Summary

**Background:** Children living at northern latitudes are at risk of vitamin D deficiency during winter due to absence of dermal vitamin D₃ production and limited dietary vitamin D intake. Vitamin D is important for normal bone growth and development in children, and it is of relevance to investigate factors, which associate with low vitamin D status to identify children at risk. Furthermore, the exact dietary requirement of vitamin D in young children is unknown, since the authoritative agencies setting recommendations rely on dose-response relations between vitamin D intake and serum 25-hydroxyvitamin D (25(OH)D) established in adults. The exact implications of a reduced winter serum 25(OH)D among young, healthy children remain to be elucidated. It is suggested that vitamin D affects muscle strength, body composition and growth factors but few randomized controlled trials have investigated if winter vitamin D supplementation in healthy, young children affects these outcomes.

**Objective:** The aims of this PhD thesis were to identify factors associated with serum 25(OH)D during autumn in young children, and establish the vitamin D intakes required to maintain wintertime serum 25(OH)D above proposed cut-offs. Furthermore, the aim was to investigate the effect of a winter vitamin D supplementation on muscle strength, body composition, and growth factors in young children living at northern latitudes.

**Design and methods:** This thesis is based on data from the ODIN Junior study, which was a randomized, double-blind, placebo-controlled dose-response trial. A total of 130 Danish children aged 4-8 years were randomly assigned to receive 0, 10 or 20 μg/day vitamin D₃ for 20 weeks during winter. Baseline and endpoint measurements took place Sep-Oct 2014 and Feb-Mar 2015, respectively, at Department of Nutrition, Exercise, and Sports, University of Copenhagen. **Paper I** reports on baseline data, and **Papers II and III** also report on data collected for the randomized trial. At baseline and endpoint we measured anthropometry, body composition with bioelectrical impedance analysis, muscle strength with hand grip dynamometer, and selected growth factors and serum 25(OH)D, which was analyzed with liquid chromatography-tandem mass spectrometry. Information on parental education, dietary vitamin D intake, physical activity, and sun behaviors was obtained by questionnaires to the parents.
Results: In Paper I we found a mean serum 25(OH)D of 56.8±12.5 nmol/L in 4-8 year-old children during autumn. Seeking shade often at sunny days and not adhering to the recommendation of being physically active 1 h/day were associated with a lower serum 25(OH)D. Moreover, fat-free mass index was positively associated with serum 25(OH)D. Dietary vitamin D intake was 1.9 μg/day and did not associate with serum 25(OH)D. In Paper II we reported that during winter, serum 25(OH)D decreased in the children receiving placebo (-24.1 ±1.2 nmol/L), and increased in both supplementation groups (+4.9 ±1.3 and +17.7 ±1.8 nmol/L, respectively) with significant differences between all three groups at endpoint. The estimated average requirement (EAR) for vitamin D was 4.4 μg/day (i.e. the intake needed for 50% to be >40 nmol/L) and the recommended dietary allowance (RDA) was 19.5 μg/day (i.e. the intake needed for 97.5% to be >50 nmol/L). In Paper III we found that the winter vitamin D supplementation did not affect children’s muscle strength or body composition but had a positive effect on the growth factor insulin-like growth factor I (IGF-1) and its binding protein IGFBP-3 in the group receiving 20 μg/day compared to placebo, as well as a tendency to a greater height increment during winter.

Conclusion: Children’s sun behaviour and physical activity level may influence autumn serum 25(OH)D and should be viewed as factors that can identify children at risk of low vitamin D status. However, advice on increased sun exposure may be unethical and strategies as fortification or supplementation are more appropriate also in light of the low intake of vitamin D from natural sources. The winter decline in serum 25(OH)D seen among children living at northern latitudes can be prevented by supplementation of both 10 and 20 μg/day of vitamin D₃, but the relation between vitamin D intake and serum 25(OH)D seems to blunt at higher intakes in children, as a curvilinear relation was found in the present study. Our finding of an RDA of 19.5 μg/day in 4-8 year-old children suggests that the current vitamin D recommendation in the Scandinavian countries of 10 μg/day is underestimated. In healthy children, neither muscle strength nor body composition was affected by winter vitamin D supplementation. Our finding of higher IGF-1 and IGFBP-3 concentrations after supplementation with 20 μg/day indicate that even in healthy children, vitamin D may affect these growth factors and potentially affect linear growth. However, larger and more long-term studies are needed to conclude on the potential implications of these findings.