

LIST OF PAPERS

The thesis is based on the following research papers:

Paper I

Petersen SB, Olsen SF, Mølgaard C, Granström C, Cohen A, Vestergaard P, Strøm M.
Maternal vitamin D status and offspring bone fractures: Prospective study over two decades
in Aarhus city, Denmark.

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Paper II

Petersen SB, Strøm M, Maslova E, Granström C, Vestergaard P, Mølgaard C, Olsen SF.
Vitamin D status during pregnancy in relation to offspring forearm fractures in childhood: A
study from the Danish National Birth Cohort

Journal: Ready for submission.

Paper III

Petersen SB, Rasmussen MA, Olsen SF, Vestergaard P, Mølgaard C, Halldorsson TI, Strøm
M. Maternal dietary patterns during pregnancy in relation to childhood forearm fractures in
the offspring: Prospective study from the Danish National Birth Cohort.

Journal: Ready for submission.

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SUMMARY

English summary

Fetal programming is an emerging concept that links environmental conditions during embryonic and fetal development with risk of diseases later in life. A hypothesis for fetal programming of bone health state that peak bone mass may be modified by environmental influences during fetal life, including maternal diet and vitamin D status. However, few studies have investigated whether these factors during pregnancy impact offspring bone health in short as well as in the long term. The overall objective of this thesis was to investigate epidemiologically whether maternal vitamin D status and dietary patterns in two prospective pregnancy cohorts, were associated with offspring risk of bone fractures in childhood.

In the first study of this thesis, we in the Danish Fetal Origin Study 1988 (DaFO88), with 18 years of follow up, analyzed the association between serum concentrations of 25-hydroxyvitamin D (25(OH)D) in maternal blood from gestation week 30 and offspring risk of bone fractures during childhood, defined by first time bone fracture diagnoses extracted from the Danish National Patient Register (DNPR). No overall association was found between maternal 25(OH)D concentrations (n=850) and first time bone fractures (n=294); however, the trend analysis indicated negative association with offspring forearm fractures. Further, offspring of mothers with a blood sample from winter vs. summer months had higher risk for fractures independently of maternal 25(OH)D concentrations.

In the second study of this thesis, we in the Danish National Birth Cohort (DNBC), with up to 16 years of follow up (recruited in 1996-2002), analyzed the association between maternal predicted status of vitamin D (based on smoking, season, dietary and supplementary vitamin D intake, tanning bed use and outdoor physical activity) and offspring forearm fractures during childhood and adolescence. Predicted vitamin D status (n=30,451) was not associated with offspring risk of forearm fractures (n=2535) in our data. No significant associations were either found for the remaining constituting elements of the prediction score model, expect of high intake of vitamin D from dietary supplements. Contrary to our hypothesis dietary supplement use, with a vitamin D dosage above 10 µg/day vs. zero intake, during mid-pregnancy was associated with increased forearm fracture risk in offspring, and especially among girls.

In the third study of this thesis we in the DNBC analyzed the association between seven maternal dietary patterns in mid-pregnancy and offspring risk of forearm fractures. The dietary patterns (Prudent, Alcohol, Western, Seafood, Nordic, Sweets and Traditional) have previously been extracted from dietary data assessed by a food frequency questionnaire that covered the dietary intake four weeks prior to gestation week 25. Offspring of mothers (n=53,922) in the fourth vs. first quintile of the Western pattern (high in fat and meat, low in fruit and vegetables) had a significant increased risk of offspring forearm fractures (n=4222), and there was a borderline significant trend of a positive association. The other dietary patterns showed no associations and neither did supplementary analyses of macro and micronutrients or single food groups, except for the intake of artificially sweetened soft drinks, which was positively associated with offspring forearm fractures.

Overall, our studies provided limited support to the hypothesis that fetal bone health is programmed by the maternal vitamin D status and overall diet during pregnancy. However, there were some indications of an increased risk for fractures when the mother consumed a Western diet and had high consumption of artificially sweetened soft drinks. Further, our results indicated that mid-pregnancy use of dietary supplements with high doses of vitamin D increased the risk for offspring fractures.

Danish summary

Føtal programmering er et nyt koncept, hvor de miljømæssige forhold i graviditeten menes at have betydning for barnets senere udvikling af sygdom. En af hypoteserne for føtal programmering kæder miljømæssige forhold i graviditeten til barnets senere knoglemasse, herunder maternelt kostindtag og D-vitamin status. Der er dog få studier, der har undersøgt sammenhængen mellem kostfaktorer i graviditeten og barnets senere knoglesundhed på både kort og lang sigt. Formålet med denne afhandling var epidemiologisk at undersøge, om maternel D-vitamin status og maternel ernæring generelt i to prospektive fødselskohorter var associeret med øget risiko for knoglebrud i barndommen.

I afhandlingens første artikel undersøgte vi i en fødselskohorte igangsat i Aarhus i 1998-1999 associationen mellem koncentrationen af maternel serum 25-hydroxyvitamin D (25(OH)D) i graviditetsuge 30 og barnets risiko for knoglefraktur i de første 18 leveår. Frakturdiagnoserne blev indhentet fra Landspatientregisteret. Resultaterne viste ingen association mellem 25(OH)D koncentrationen hos 850 mødre og børnenes risiko for senere fraktur. I alt observerede vi 294 frakturer i studiepopulationen. Vi fandt dog en tendens til en negativ association mellem 25(OH)D og børnenes risiko for senere underarmsfraktur. Desuden viste sæson-analysen, at børn af mødre, der havde fået taget blodprøven i løbet af vintermånederne, havde signifikant øget risiko for frakturer sammenholdt med børn af mødre, der fik blodprøven taget i løbet af sommermånederne. Denne sammenhæng var uafhængig af den materielle 25(OH)D koncentration.

I afhandlingens anden artikel undersøgte vi sammenhængen mellem moderes prædikterede status af D-vitamin (baseret på rygning, sæson, kost, kosttilskud med D-vitamin, solariebrug og udendørs fysisk aktivitetsniveau) og børnenes risiko for senere underarmsfraktur i fødselskohorten "Bedre Sundhed for Mor og Barn (BSMB)" med op til 16 års opfølgning. Rekruttering til kohorten foregik i 1996-2002. Vores studie viste ingen signifikant association mellem den prædikterede D-vitamin status og barnets risiko for senere underarmsfraktur i 30,451 mødre og deres børn, hvor der i alt blev observeret 2535 pædiatriske underarmsfrakturer. Der blev heller ikke fundet signifikant association for prædiktionsmodellens øvrige komponenter. Modsat vores hypotese fandt vi dog, at et maternelt indtag af kosttilskud på mere end 10 µg D-vitamin pr. dag signifikant øgede barnets risiko for senere underarmsfraktur, hvilket især var gældende for piger.

I afhandlingens tredje artikel undersøgte vi i BSMB associationen mellem indtaget af syv forskellige kosttyper (frugt og frønt, festlig, fisk og skaldyr, nordisk, sukkerholdig og traditionel) og barnets risiko for senere underarmsfraktur. Kosttyperne er tidligere blevet ekstraheret fra kostdata indsamlet midt i graviditeten via et frekvens kostspørgeskema, der dækkede kostindtaget i de forudgående 4 uger fra graviditetsuge 25. Børn af mødre (n=53.922), der lå i fjerde versus første kvartil for vestlig kost (højt indtag af fedt og kød; lavt indtag af frugt og grønt) havde signifikant øget risiko for senere underarmsfraktur. Der blev i alt observeret 4222 underarmsfrakturer i studiepopulationen. Der var desuden en tendens til en positiv association i trendanalysen. Der blev ikke fundet nævneværdige associationer for makro- og mikronæringsstoffer eller enkelte fødevaregrupper, dog med undtagelse af kunstigt sødet læskedrikke. Der var en positiv association mellem indtaget af kunstigt sødet læskedrikke og børnenes risiko for senere underarmsfrakturer.

Samlet set kunne vores studier ikke underbygge hypotesen om, at føtal knoglesundhed programmeres af den materielle ernæring i graviditeten eller den materielle D-vitamin status. Vores resultater indikerede dog, at et højt indtag af vestlig kost og kunstigt sødet læskedrikke i graviditeten kan øge børnenes risiko for senere knoglefrakturer. Desuden indikerede vores resultater, at kosttilskud med høje doser D-vitamin kan øge risikoen for senere frakturer hos børnene.