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Vitamin D metabolism in relation to immune dysfunction.

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Vitamin D has been shown to possess immunomodulatory effects with a significant impact on immune function. These effects involve both the innate and adaptive immune responses. These might have important implications for the predisposition of individuals with vitamin D deficiency to acute diseases characterized by sudden onset as well as long-developing chronic conditions. Lymphoma, a cancer originating in cells of the immune system, represents an example of chronic immune-related diseases, which are generally more common among adult populations. Conversely, the major burden of LRTI falls on infants. This could be attributed in part to immaturity of their immune system and limited prior exposure to antigens. The present thesis tested the hypothesis that vitamin D is crucial for efficient immune responses against infectious agents and therefore protects against both acute manifestations of infections as in pediatric LRTI and chronic consequences of infectious insults as in adult lymphoma.

The first part of the thesis focused on the exploration of prediagnostic plasma vitamin D levels in the context of the study of 1,127 lymphoma cases and 1,127 matched controls nested within the European Prospective Investigation into Cancer and Nutrition (EPIC). The second part of the thesis examined whether 25(OH)D concentrations measured at birth influenced susceptibility to LRTI in the first year of life using the resources of the Ulm Birth Cohort. The study consisted of 777 mother-infant pairs.

Vitamin D status was quantitatively determined by measuring the level of 25(OH)D, the most reliable estimate for vitamin D status, using two methods: fully automated IDS-iSYS 25(OH)D assay (Immunodiagnostic systems Ltd, Boldon, UK) and manual EIA 25-(OH)D enzyme immunoassay (IDS, Immunodiagnostic systems Ltd, Boldon, UK). The automated method was used in most the EPIC cohort excluding samples from Sweden, while Swedish samples and samples from Ulm Birth Cohort were measured with the manual method.

Within the EPIC cohort conditional logistic regression was used to estimate multivariable adjusted incidence rate ratios (RRs) of lymphoma risk in relation to plasma 25(OH)D. To account for the seasonal variation in 25(OH)D levels season standardized and season-specific 25(OH)D quartiles were employed. 25(OH)D was also analysed as a continuous variable and using clinical predefined cutpoints of vitamin D deficiency, insufficiency and sufficiency. Within the Ulm Birth Cohort relative risks (RRs) of LRTI in relation to 25(OH)D cord blood levels were estimated by log-binomial regression after adjustment for potential confounders. To account for seasonal variation in both vitamin D levels and infections, the association was examined in different seasons. Analyses were conducted using clinical predefined cutpoints, quartiles, and season-standardized 25(OH)D quartiles.

The results from the EPIC cohort revealed much higher plasma vitamin D concentrations in northern Europe in comparison to south European countries. No statistically significant association between plasma 25(OH)D and overall lymphoid cancer risk was observed.

A positive association for B-cell non-Hodgkin lymphoma (B-NHL) was noted only in people diagnosed during the first two years of follow-up (P_{het}=0.03), suggesting the possibility of reverse causality. Further analysis restricted to participants with two or more years of follow-up time demonstrated a significant inverse association between 25(OH)D and chronic lymphocytic leukaemia (CLL) (n=161): adjusted RR was 0.40 (95% CI 0.18, 0.90; P_{trend} = 0.05) and 0.31 (0.13, 0.76; P_{trend} = 0.03) for the top vs bottom season-standardized and season-specific quartiles, respectively. Data on dietary vitamin D intake provided further support for the observed association (RR=0.41, 95% CI 0.18, 0.96, P_{trend} = 0.02).

The results from the Ulm Birth Cohort showed a high prevalence of vitamin D deficiency in neonates born in Germany. A statistically significant association between 25(OH)D status in cord blood and risk of LRTI across the year using clinical cutpoints was observed. The adjusted RR of LRTI for individuals with vitamin D deficiency (<25 nmol/L) in comparison to the referent category (>50 nmol/L) was 1.32 (95% CI 1.00, 1.73). The association differed by maternal allergy status; children born to mothers without allergy demonstrated a RR of 1.45 (95% CI 1.03, 2.03). The effect was largely driven by a strong association between 25(OH)D and LRTI in infants born in fall with a RR of 3.07 (95% CI 1.37, 6.87).

In conclusion, the here present findings do not support a protective role of high 25(OH)D concentration in lymphoid cancers overall. However, they suggest that higher concentrations of 25(OH)D are associated with reduced risk of CLL. An inverse association between rising vitamin D concentrations and CLL risk would be in line with an infectious contribution to this lymphoma subtype.

Vitamin D deficiency at birth has been shown to be associated with increased risk of LRTI particularly in infants born to mothers without allergy. The association seems strongest in infants born in fall.
Overall, the present results strengthen the cumulative evidence of health beneficial effects of vitamin D with regard to both acute infectious episodes and chronic infection-related conditions.