) and type 1 diabetes (T1D) (2). One of the most enigmatic features of MS and T1D is that season of birth influences the risk of developing these diseases (Fig. 1*A*) (3–6). Seasonality dominates global environment, and the effects of changing climate encompass a number of issues; thus, isolating the causative factor(s) is extremely difficult. However, season of birth effects appear to be related to latitude, implicating sunshine exposure and, consequently, vitamin D levels in the association (Fig. 1*B*) (7).

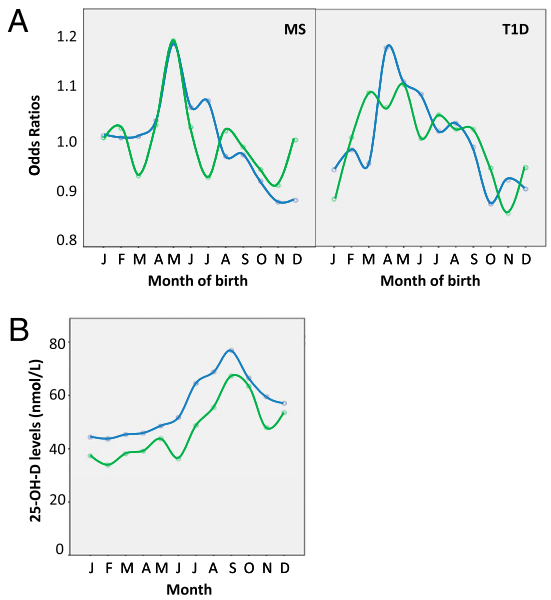

FIGURE 1 *A*, Risk of MS and T1D based on the month of birth in England and Wales (blue) and Scotland (green). *A*, From Willer et al. (3) (reproduced from *British Medical Journal*, Timing of birth and risk of multiple sclerosis: population based study, Willer C.J., Dyment D.A., Sadovnick A.D., Rothwell P.M., Murray T.J., Ebers G.C., 330: 120, 2005, with permission from BMJ Publishing Group, Ltd.) and Rothwell et al. (6) (reproduced from *British Medical Journal*, Seasonality of birth of patients with childhood diabetes in Britain, Rothwell P.M., Staines A., Smail P., Wadsworth E., McKinney P., 312: 1456, 1996, with permission from BMJ Publishing Group, Ltd.). *B*, Average monthly vitamin D [25(OH)D] levels in women from England and Wales (blue) and Scotland (green). *B*, From Hyppönen et al. (7) (reproduced with permission from *Am. J. Clin. Nutr.* [2007; 85: 860–868]).

It remains to be determined how vitamin D exposure in utero can influence disease risk years later. The authors state that epigenetics may play a role, but they did not directly test this. Epigenetics is defined as heritable changes in gene expression that do not involve a change in DNA sequence and includes DNA methylation (8). Interestingly, studies have shown that DNA methylation patterns can be altered by seasonal factors acting during gestation and that vitamin D can directly influence methylation (9, 10). Taken together, these observations support the hypothesis that vitamin D deficiency during gestation may impair immune function through long-term epigenetic modifications.

These findings are extremely relevant because vitamin D supplementation is being considered as a preventative measure for autoimmune disease. In what could be an equivalent human experiment, the rare disease vitamin D-dependent rickets 1 (VDDR1), three patients with VDDR1 were identified who later developed MS despite vitamin D supplementation from early childhood, perhaps analogous to the mouse data suggesting that in utero vitamin D deficiency may have long-lasting effects (11). Prospective studies should be conducted to investigate the effect of gestational vitamin D on the epigenome and to discover whether any changes are correctable to aid research on disease prevention.

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Abbreviations used in this article: MS, multiple sclerosis; T1D, type 1 diabetes; VDDR1, vitamin D-dependent rickets 1.

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