Prenatal vitamin D3 supplementation: pharmacology and offspring health outcomes

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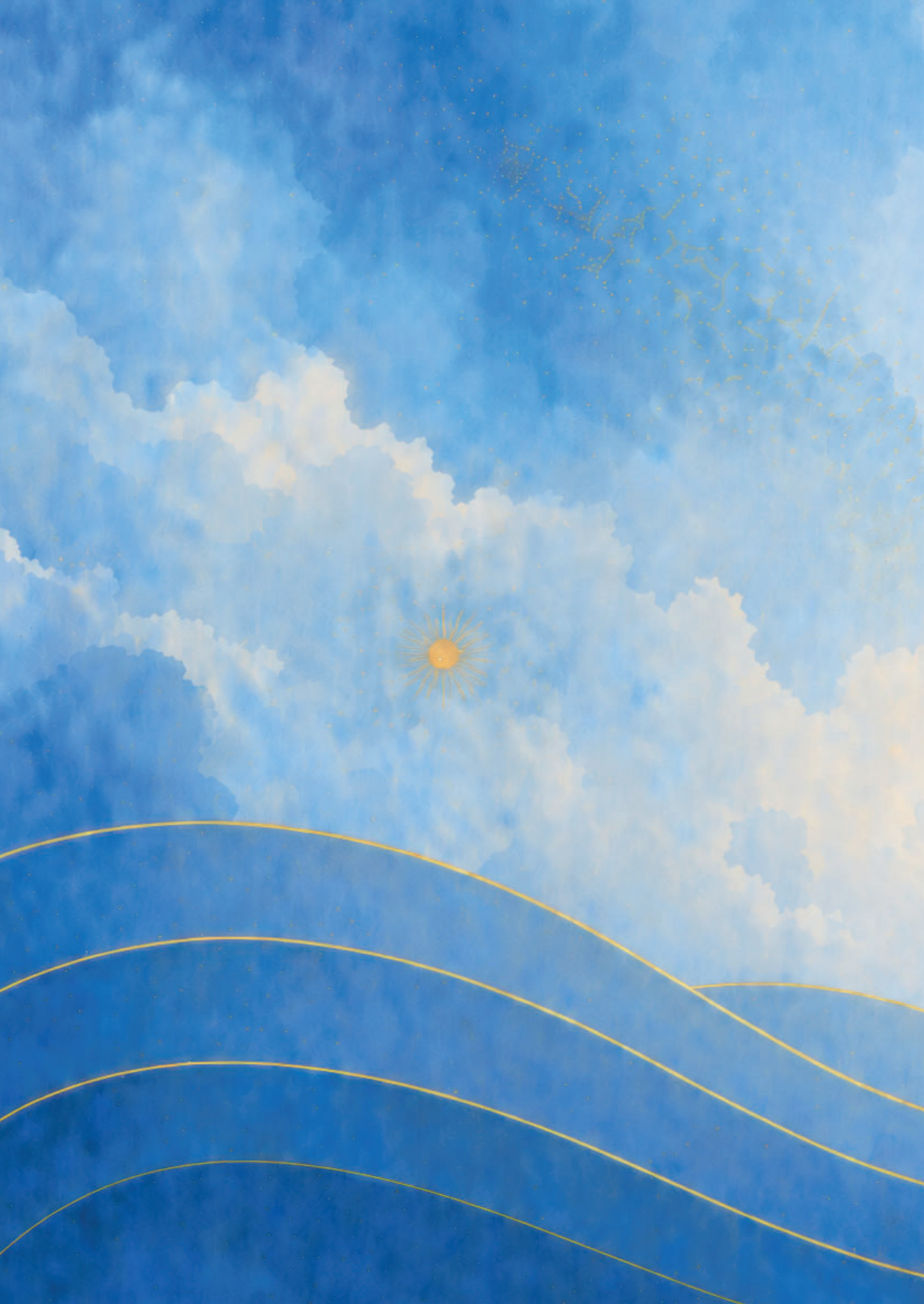

Chapter 12

English summary
Nederlandse samenvatting

English summary

Vitamin D deficiency is prevalent in the general population. Pregnancy significantly alters vitamin D metabolism, increasing the overall demand, and therefore further increases the risk of vitamin D deficiency during this critical window in life. Deficiency during gestation is associated with adverse maternal and neonatal outcomes and should be corrected by prenatal vitamin D supplementation. One notable outcome that may be prevented by achieving gestational vitamin D sufficiency is offspring asthma or recurrent wheezing, conditions that can have a long-term negative impact on the child. Still, current supplementation regimens frequently fail to attain and sustain serum 25-hydroxyvitamin D [25(OH)D] concentration that commonly constitute sufficiency.

In this thesis, we explored how pregnancy reshapes the pharmacokinetics (PK) of vitamin D supplementation and redistributes its metabolites across tissues, how the gestational 25(OH)D exposure relates to offspring respiratory outcomes and how perinatal factors, such as preeclampsia, infant growth, the microbiome and maternal inflammation affect maternal and offspring health.

The first chapter aims to go beyond the endocrine and blood-centric view of vitamin D and explores local tissue concentrations. Serum 25(OH)D is a validated, accessible biomarker of vitamin D exposure, but might be inaccurate as a marker of tissue availability, which is important for paracrine and autocrine functions of vitamin D metabolites. Studies on the tissue distribution of vitamin D metabolites are sparse, but the available data shows selective tissue retention and tight control of metabolites across organs. Pregnancy loosens the regulation of active $1,25(OH)_2D$ and vitamin D metabolites are increasingly redirected to the maternal kidneys for activation, and the placenta for local effects and transfer to the fetus. Overall, the data cautions against the use of 25(OH)D serum thresholds as universal markers of sufficiency for potentially associated extra-skeletal outcomes, such as gestational lung and immune development, which may be better reflected by local concentrations. Most importantly, it advices against extrapolating lessons from non-pregnant individuals to pregnant ones and encourages improved PK characterization and biomarker-driven design of clinical trials on prenatal vitamin D supplementation.

The second chapter addresses the PK of prenatal vitamin D experimentally. In a mouse supplementation study, pregnancy significantly increased the conversion of 25(OH)D to $1,25(OH)_2D$ and altered tissue distribution of vitamin D metabolites. Under high maternal vitamin D intake, the murine kidneys and placenta were the major tissue targets. Transfer

of vitamin D metabolites to the fetus was saturable, indicating active regulation of vitamin D transport by the placenta. Also, high 25(OH)D contents in the lung tissue were found, supporting the concept that the lungs are a key vitamin D target. Mechanistically, these patterns suggest a potential role for vitamin D in the respiratory (immune) system and placental function, while high intake of vitamin D in mice might not linearly increase fetal exposure. Pregnancy therefore induces reallocation of vitamin D metabolites and maternal uncoupling of circulating 25(OH)D and $1,25(OH)_2D$, while maintaining adaptive regulatory mechanisms at the maternal-fetal interface.

The third chapter explores clinical evidence of a link between prenatal vitamin D exposure and offspring asthma or recurrent wheeze, using a population pharmacokinetic (popPK) model. The PK model of prenatal vitamin D generated individual area under the curve (AUC) estimates of maternal serum 25(OH)D across the two largest RCTs on prenatal vitamin D and offspring respiratory outcomes to date; the VDAART and COPSAC. Across the two cohorts, higher exposure to gestational 25(OH)D was associated with lower odds of offspring asthma or recurrent wheeze and improved lung function measures in early life. Clearance of serum 25(OH)D increased with gestational age and higher maternal body weight and inversely related to baseline 25(OH)D at trial enrollment, suggesting that personalized dosing strategies may help to provide consistent prenatal vitamin D exposure for all mothers. Collectively, these insights are supportive of the hypothesis that correcting maternal vitamin D levels may reduce the risk of offspring asthma or recurrent wheeze.

To identify subpopulations that may achieve more benefit from supplementation and optimize the design of future clinical trials on prenatal vitamin D supplementation, we investigated how baseline 25(OH)D status and timing of supplementation initiation modified treatment response in VDAART. Earlier initiation (first trimester) was associated with a more pronounced reduction in offspring asthma/wheeze, consistent with the practical consideration that achieving sufficiency at steady state takes time and the preclinical evidence implicating vitamin D in fetal lung morphogenesis during the first trimester. Furthermore, the signal was strongest among mothers who were severely deficient at baseline, highlighting their greater physiological requirement for supplementation, reflecting previous PK observations, and reiterating the importance of enrolling a truly vitamin D deficient population to reliably detect the effects of supplementation in clinical trials.

The fourth chapter describes other perinatal risk factors relating to respiratory disease and overall maternal and offspring health. Higher weight-for-age was found to increase the odds of offspring asthma/wheeze in early life, with an important divergence: the increased

risk was driven by term children, whereas catch-up growth in preterm children was linked to a reduced risk of asthma/wheeze. Excessive body weight or adiposity in term children may expose them to airway dysanapsis, while catch-up growth in preterms might support lung maturation and allow for improved alveolarization and additional surface area for gas-exchange. These findings motivate context-specific guidance on early life weight gain as more weight gain might not be uniformly beneficial or detrimental.

Moreover, a key predictor of excessive offspring weight trajectories from birth through age 8 years was confirmed to be maternal pre-pregnancy BMI and gestational weight gain. Higher maternal adiposity predisposed children to increased early life weight gain; the same trajectory linked to increased asthma/wheeze in term children. Given that maternal BMI is associated with increased risk of offspring asthma/wheeze and taking into account that higher maternal bodyweight and/or adiposity affects the PK of prenatal vitamin D supplementation, weight-based vitamin D supplementation may be warranted in these mothers to achieve similar exposure and equalize health outcomes.

Besides weight management, adverse pregnancy outcomes, such as preeclampsia (PE), may influence offspring health beyond birth. Neonates from PE pregnancies showed differential DNA methylation signatures in cord blood, enriched for cardiovascular and angiogenic pathways, including the apelin and cGMP/Notch signaling pathways. These results suggest that prenatal complications could induce fetal epigenetic reprogramming, imprinting alterations in cardiovascular pathways, which may have long-term health implications for the children.

Other pathways may also mediate long-term health impact for children born after adverse pregnancy outcomes. Therefore, we explored if PE or spontaneous preterm birth (sPTB) affects the offspring microbiome during early life. The development of the microbiome in terms of alpha and beta diversity occurred along trajectories comparable to normal pregnancies, but both offspring of PE and sPTB pregnancies showed differences at taxa-level (e.g., altered abundances of Firmicutes, Actinobacteriota and Fusobacteriota). Breastfeeding and mode of delivery further shaped the maturation of the early life microbiome. This suggest that high-level microbiome development may appear unafflicted, while imbalances persist at taxa-level, which could have functional consequences. The potential relationship between prenatal adversity and signs of microbial dysbiosis from birth to age 5 years points to yet another mechanism by which gestational exposures may influence longer-term postnatal health.

Finally, maternal inflammation is important factor in pregnancy, as pregnancy is naturally characterized by controlled inflammation. In VDAART, women carrying male fetuses had higher concentrations of C-reactive protein (CRP) in early to mid-pregnancy. Differential concentrations of CRP and interleukin-8 (IL-8) by maternal race/ethnicity and BMI were also observed, independent of pregnancy complications. These variations illustrate the heterogeneity in the maternal gestational immune milieu. Thus, it may be relevant to account for fetal sex, genetic ancestry (instead of race) and maternal adiposity when designing supplementation strategies for compounds known to act on immune cells and modify inflammation, such as vitamin D.

Collectively, the thesis explores if a sufficient prenatal vitamin D status can contribute to lower early-life wheeze/asthma risk and improved lung function when prenatal supplementation is optimized. Mechanistic animal and systems data suggests that serum thresholds for bone health may not translate fully to pregnancy and how tissue-reflective biomarkers and precision dosing are desired. Enrolling and prioritizing mothers most likely to benefit, starting early, dosing to a target with monitoring, incorporating variables affecting vitamin D PK and broadening biomarker ratios beyond total 25(OH)D may all help to optimize the design of clinical trials to investigate the benefits of prenatal vitamin D supplementation. If adopted, these steps would align vitamin D biology, trial design, and clinical prenatal care to ensure a sufficient vitamin D status is achievable for all pregnant women. Only then can we begin to uncover the benefits of vitamin D supplementation and robustly evaluate whether it can achieve a clinically meaningful reduction in early respiratory morbidity, while more broadly advancing maternal and child health.