SUPPLEMENTARY MATERIAL

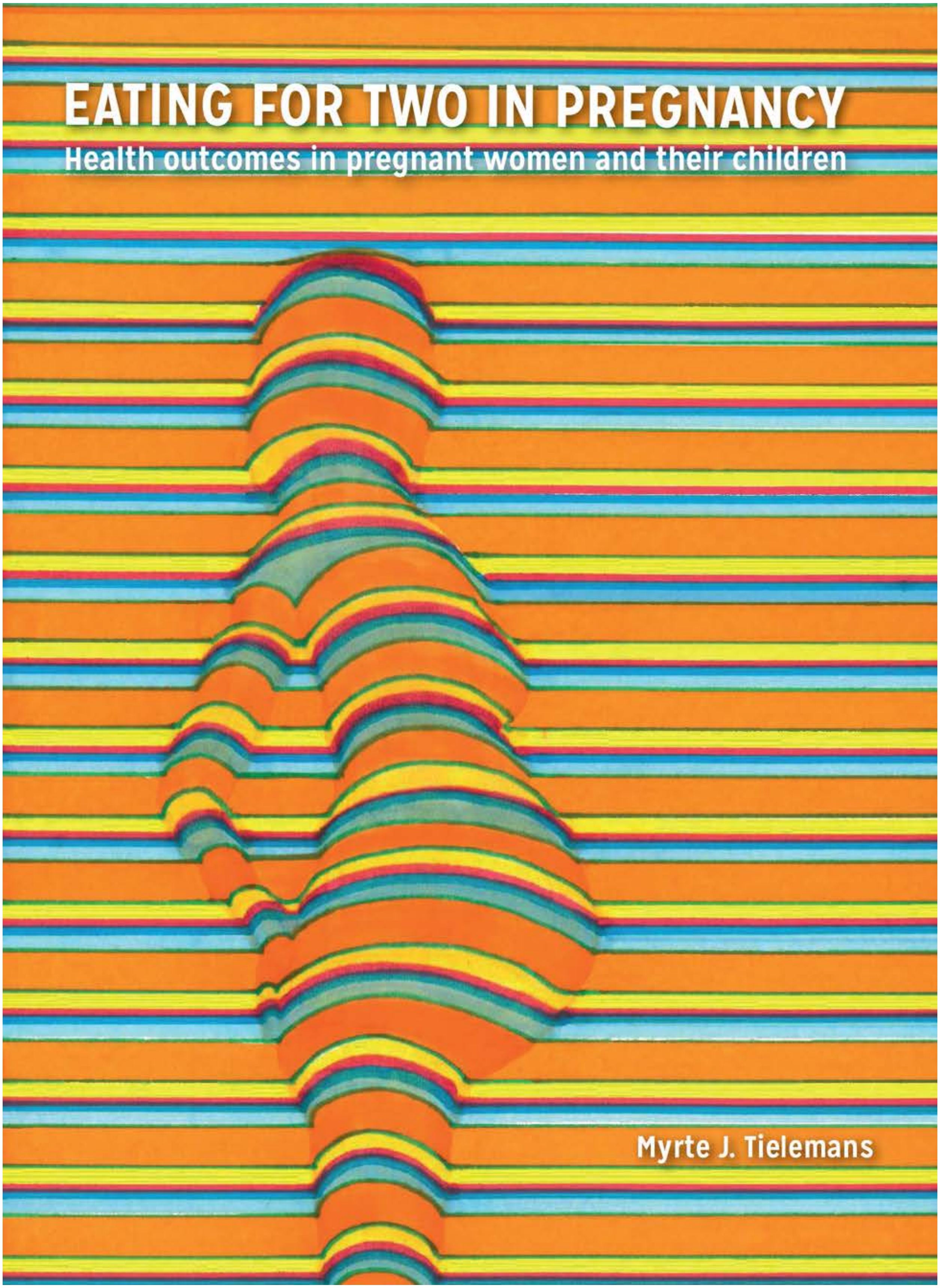


Table of contents

Chapter 2.1

Macronutrient composition and gestational weight gain: a systematic review

Myrte J. Tielemans, Audry H Garcia*, André Peralta Santos*, Wichor M. Bramer, Nellija Luksa, Mateus J. Luvizotto, Eduardo Moreira, Geriolda Topi, Ester A.L. de Jonge, Thirsa L. Visser, Trudy Voortman, Janine F. Felix, Eric A.P. Steegers, Jessica C. Kiefte-de Jong, Oscar H. Franco

* Contributed equally

The American Journal of Clinical Nutrition; 2016 Jan; 103: 83-99

Supplementary material 2.1.1. Search strategy

Relevant articles, published before 12 August 2015, were identified through eight electronic databases (Embase (in embase.com), Medline (in OvidSP), Cochrane central (in Wiley), Web-of-Science, CINAHL (in EBSCOhost), PsychINFO (in OvidSP), PubMed as supplied by publisher, and Google Scholar). The following search terms were used without language restriction:

Embase

('weight gain'/de OR 'weight change'/de OR (((weight OR 'body mass' OR bmi OR quetelet) NEAR/3 (gain* OR increase* OR chang*))):ab,ti) AND (('maternal nutrition'/de OR ((nutrition* OR malnutrition* OR diet* OR intake OR consum* OR calor* OR feeding OR food OR glycemic* OR eating OR meal* OR fasting OR macronutrient* OR nutrient* OR eating) NEAR/6 (matern* OR pregnan* OR mother* OR prenatal OR gravid* OR gestation*)):ab,ti) OR ((pregnancy/exp OR 'pregnant woman'/de OR (pregnan*):ab,ti) AND (nutrition/exp OR diet/exp OR 'dietary intake'/exp OR (nutrit* OR diet* OR eating):ab,ti))) NOT ([animals]/lim NOT [humans]/lim)

Medline (in OvidSP)

("weight gain"/ OR "Body Weight Changes"/ OR (((weight OR "body mass" OR bmi OR quetelet) ADJ3 (gain* OR increase* OR chang*))).ab,ti.) AND (("Maternal Nutritional Physiological Phenomena"/ OR ((nutrition* OR malnutrition* OR diet* OR intake OR consum* OR calor* OR feeding OR food OR glycemic* OR eating OR meal* OR fasting OR macronutrient* OR nutrient* OR eating) ADJ6 (matern* OR pregnan* OR mother* OR prenatal OR gravid* OR gestation*)).ab,ti.) OR ((exp pregnancy/ OR "pregnant women"/ OR exp "Pregnancy Trimesters"/ OR (pregnan*).ab,ti.) AND (exp "Nutritional Physiological Phenomena"/ OR "Diet Records"/ OR (nutrit* OR diet* OR eating).ab,ti.))) NOT (exp animals/ NOT humans/)

Cochrane Central

((((weight OR 'body mass' OR bmi OR quetelet) NEAR/3 (gain* OR increase* OR chang*))):ab,ti) AND ((nutrition* OR malnutrition* OR diet* OR intake OR consum* OR calor* OR feeding OR food OR glycemic* OR eating OR meal* OR fasting OR macronutrient* OR nutrient* OR eating) NEAR/6 (matern* OR pregnan* OR mother* OR prenatal OR gravid* OR gestation*)):ab,ti

Web-of-Science

TS=(((((weight OR "body mass" OR bmi OR quetelet) NEAR/3 (gain* OR increase* OR chang*)))) AND ((nutrition* OR malnutrition* OR diet* OR intake OR consum* OR calor* OR feeding OR food OR glycemic* OR eating OR meal* OR fasting OR macronutrient* OR nutrient* OR eating) NEAR/6 (matern* OR pregnan* OR mother* OR prenatal OR gravid* OR gestation*)) NOT ((animal* OR sheep OR rat OR rats OR ovine* OR rodent* OR baboon* OR monkey* OR primate* OR cattle OR swine OR horse* OR sow OR sows OR cow OR cows OR rabbit* OR mare OR mares OR goat* OR hamster*) NOT (human* OR wom?n OR patient*)))

CINAHL

(MH "weight gain"+ OR MH "Body Weight Changes" OR TX (((weight OR "body mass" OR bmi OR quetelet) N3 (gain* OR increase* OR chang*)))) AND ((MH "Maternal Nutritional Physiology"+ OR TX ((nutrition* OR malnutrition* OR diet* OR intake OR consum* OR calor* OR feeding OR food OR glycemic* OR eating OR meal* OR fasting OR macronutrient* OR nutrient* OR eating) N6 (matern* OR pregnan* OR mother* OR prenatal OR gravid* OR gestation*))) OR ((MH pregnancy+ OR MH "Expectant Mothers"+ OR MH "Pregnancy Trimesters"+ OR TX (pregnan*)) AND (MH "Nutrition"+ OR MH "Diet"+ OR TX (nutrit* OR diet* OR eating)))) NOT (MH animals+ NOT human+)

PsycINFO (in OvidSP)

("weight gain"/ OR (((weight OR "body mass" OR bmi OR quetelet) ADJ3 (gain* OR increase* OR chang*))).ab,ti.) AND ((((nutrition* OR malnutrition* OR diet* OR intake OR consum* OR calor* OR feeding OR food OR glycemic* OR eating OR meal* OR fasting OR macronutrient* OR nutrient* OR eating) ADJ6 (matern* OR pregnan* OR mother* OR prenatal OR gravid* OR gestation*)).ab,ti.) OR ((exp pregnancy/ OR (pregnan*).ab,ti.) AND ((nutrit* OR diet* OR eating).ab,ti.))) NOT (exp animals/ NOT humans/)

PubMed as supplied by publisher

((((weight[tiab] OR "body mass"[tiab] OR bmi[tiab] OR quetelet[tiab]) AND (gain*[tiab] OR increase*[tiab] OR chang*[tiab])))) AND ((((nutrition*[tiab] OR malnutrition*[tiab] OR diet*[tiab] OR intake[tiab] OR consum*[tiab] OR calor*[tiab] OR feeding[tiab] OR food[tiab] OR glycemic*[tiab] OR eating[tiab] OR meal*[tiab] OR fasting[tiab] OR macronutrient*[tiab] OR nutrient*[tiab]) AND (matern*[tiab] OR pregnan*[tiab] OR mother*[tiab] OR prenatal[tiab] OR gravid*[tiab] OR gestation*[tiab]))) OR (((pregnan*[tiab])) AND ((nutrit*[tiab] OR diet*[tiab] OR eating[tiab])))) AND publisher[sb]

Google Scholar

"maternal|gestational weight|mass gain|increase|change" nutrition|malnutrition|diet|intake|consumption|caloric|feeding|food|eating|fasting|macronutrient

Supplementary material 2.1.2. Quality score

This quality score was used to assess the quality of included studies in this systematic review and is applicable to both interventional and observational studies. The score was designed based on previously published scoring systems (1, 2). The quality score consists of 5 items, and each item is allocated 0, 1 or 2 points. This allows a total score between 0 and 10 points, 10 representing the highest quality.

1. Study design

   0 for studies with cross-sectional data collection
   1 for studies with longitudinal data collection
   2 for intervention studies

2. Study size

Observational studies	*Intervention studies*
0 if n<500	**0** if n<50
1 if n 500 to 2000	**1** if n 50 to 100
2 if >2000	**2** if n>100

3. Exposure

   Observational studies
   0 if the study used no appropriate standard diet assessment or if not reported
   1 if the study used a one-day food record, a one-day 24h recall or an inappropriate FFQ
   2 if the study used an appropriate FFQ, multiple day food records, or multiple 24h recalls

   Intervention studies
   0 if the intervention was not described or not blinded
   1 if the intervention was adequately single-blinded
   2 if the intervention was adequately double-blinded

4. Outcome

   0 if the study used no appropriate outcome measurement method or if not reported
   1 if the study used a self-reported (pre-pregnancy) weight and a measured weight (at end of observation) or a self-reported gestational weight gain
   2 if the study used a measured weight at start and end of the study to calculate gestational weight gain

5. Adjustments

   0 if findings are not controlled for at least the two key covariates† mentioned below
   1 if findings are controlled for:
   - Pre-pregnancy body mass index or pre-pregnancy weight
   - Maternal age

   2 if an intervention study is adequately randomized or if findings are additionally controlled for at least two of the following covariates†:
   - Total energy intake
   - Birth weight
   - Ethnicity
   - Gestational age at delivery
   - Parity
   - Physical activity
   - Social economic status

† Either adjusted for in the statistical analyses; stratified for in the analyses; or not applicable (e.g., a study in nulliparous women only does not require controlling for parity).
Abbreviation: FFQ, food-frequency questionnaire.

Supplementary Table 2.1.1. Associations between energy intake and gestational weight gain (N=42)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
High-income countries							
Intervention studies							
Bompiani, 1986 (3)	Unpaired student *t*-test	Difference in GWG (kg)between low energy diet and control diet				+	<0.05
Rae, 2000 (4)	NR	Difference in GWG (kg)between moderately energy restricted diet and control diet[2]				null	0.25
Longitudinal studies							
Althuizen, 2009 (5)	Linear regression	Association between energy intake (kJ/day) and GWG (kg)	Gestational age at delivery			0.00 (NR)	0.3
	Logistic regression	Energy intake (kJ/day) and the odds of excessive GWG (vs. inadequate and adequate GWG)	Gestational age at delivery			1.00 (NR)	0.3
Ancri, 1977 (6)	Rank correlation	Correlation between energy intake (kcal) and GWG (kg)	Stratified by maternal age			NR	NS
Anderson, 1986 (7)	None[3]	Difference in energy intake (kcal) between categories of GWG adequacy				null	≥0.05
Bellati, 1995 (8)	NR	Association between energy intake (categories) and GWG (kg)				null	NS
Bergmann, 1997 (9)	ANOVA	Difference in GWG (kg) between categories of energy intake	Age, parity, pre-pregnancy BMI, maternal education, smoking during pregnancy			null	0.06
Blumfield, 2015 (10)	Pearson correlation	Correlation between energy intake (kJ) and GWG (kg)				0.18	0.04
	Pearson correlation	Correlation between energy intake (kJ) and GWG adequacy				0.17	<0.05
	Kruskal-Wallis test	Difference in energy intake (kJ) between categories of GWG adequacy				null	≥0.05
Chasan-Taber, 2008 (11)	Chi-square test for trend	Association between energy intake (categories) and GWG (lbs)				null	0.78[4]

Supplementary Table 2.1.1 (continued). Associations between energy intake and gestational weight gain (N=42)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
Gaillard, 2013 (12)	Logistic regression	Energy intake per SD (1 SD = 563 kcal) and the odds of excessive GWG	Age, parity, pre-pregnancy BMI, maternal education, ethnicity, smoking during pregnancy, folic acid supplementation, alcohol consumption during pregnancy			1.13 (1.03, 1.23)	<0.01
Heery, 2015 (13)	Linear regression	Association between energy intake (kcal/day) and GWG (kg)				+	<0.05
	Linear regression	Association between energy intake (tertiles) and GWG (kg)				NR	≥0.05
Heery, 2015 (13)	Logistic regression	Energy intake (tertiles) and the odds of inadequate (vs. not inadequate GWG)				NR	≥0.05
	Logistic regression	Energy intake (tertiles) and the odds of excessive (vs. not excessive GWG)				NR	≥0.05
Lagiou, 2004 (14)	Linear regression	Association between energy intake (per SD increase) and GWG (kg)	Age, parity, pre-pregnancy BMI, maternal education, smoking during pregnancy, gestational age at delivery, gender of the baby, maternal height, pre-pregnancy OC use			0.91 (0.26, 1.56)[5]	<0.01[4]
Langhoff-Roos, 1987 (15)	Linear regression	Association between energy intake (MJ) and GWG (kg)	Physical activity, lean body mass			-0.30 (-1.28, 0.67)[5]	0.55
Maple-Brown, 2013 (16)	Pearson correlation	Correlation between energy intake and GWG (kg)				NR	NS
Montpetit, 2012 (17)	Multiple regression analysis	Association between energy intake (1,000 kcal/day) and GWG (kg)	Pre-pregnancy BMI, physical activity			1.69 (NR)	0.31
	Pearson correlation	Correlation between energy intake (kcal) and GWG (kg)				0.11	0.42
Olafsdottir, 2006 (18)	ANOVA	Difference in energy intake (kJ/day) between categories of GWG adequacy		BMI < 25 BMI ≥ 25		NR +	NS 0.02
Ostachowska-Gasior, 2003 (19)	NR	Difference in energy intake (kcal) between adequate and excessive GWG			T1 T2 T3	null null null	NS NS NS

Supplementary Table 2.1.1 (continued). Associations between energy intake and gestational weight gain (N=42)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
Papoz, 1980 (20)	Pearson correlation	Correlation between energy intake (kcal) and GWG (kg)			T1 cT1[6] cT1-3[6]	0.28 0.18 -0.25	<0.01 <0.05 <0.01
Picone, 1982 (21)	ANOVA	Difference in energy intake (kcal) between categories of GWG adequacy		All		null	NS
				Non smokers		+	<0.02
	Pearson correlation	Correlation between energy intake (kcal) and GWG (Lbs)		All		NR	NR
				Non smokers		0.44	<0.02
Scholl, 1993 (22)	NR	Association between energy intake (kcal/day) and GWG adequacy	Age, parity, pre-pregnancy BMI, ethnicity, smoking during pregnancy, clinic payment status, prior low birth weight, multivitamin use			+	<0.05
Shin, 2014 (23)	Wald F test	Difference in energy intake (kcal/day) between categories of GWG adequacy	Age, pre-pregnancy BMI, education, family poverty income ratio, ethnicity, smoking during pregnancy, physical activity, trimester of gestation, marital status, daily supplement use			null	0.31
Stuebe, 2009 (24)	Logistic regression	Energy intake (per 500 kcal/day) and the odds of excessive (vs. not excessive) GWG	Age, pre-pregnancy BMI, ethnicity, smoking during pregnancy, gestational age at delivery and nausea during first trimester of pregnancy			1.11 (1.00, 1.23)	NR
Uusitalo, 2009 (25)	Linear regression	Association between energy intake and GWG (kg)	Age, parity, pre-pregnancy BMI, maternal education, smoking during pregnancy, birth weight, living area, gestational age at first weight measurement			0.02 (NR)	<0.01

Supplementary Table 2.1.1 (continued). Associations between energy intake and gestational weight gain (N=42)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
Low- and middle-income countries							
Longitudinal studies							
Ali, 2002 (26)	Linear regression	Association between energy intake and GWG (kg)	Age, pre-pregnancy weight and height, weight-for-height ratio index, weight-height-product index, mid-arm circumference			2.24 (1.16, 3.32)[5]	<0.01
Castro, 2013 (27)	Mixed effects model for repeated measurements	Difference in GWG (kg) between excessive energy intake (>20% recommended [7]) vs. adequate energy intake.	Age, parity, pre-pregnancy BMI, maternal education, ethnicity			1.70 (0.86, 2.54)[5]	<0.01
Changamire, 2014 (28)	GEE	Difference in GWG (g/month) per 100 kcal increase in energy intake	Parity, pre-pregnancy BMI, maternal education, socio-economic indicator, maternal height, baseline haemoglobin level, marital status, season, trimester of pregnancy, multivitamin regimen assignment			6 (1,12)	0.03
Das, 1976 (29)	ANOVA	Difference in GWG (kg) per energy intake category				+[8]	<0.05
Drehmer, 2010 (30)	Poisson regression	Relative risk (RR) of inadequate (vs. adequate and excessive) GWG in women with low or high (vs. normal) energy intake (kcal/day)				Low: 0.92 (0.62, 1.38) Normal: reference High: 0.73 (0.50, 1.19)	0.71 0.24
	Poisson regression	Relative risk (RR) of excessive (vs. inadequate and adequate) GWG in women with low or high (vs. normal) energy intake (kcal/day)				Low: 1.05 (0.78, 1.39) Normal: reference High: 1.07 (0.80, 1.44)	0.74 0.63
Ebrahami, 2015 (31)	Logistic regression	Energy intake (kcal) and the odds of inadequate (vs. adequate) GWG	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			<1.00(<1.00, 1.00)	≥0.05
	Logistic regression	Energy intake (kcal) and the odds of inadequate (vs. excessive) GWG	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			0.998 (0.997, 0.999)	<0.05

Supplementary Table 2.1.1 (continued). Associations between energy intake and gestational weight gain (N=42)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
Ebrahami, 2015 *(continued)*	Logistic regression	Energy intake (kcal) and the odds of adequate (vs. excessive) GWG	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			1.00 (<1.00, 1.00)	≥0.05
	Cumulative Logit Model for Ordinal Responses	Odd ratio between energy intake (kcal) and adequacy of GWG (inadequate, adequate and excessive GWG)	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			1.00 (1.00, 1.00)	0.25
Ho, 2005 (32)	ANOVA	Difference in GWG (kg) per energy intake (in tertiles)				null	NS
Hsu, 2013 (33)	Pearson correlation	Correlation between energy intake (kcal/day) and GWG (kg)			T1 T2 T3	0.20 0.19 0.22	<0.01 <0.01 <0.01
Jaruratanasiriku, 2009 (34)	Logistic regression	Energy intake (kcal) and the odds of inadequate (vs. adequate) GWG	Pre-pregnancy BMI, maternal education, family income, intake of calcium and iron			0.91 (0.62, 2.72)	0.33
Kardjati, 1990 (35)	Regression	Association between energy Intake (kcal) and GWG (kg)	Parity, pre-pregnancy BMI, gender of the child, protein intake, compliance to the supplementation intake		T2 T3	NR NR	NS NS
	Correlation	Correlation between energy intake (kcal)and GWG (kg)			T2 T3	0.15 0.08	<0.05 NS
Lechtig, 1978 (36)	Student *t*-test	Difference in percentage mothers with a monthly adequate GWG per energy intake (high energy supplemented vs. low energy supplemented)				null	<0.10
Popa, 2014 (37)	Chi-square test	Difference in energy intake (kcal) between women with inadequate GWG and adequate GWG				+	<0.01
	Chi-square test	Difference in energy intake (kcal) between women with adequate GWG and excessive GWG				+	<0.01
	Multinomial logistic regression	Energy intake (quartiles) and the odds of inadequate GWG (vs. adequate GWG)	Age, pre-pregnancy BMI, adequacy of prenatal care utilization index, area of residence			Q1: 1.41 (0.73, 2.72) Q2+Q3: reference Q4: 1.82 (0.89, 3.74)	0.31 0.10

Supplementary Table 2.1.1 (continued). Associations between energy intake and gestational weight gain (N=42)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
Popa, 2014 *(continued)*	Multinomial logistic regression	Energy intake (quartiles) and the odds of excessive GWG (vs. adequate GWG)	Age, pre-pregnancy BMI, adequacy of prenatal care utilization index, area of residence			Q1: 0.66 (0.35, 1.23) Q2+Q3: reference Q4: 2.04 (1.12, 3.70)	0.19 0.02
Rodrigues, 2008 (38)	Linear mixed model	Adequacy of energy intake (%) and change in weight (kg)	Age, gestational age at delivery, age at menarche, triglycerides, blood glucose			-0.06 (-0.10, -0.03)[5]	<0.01
Saowakontha, 1992 (39)	Linear regression	Explained variance of GWG (R^2) by energy intake (kcal)		Rural[9]	T1	NR	NS
				Rural	T2	NR	NS
				Rural	T3	NR	NS
				Urban[9]	T1	14.0	≤0.05
				Urban	T2	26.3	≤0.05
				Urban	T3	28.1	≤0.05
Siega-Riz, 1993 (40)	Linear regression	Association between energy intake (kJ) and GWG (kg)	Maternal age, parity, pre-pregnancy BMI, gestational age at delivery, physical activity			0.50 (0.05, 0.95)[5]	<0.05
Smith, 1997 (41)	Stepwise regression analysis	Association between energy intake and GWG (kg)				NR	NS
Wagner, 1975 (42)	Student *t*-test	Difference in GWG (g/week) between energy intake (3 categories)				+[10]	<0.05
Zulfiqar, 2011 (43)	Regression	Association between energy intake (kcal/day) and GWG (g/week)				0.05 (NR)	0.33
Case control study							
Costa, 2011 (44)	Spearman correlation	Correlation between energy intake (kcal) and adequacy of GWG				0.15	0.04
	Linear regression	Association between energy intake (kcal) and adequacy of GWG	Maternal age, pre-pregnancy BMI, protein intake, total cholesterol, several micronutrients			0.04 (NR)	0.87

[1.] Parameter estimate of the used statistical method, + = positive value, - = negative value, null = no association; [2.] Slightly different macronutrient composition among the two diets; [3.] Only descriptive, no statistical analysis. Based on reported numbers and the assumption of a normal distribution of carbohydrate intake, we have a Welch *t*-test performed; [4.] *p* for trend; [5.] 95% confidence interval calculated using reported mean and standard error; [6.] Change in energy intake as compared with previous dietary assessment (cT1: change during 1st trimester of pregnancy, cT1-3: change during 3rd until 8th month of pregnancy); [7.] Recommended energy intake based on IOM 2009 recommendation and uses maternal age, weight, height and physical activity level (45); [8.] Category 1 (lowest caloric intake) versus all other 4 categories; [9.] Living location of the women (rural vs. urban); [10.] Highest category of energy intake compared with lowest category energy intake (in total 3 categories). **Abbreviations**: ANOVA, Analysis of Variance; BMI, body mass index (kg/m^2); CI, confidence interval; GEE, generalized estimating equation; GWG, gestational weight gain; lbs, pounds; NR, not reported; NS, not significant; OC, oral contraceptive; Q, quartile; SD, standard deviation; T, trimester of pregnancy.

Supplementary Table 2.1.2. Associations between macronutrient supplementation and gestational weight gain (N=11)

First author, year	Statistical analysis	Measure of association	Details supplementation	Subgroups	Trimester	Effect estimate[1]	P-value
High-income countries							
Intervention studies							
Viegas, 1982a (46)	NR	Difference in GWG (g/week) between 3 groups (En/Pr/Vi vs. En/Vi vs. Vi)	En/Pr/Vi: 273 kcal/day (11% protein) En/Vi: 273 kcal/day (100% carbohydrate)Supplemented during T2 and T3		T2 T3	+[2] null[2]	<0.05 NS
Viegas, 1982b (47)	NR	Difference in GWG (g/week) between 3 groups (En/Pr/Vi vs. En/Vi vs. Vi)	En/Pr/Vi: 425 kcal/day (10% protein) En/Vi: 425 kcal/day (100% carbohydrate)Supplemented during T3	Inadequate fat increase[3]	T3	null[4]	>0.05
				Adequate fat increase[3]	T3	null[2]	NS
Low- and middle-income countries							
Intervention studies							
Adair, 1984 (48)	NR	Different in GWG (kg) between 2 groups (En vs. placebo)	En: 400 kcal/day (50% carbohydrate, 20% protein, 30% fat) Placebo (<June 1971): 3 kcal/day; Placebo (≥June 1971): 43 kcal/day (93% carbohydrate, trace protein and fat) Supplemented during T1, T2 and T3			null	NS
Begum, 1991 (49)	NR	Difference in GWG (kg and kg/week) between 2 groups (En vs. NoS)	En: 520 kcal (13% protein, 31% fat) Supplemented during T3 (subgroup: T2 and T3)			+	<0.05
Hussain, 1988 (50)	NR	Difference in GWG (kg/week) between 2 groups (En vs. NoS)	En: 488 kcal (14% protein, 27% fat) Supplemented during T2 and T3 (duration: 12 weeks)			+	<0.05
	NR	Difference in GWG (kg) between 2 groups (En vs. NoS)	En: 488 kcal (14% protein, 27% fat) Supplemented during T2 and T3 (duration: 12 weeks)			null	NS
Kardjati, 1990 (35)	ANOVA	Difference in GWG (kg) between 2 groups (HEn vs. LEn) and divided into categories based on compliance supplement intake	HEn: 465 kcal/day (40% carbohydrate, 10% protein, 50% fat) LEn: 52 kcal/day (25% carbohydrate, 50% protein) Supplemented during T3		T2 T3	null null	NS NS
Kaseb, 2002 (51)	Students *t*-test	Difference in GWG (kg) between 2 groups (En/Pr vs. NoS)	En/Pr: 400 kcal/day (5 days/week; 15% protein) Supplemented during T2 and T3			+	<0.02

Supplementary Table 2.1.2. (continued) Associations between macronutrient supplementation and gestational weight gain (N=11)

First author, year	Statistical analysis	Measure of association	Details supplementation	Subgroups	Trimester	Effect estimate[1]	P-value
Nahar, 2009 (52)	ANOVA	Difference in GWG (kg) between 2groups (En vs. NoS)	En: 600 kcal/day (6 days/week; 80% carbohydrate, 12% protein, 8% fat) Supplemented during T2 and T3	BMI <18.5 BMI ≥18.5		NR NR	NS NS
Ortolano, 2003 (53)	Two-sided *t*-test	Difference in GWG (kg/month) between 2 groups[5] (En vs NoS)	En: 600 kcal/day Supplemented period NR			+	<0.01
	Two-sided *t*-test	Difference in GWG adequacy between 2 groups[5] (En vs NoS)	En: 600 kcal/day Supplemented period NR			+	<0.01
Qureshi, 1973 (54)	None[6]	Difference in GWG (kg) between 2 groups (En/Pr/MiN vs MiN) supplementation)	En/Pr/MiN: 500 kcal/day (16% protein) Supplemented during T2 and T3			null	0.09
Tontisirin, 1986 (55)	Unpaired *t*-test	Difference in GWG (kg/week) between 3 groups (I (En/Pr) and II (En/Pr) vs. III (NoS))	En/Pr (group I and II): 350 kcal/day (15% protein) Supplemented during T3			+[7]	<0.01

[1.] Parameter estimate of the used statistical method, + = positive value, - = negative value, null = no association; [2.] Pr/En/Vi supplementation compared with Vi supplementation; [3.] Adequacy of fat accretion was based on increase in triceps skinfold thickness increment during the second trimester; [4.] Pr/En/Vi supplementation compared with En/Vi supplementation and Vi supplementation; [5.] Significant difference in BMI between supplemented group and control group (BMI resp. 17 and 20 kg/m^2); [6.] Results were only descriptive. Using reported mean weight gains and standard deviations, we calculated a p-value using an independent sample *t*-test; [7.] Group I and group II vs group III (supplemented groups vs not-supplemented group); **Abbreviations:** ANOVA, analysis of variance; BMI, body mass index (kg/m^2); En, energy supplementation; En/Pr, energy/protein supplementation; En/Pr/MiN, energy/protein and micronutrient supplementation; En/Pr/Vi, energy/protein/vitamin supplementation; GWG, gestational weight gain; HEn, high energy supplementation; Len, low energy supplementation; MiN, micronutrient supplementation; NoS, no supplementation; NR, not reported; NS, not significant; T, trimester of pregnancy; Vi, vitamin supplementation.

Supplementary Table 2.1.3: Associations between protein intake and gestational weight gain (N=29)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
High-income countries							
Longitudinal studies							
Ancri, 1977 (6)	Rank correlation	Correlation between protein intake (g) and GWG (kg)	Stratified by age	18-19 y 20-24 y 25-32 y		NR NR +0.47	NS NS <0.05
Anderson, 1986 (7)	None[2]	Difference in protein intake (E%) between categories of GWG adequacy				null	≥0.05
Blumfield, 2015 (10)	Kruskal-Wallis test	Difference in protein intake (E%) between categories of GWG adequacy				null	≥0.05
Gaillard, 2013 (12)	Logistic regression	Protein intake per SD (1 SD =2.6 E%) and the odds of excessive GWG	Age, parity, pre-pregnancy BMI, maternal education, ethnicity, smoking during pregnancy, energy intake, folic acid supplementation, alcohol consumption during pregnancy			1.91 (1.26, 2.88)	<0.01
Lagiou, 2004 (14)	Linear regression	Association between protein intake (per SD increase) and GWG (kg)	Age, parity, pre-pregnancy BMI, maternal education, smoking during pregnancy, energy intake, gestational age at delivery, gender of the baby, maternal height, pre-pregnancy OC use			3.11 (1.72, 4.50)[3]	<0.01[4]
Maple-Brown, 2013 (16)	Pearson correlation	Correlation between protein intake and GWG (kg)				NR	NS
Maslova, 2015 (56)	Linear regression	Difference in GWG (g/week) when substituting energy-adjusted carbohydrate for energy-adjusted protein (in quintiles)	Age, parity, pre-pregnancy BMI, socio-economic indicators, smoking during pregnancy, physical activity, maternal height, fat intake			Q1: reference Q2: -10 (-17, -4) Q3: -8 (-14, -1) Q4: -12 (-18, -5) Q5: -13 (-20, -7)	<0.01[4]
	Linear regression	Difference in GWG (g/week) when substituting energy-adjusted fat for energy-adjusted protein	Age, parity, pre-pregnancy BMI, socio-economic indicators, smoking during pregnancy, physical activity, maternal height, carbohydrate intake			NR	<0.05

Supplementary Table 2.1.3 (continued). Associations between protein intake and gestational weight gain (N=29)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
Maslova, 2015 (cont'd)	Linear regression	Difference in GWG (g/week) for energy-adjusted protein: carbohydrate ratio z-score (in quintiles)	Age, parity, pre-pregnancy BMI, socio-economic indicators, smoking during pregnancy, physical activity, maternal height, fat intake	Normal weight		Q1: reference Q5: -15 (-12, -8)	<0.01[4]
				Overweight		Q1: reference Q5: -26 (-43, -10)	<0.01[4]
				Obese		Q1: reference Q5: 11 (-21, 43)	0.57[4]
	Linear regression	Difference in GWG (g/week) for <12 E% protein vs. ≥12 E% protein	Age, parity, pre-pregnancy BMI, socio-economic indicators, smoking during pregnancy, physical activity, maternal height, carbohydrate intake			17 (8, 26)	<0.01
	Linear regression	Difference in GWG (g/week) for >20 E% protein vs. ≤20 E% protein	Age, parity, pre-pregnancy BMI, socio-economic indicators, smoking during pregnancy, physical activity, maternal height, carbohydrate intake			-15 (-25, -5)	<0.01
	Linear regression	Difference in GWG (g/week) for <12 E% protein vs. >20 E% protein	Age, parity, pre-pregnancy BMI, socio-economic indicators, smoking during pregnancy, physical activity, maternal height, carbohydrate intake			36 (20, 53)	<0.01
Olafsdottir, 2006 (18)	ANOVA	Difference in protein intake (E%) between categories of GWG adequacy		BMI < 25 BMI ≥ 25		NR null	NS NS
Ostachowska-Gasior, 2003 (19)	NR	Difference in protein intake (E%) between adequate and excessive GWG			T1 T2 T3	null null null	NS NS NS
Papoz, 1980 (20)	Pearson correlation	Correlation between protein intake (g) and GWG (kg)			T1 cT1[5] cT1-3[5]	0.19 0.27 -0.21	<0.01 <0.01 <0.01
Picone, 1982 (21)	ANOVA	Difference in protein intake (g) between categories of GWG adequacy				null	NS
Renault, 2015 (57)	Linear regression	Difference in GWG (kg) when substituting carbohydrates (E%) for protein (E%) (in quartiles)	Age, parity, pre-pregnancy BMI, smoking during pregnancy, energy intake, intervention group			Q1: reference Q2: 0.4 (-1.5, 2.2) Q3: 0.9 (-1.0, 2.7) Q4: 0.0 (-1.9, 1.9)	0.86[4]

Supplementary Table 2.1.3 (continued). Associations between protein intake and gestational weight gain (N=29)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
Shin, 2014 (23)	Wald F test	Difference in protein intake (E%) between categories of GWG adequacy (inadequate vs. adequate GWG)	Age, pre-pregnancy BMI, education, family poverty income ratio, ethnicity, smoking during pregnancy, physical activity, trimester of gestation, marital status, daily supplement use			+	0.03
Sloan, 2001 (58)	NR	Difference in GWG (kg) between protein intake (categories; g/day)				null	NS
Stuebe, 2009 (24)	Logistic regression	Protein intake (per 5 E% compared to carbohydrates) and the odds of excessive (vs. not excessive) GWG	Age, pre-pregnancy BMI, ethnicity, smoking, gestational age at delivery, nausea during first trimester of pregnancy, other macronutrients (E%)			1.10 (0.86, 1.42)	NS
Uusitalo, 2009 (25)	Linear regression	Association between protein intake (E%) and GWG (kg)	Age, parity, pre-pregnancy BMI, maternal education, smoking, birth weight, living area, gestational duration at first weight measurement			-0.00 (NR)	<0.01
Low- and middle-income countries							
Longitudinal studies							
Ali, 2002 (26)	Linear regression	Association between protein intake and GWG (kg)	Age, pre-pregnancy weight and height, energy intake, weight-for-height ratio index, weight-height-product index, mid arm circumference			1.92 (1.42,2.42)[3,6]	0.50[6]
Changamire, 2014 (28)	GEE	Difference in GWG (g/month) when substituting 5E% from fat with protein	Parity, pre-pregnancy BMI, maternal education, socio-economic position indicator, energy intake, maternal height, baseline haemoglobin level, marital status, season, trimester of pregnancy, multivitamin regimen assignment , other macronutrients			-72 (-140, -6)	0.03

Supplementary Table 2.1.3 (continued). Associations between protein intake and gestational weight gain (N=29)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
Changamire, 2014 (cont'd)	GEE	Difference in GWG (g/month) when substituting 5E% from carbohydrate with protein	Parity, pre-pregnancy BMI, maternal education, socio-economic position indicator, energy intake, maternal height, baseline haemoglobin level, marital status, season, trimester of pregnancy, multivitamin regimen assignment , other macronutrients			-70 (-124, -15)	0.01
Das, 1976 (29)	ANOVA	Difference in GWG (kg) per protein intake category				NR	NS
Ebrahimi, 2015 (31)	Logistic regression	Protein intake (g) and the odds of inadequate (vs. adequate) GWG	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			<1.00 (0.97, 1.00)	≥0.05
	Logistic regression	Protein intake (g) and the odds of inadequate (vs. excessive) GWG	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			0.99 (0.97, 1.01)	≥0.05
	Logistic regression	Protein intake (g) and the odds of adequate (vs. excessive) GWG	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			1.00 (0.99, 1.01)	≥0.05
	Cumulative Logit Model for Ordinal Responses	Odds ratio between protein intake (g) and adequacy of GWG (inadequate, adequate and excessive GWG)	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			1.00 (0.99, 1.01)	0.64
Hsu, 2013 (33)	Pearson correlation	Correlation between protein intake (g/day) and GWG (kg)			T1 T2 T3	0.21 0.17 0.20	<0.01 <0.01 <0.01
Jaruratanasirikul, 2009 (34)	Logistic regression	Protein intake (g) and the odds of Inadequate (vs. adequate) GWG	Pre-pregnancy BMI, maternal education, energy intake, family income, intake of calcium and iron			0.57 (0.21, 1.54)	0.27
Kardjati, 1990 (35)	Regression	Association between protein intake (g) and GWG (kg)	Parity, pre-pregnancy BMI, energy intake, gender of the child, compliance to the supplementation intake		T2 T3	0.04 (NR) NR	<0.01 NS
	Correlation	Correlation between protein intake (g)and GWG (kg)			T2 T3	0.19 0.08	<0.01 NS
Popa, 2014 (37)	Chi-square test	Difference in protein intake (E%) between women with inadequate GWG and excessive GWG				+	0.02

Supplementary Table 2.1.3 (continued). Associations between protein intake and gestational weight gain (N=29)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
Popa, 2014 (cont'd)	Chi-square test	Difference in protein intake (E%) between women with adequate GWG and excessive GWG				null	NS
Rodrigues, 2008 (38)	Linear regression	Association between protein intake (g/day) and GWG (kg)				-0.01 (-0.04,0.03)[3]	0.65
Saowakontha, 1992 (39)	Linear regression	Explained variance of GWG (R^2) by protein intake (g)		Rural[7]	T1	NR	NS
				Rural	T2	NR	NS
				Rural	T3	NR	NS
				Urban[7]	T1	NR	NS
				Urban	T2	27.8	≤0.05
				Urban	T3	20.6	≤0.05
Wagner, 1975 (42)	Student *t*-test	Difference in GWG (g/week) between protein intake (3 categories)				null	NS
Zulfiqar, 2011 (43)	Regression	Association between protein intake (g/day) and GWG (g/week)				0.81 (NR)	0.44
Case control study							
Costa, 2011 (44)	Spearman correlation	Correlation between protein intake (g) and GWG (kg)				0.16	0.03
	Linear regression	Association between protein intake (g/day) and adequacy of GWG	Age, pre-pregnancy BMI, energy intake, total cholesterol, several micronutrients			0.48 (NR)	0.10

1. Parameter estimate of the used statistical method, + = positive value, - = negative value, null = no association; 2. Only descriptive, no statistical analysis. Based on reported numbers and the assumption of a normal distribution of carbohydrate intake, we have a Welch *t*-test performed; 3. 95% confidence interval calculated using reported mean and standard error; 4. *p* for trend; 5. Change in protein intake as compared with previous dietary assessment (cT1: change during 1st trimester of pregnancy, cT1-3: change during 3rd until 8th month of pregnancy); 6. Reported p-value and mean, however calculated 95% CI (based on reported standard error) is in disagreement with this reported p-value. 7. Living location of the women (rural vs. urban); **Abbreviations**: ANOVA, Analysis of Variance; BMI, body mass index (kg/m^2); CI, confidence interval; E%, energy percent; GEE, generalized estimating equation; GWG, gestational weight gain; NR, not reported; NS, not significant; OC, oral contraceptive; Q, quartiles or quintiles; SD, standard deviation; T: trimester of pregnancy.

Supplementary Table 2.1.4: Associations between source of protein and gestational weight gain (N=2)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Effect estimate (95% CI)	P-value
Animal source					
Longitudinal studies, high-income countries					
Maslova, 2015 (56)	Linear regression	Difference in GWG (g/week) when substituting carbohydrate for animal protein (in quintiles)	Age, parity, pre-pregnancy BMI, socio-economic indicators, smoking during pregnancy, physical activity, maternal height, fat intake, subtypes of protein	Q1: reference Q2: -6 (-13, 0) Q3: -5 (-12, 1) Q4: -9 (-16, -2) Q5: -10 (-17, -3)	<0.01[1]
	Linear regression	Difference in GWG (g/week) when substituting carbohydrate for meat protein (in quintiles)	Age, parity, pre-pregnancy BMI, socio-economic indicators, smoking during pregnancy, physical activity, maternal height, fat intake, subtypes of protein	Q1: reference Q2: -6 (-12, 0) Q3: -11 (-18, -5) Q4: -11 (-17, -4) Q5: -17 (-24, -11)	<0.01[1]
	Linear regression	Difference in GWG (g/week) when substituting carbohydrate for fish protein (in quintiles)	Age, parity, pre-pregnancy BMI, socio-economic indicators, smoking during pregnancy, physical activity, maternal height, fat intake, subtypes of protein	Q1: reference Q2: -7 (-13, -1) Q3: -10 (-17, -4) Q4: -14 (-20, -7) Q5: -19 (-26, -13)	<0.01[1]
	Linear regression	Difference in GWG (g/week) when substituting carbohydrate for dairy protein (in quintiles)	Age, parity, pre-pregnancy BMI, socio-economic indicators, smoking during pregnancy, physical activity, maternal height, fat intake, subtypes of protein	Q1: reference Q2: 4 (-3, 10) Q3: 0 (-6, 7) Q4: -3 (-10, 4) Q5: 0 (-7, 7)	0.53[1]
Renault, 2015 (57)	Linear regression	Difference in GWG (kg) when substituting carbohydrates (E%) for animal protein (E%) (in quartiles)	Age, parity, pre-pregnancy BMI, smoking during pregnancy, energy intake, intervention group	Q1: reference Q2: -0.1 (-1.9, 1.8) Q3: 0.4 (-1.4, 2.2) Q4: 0.0 (-1.9, 1.9)	0.87[1]
Vegetable source					
Longitudinal studies, high-income countries					
Maslova, 2015 (56)	Linear regression	Difference in GWG (g/week) when substituting carbohydrate for vegetable protein (in quintiles)	Age, parity, pre-pregnancy BMI, socio-economic indicators, smoking during pregnancy, physical activity, maternal height, fat intake, subtypes of protein	Q1: reference Q2: 8 (1, 14) Q3: -2 (-8, 5) Q4: 0 (-7, 7) Q5: -10 (-17, -2)	<0.01[1]
Renault, 2015 (57)	Linear regression	Difference in GWG (kg) when substituting carbohydrates (E%) for vegetable protein (E%) (in quartiles)	Age, parity, pre-pregnancy BMI, smoking during pregnancy, energy intake, intervention group	Q1: reference Q2: 0.9 (-0.9, 2.7) Q3: 1.4 (-0.4, 3.3) Q4: -0.2 (-2.1, 1.7)	0.99[1]

[1.] P for trend. **Abbreviations**: BMI, body mass index; CI, confidence interval; E%, energy percentage; Q, quartile or quintile.

Supplementary Table 2.1.5: Associations between total fat intake and gestational weight gain (N=21)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
High-income countries							
Longitudinal studies							
Althuizen, 2009 (5)	Linear regression	Association between fat intake (E%) and GWG (kg)	Gestational age at delivery			-0.01 (NR)	0.9
	Logistic regression	Fat intake (E%) and the odds of excessive GWG (vs. inadequate and adequate GWG)	Gestational age at delivery			0.98 (NR)	0.6
Anderson, 1986 (7)	None[2]	Difference in fat intake (E%) between categories of GWG adequacy				null	>0.2
Blumfield, 2015 (10)	Kruskal-Wallis test	Difference in fat intake (E%) between categories of GWG adequacy				null	≥0.05
Gaillard, 2013 (12)	Logistic regression	Fat intake per SD (1 SD = 5.6 E%) and the odds of excessive GWG	Age, parity, pre-pregnancy BMI, maternal education, ethnicity, smoking during pregnancy, energy intake, folic acid supplementation, alcohol consumption during pregnancy			4.00 (1.62, 9.83)	<0.01
Maple-Brown, 2013 (16)	Pearson correlation	Correlation between total fat intake and GWG (kg)				NR	NS
Olafsdottir, 2006 (18)	ANOVA	Difference in fat intake (E%) between categories of GWG adequacy		BMI < 25 BMI ≥ 25		NR +	NS <0.01
Ostachowska-Gasior, 2003 (19)	NR	Difference in fat intake (E%) between adequate and excessive GWG			T1 T2 T3	null null null	NS NS NS
Papoz, 1980 (20)	Pearson correlation	Correlation between fat intake (g) and GWG (kg)			T1 cT1[3] cT1-3[3]	0.28 0.11 -0.28	<0.01 NS NS
Picone, 1982 (21)	ANOVA	Difference in fat intake (g) between categories of GWG adequacy				null	NS
Shin, 2014 (23)	Wald F test	Difference in fat intake (E%) between categories of GWG adequacy	Age, pre-pregnancy BMI, education, family poverty income ratio, ethnicity, smoking during pregnancy, physical activity, trimester of gestation, marital status, daily supplement use			null	0.45
Stuebe, 2009 (24)	Student *t*-test	Difference in fat intake (E%) between categories of GWG adequacy				null	0.41

Supplementary Table 2.1.5 (continued) Associations between total fat intake and gestational weight gain (N=21)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
Low- and middle-income countries							
Longitudinal studies							
Changamire, 2014 (28)	GEE	Difference in GWG (g/month) when substituting 5E% from protein with fat	Parity, pre-pregnancy BMI, maternal education, socio-economic position indicator, energy intake maternal height, baseline haemoglobin level, marital status, season, trimester of pregnancy, multivitamin regimen assignment , other macronutrients			72 (6, 140)	0.03
	GEE	Difference in GWG (g/month) when substituting 5E% from carbohydrate with fat	Parity, pre-pregnancy BMI, maternal education, socio-economic position indicator, energy intake maternal height, baseline haemoglobin level, marital status, season, trimester of pregnancy, multivitamin regimen assignment , other macronutrients			1 (-20,21)	0.96
Ebrahimi, 2015 (31)	Logistic regression	Fat intake (g) and the odds of inadequate (vs. adequate) GWG	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			1.00 (0.99, 1.02)	≥0.05
	Logistic regression	Fat intake (g) and the odds of inadequate (vs. excessive) GWG	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			1.00 (0.98, 1.02)	≥0.05
	Logistic regression	Fat intake (g) and the odds of adequate (vs. excessive) GWG	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			<1.00 (0.98, 1.01)	≥0.05
	Cumulative Logit Model for Ordinal Responses	Odds ratio between fat intake (g) and adequacy of GWG (inadequate, adequate and excessive GWG)	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			1.00 (0.99, 1.01)	0.74
Hsu, 2013 (33)	Pearson correlation	Correlation between total fat intake (g/day) and GWG (kg)			T1 T2 T3	0.19 0.14 0.20	<0.01 <0.01 <0.01
Jaruratanasirikul, 2009 (34)	Logistic regression	Fat intake (g) and the odds of inadequate (vs. adequate) GWG	Pre-pregnancy BMI, maternal education, energy intake, family income, intake of calcium and iron			0.80 (0.52, 3.27)	0.44
Kardjati, 1990 (35)	Correlation	Correlation between fat intake (g) and GWG (kg)			T2 T3	0.14 0.10	NS NS

Supplementary Table 2.1.5 (continued) Associations between total fat intake and gestational weight gain (N=21)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
Popa, 2014 (37)	Chi-square test	Difference in fat intake (E%) between inadequate, adequate and excessive GWG				null	NS
Rodrigues, 2008 (38)	Linear regression	Association between fat intake (g/day) and GWG (kg)				-0.01 (-0.05, 0.03)[4]	0.64
Saowakontha, 1992 (39)	Linear regression	Explained variance of GWG (R^2) by fat intake (g)		Rural[5]	T1	NR	NS
				Rural	T2	NR	NS
				Rural	T3	NR	NS
				Urban[5]	T1	NR	NS
				Urban	T2	NR	NS
				Urban	T3	20.7	≤0.05
Zulfiqar, 2011 (43)	Regression	Association between fat intake (g/day) and GWG (g/week)				2.06 (NR)	0.04
Case control study							
Costa, 2011 (44)	Spearman correlation	Correlation between fat intake (g) and total GWG				0.11	0.11

[1.] Parameter estimate of the used statistical method, + = positive value, - = negative value, null = no association; [2.] Only descriptive, no statistical analysis. Based on reported numbers and the assumption of a normal distribution of carbohydrate intake, we have a Welch *t*-test performed; [3.] Change in fat intake as compared with previous dietary assessment (cT1: change during 1[st] trimester of pregnancy, cT1-3: change during 3[rd] until 8[th] month of pregnancy); [4.] 95% confidence interval calculated using reported mean and standard error; [5.] Living location of the women (rural vs. urban); **Abbreviations:** ANOVA, Analysis of Variance; BMI, body mass index (kg/m^2); CI, confidence interval; E%, energy percentage; GEE, generalized estimating equation; GWG, gestational weight gain; NR, not reported; NS, not significant; OC, oral contraceptive; SD, standard deviation; T: trimester of pregnancy.

Supplementary Table 2.1.6: Associations between types of fat intake and gestational weight gain (N=9)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Effect estimate[1] (95% CI)	P-value
Saturated fat intake						
Longitudinal studies, high-income countries						
Althuizen, 2009 (5)	Linear regression	Association between saturated fat intake (E%) and GWG (kg)	Gestational age at delivery		0.02 (NR)	0.9
	Logistic regression	Saturated fat intake (E%) and the odds of excessive GWG (vs. inadequate and adequate GWG)	Gestational age at delivery		0.98 (NR)	0.7
Blumfield, 2015 (10)	Kruskal-Wallis test	Difference in saturated fat intake (E%) between categories of GWG adequacy			null	≥0.05
Maple-Brown, 2013 (16)	Pearson correlation	Correlation between saturated fat intake and GWG (kg)			NR	NS
Renault, 2015 (57)	Linear regression	Difference in GWG (kg) when substituting monounsaturated or polyunsaturated fat (E%) for saturated fat (E%) (in quartiles)	Age, parity, pre-pregnancy BMI, smoking during pregnancy, energy intake, intervention group		Q1: reference Q2: -0.5 (-2.3, 1.3) Q3: -0.2 (-2.0, 1.5) Q4: -0.3 (-2.2, 1.6)	0.83[2]
Shin, 2014 (23)	Logistic regression	<10E% of saturated fat intake (vs. ≥10E%) and odds of inadequate GWG (vs. adequate GWG)	Age, pre-pregnancy BMI, education, family poverty income ratio, ethnicity, smoking during pregnancy, physical activity, trimester of gestation, marital status, daily supplement use		1.3 (0.2, 7.0)	0.77
	Logistic regression	<10E% of saturated fat intake (vs. ≥10E%) and odds of excessive GWG (vs. adequate GWG)	Age, pre-pregnancy BMI, education, family poverty income ratio, ethnicity, smoking during pregnancy, physical activity, trimester of gestation, marital status, daily supplement use		0.8 (0.2, 3.5)	0.76
Stuebe, 2009 (24)	Logistic regression	Saturated fat intake (per 5 E%, compared to carbohydrates) and the odds of excessive GWG	Age, pre-pregnancy BMI, ethnicity, smoking during pregnancy, gestational age at delivery, nausea during first trimester of pregnancy, other macronutrients (E%)		1.33 (0.87, 2.02)	NS
Uusitalo, 2009 (25)	Linear regression	Association between saturated fat intake (E%) and GWG (kg)	Age, parity, pre-pregnancy BMI, maternal education, smoking during pregnancy, birth weight, living area, gestational age at first weight measurement		0.00 (NR)	0.04

Supplementary Table 2.1.6 (continued). Associations between types of fat intake and gestational weight gain (N=9)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Effect estimate[1] (95% CI)	P-value
Longitudinal study, low- and middle-income countries						
Martins, 2011 (59)	Linear regression	Association between saturated fat intake (g, in tertiles) and weight retention (kg)	Age, pre-pregnancy BMI, maternal education, smoking during pregnancy, height, per capita family income	Tertile 1 Tertile 2 Tertile 3	Reference 2.63 (NR) 3.31 (NR)	 0.02 <0.01 <0.01[2]
Case control study, low- and middle-income countries						
Costa, 2011 (44)	Spearman correlation	Correlation between saturated fat intake (g) and total GWG			0.14	0.06
Unsaturated fat intake						
Longitudinal studies, high-income countries						
Blumfield, 2015 (10)	Kruskal-Wallis test	Difference in monounsaturated fat intake (E%) between categories of GWG adequacy			null	≥0.05
	Kruskal-Wallis test	Difference in polyunsaturated fat intake (E%) between categories of GWG adequacy			null	≥0.05
Maple-Brown, 2013 (16)	Pearson correlation	Correlation between monounsaturated fat intake and GWG (kg)			NR	NS
	Pearson correlation	Correlation between polyunsaturated fat intake and GWG (kg)			NR	NS
Renault, 2015 (57)	Linear regression	Difference in GWG (kg) when substituting monounsaturated or saturated fat (E%) for poly-unsaturated fat (E%) (in quartiles)	Age, parity, pre-pregnancy BMI, smoking during pregnancy, energy intake, intervention group		Q1: reference Q2: -1.0 (-2.8, 0.8) Q3: 1.3 (-0.5, 3.1) Q4: -0.4 (-2.2, 1.4)	0.75[2]
Stuebe, 2009 (24)	Logistic regression	Monounsaturated fat intake (per 5 E%, compared to carbohydrates) and the odds of excessive GWG	Age, pre-pregnancy BMI, ethnicity, smoking during pregnancy, gestational age at delivery, nausea during first trimester of pregnancy, other macronutrients (E%)		0.63 (0.40, 0.99)	NR
	Logistic regression	Polyunsaturated fat intake (per 5 E%, compared to carbohydrates) and the odds of excessive GWG	Age, pre-pregnancy BMI, ethnicity, smoking during pregnancy, gestational age at delivery, nausea during first trimester of pregnancy, other macronutrients (E%)		1.32 (0.80, 2.18)	NS

Supplementary Table 2.1.6 (continued). Associations between types of fat intake and gestational weight gain (N=9)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Effect estimate[1] (95% CI)	P-value
Case control study, low- and middle-income country						
Costa, 2011 (44)	Spearman correlation	Correlation between unsaturated fat intake (g) and total GWG			0.09	0.19
Trans-fat intake						
Longitudinal studies, high-income country						
Stuebe, 2009 (24)	Logistic regression	Trans-fat intake (per 2E%, compared with carbohydrates) and the odds of excessive GWG	Age, pre-pregnancy BMI, ethnicity, smoking during pregnancy, gestational age at delivery, nausea during first trimester of pregnancy, other macronutrients (E%)		1.27 (0.39, 4.13)	NS

[1.] Parameter estimate of the used statistical method, + = positive value, - = negative value, null = no association; [2.] *p* for trend. **Abbreviations:** BMI, body mass index (kg/m^2); CI, confidence interval; E%, energy percentage; GWG, gestational weight gain; NR, not reported; NS, not significant; Q, quartile.

Supplementary Table 2.1.7: Associations between source of fat and gestational weight gain (N=1)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Effect estimate (95% CI)	P-value
Animal source					
Longitudinal study, high-income country					
Lagiou, 2004 (14)	Linear regression	Association between fat intake from animal sources (per SD increase) and GWG (kg)	Age, parity, pre-pregnancy BMI, maternal education, smoking, energy intake, gestational age at delivery, gender of the baby, maternal height, pre-pregnancy OC use	2.56 (1.64, 3.48)[1]	<0.01[2]
Vegetable source					
Longitudinal study, high-income country					
Lagiou, 2004 (14)	Linear regression	Association between fat intake from vegetable sources (per SD increase) and GWG (kg)	Age, parity, pre-pregnancy BMI, maternal education, smoking, energy intake, gestational age at delivery, gender of the baby, maternal height, pre-pregnancy OC use	0.77 (-0.17, 1.71)[1]	0.11[2]

[1.] 95% confidence interval calculated using reported mean and standard error; [2.] *p* for trend. **Abbreviations**: BMI, body mass index (kg/m^2); CI, confidence interval; GWG, gestational weight gain; OC, oral contraceptive; SD, standard deviation.

Supplemental Table 2.1.8: Associations between carbohydrate intake and gestational weight gain (N=18)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
High-income countries							
Longitudinal studies							
Anderson, 1986 (7)	None[2]	Difference in carbohydrate intake (E%) between categories of GWG				null	≥0.05
Blumfield, 2015 (10)	Kruskal-Wallis test	Difference in carbohydrate intake (E%) between categories of GWG adequacy				null	≥0.05
Gaillard, 2013 (12)	Logistic regression	Carbohydrate intake per SD (1 SD = 6.5 E%) and the odds of excessive GWG	Age, parity, pre-pregnancy BMI, maternal education, ethnicity, smoking during pregnancy, energy intake, folic acid supplementation, alcohol consumption during pregnancy			4.49 (1.61, 12.46)	<0.01
Lagiou, 2004 (14)	Linear regression	Association between carbohydrate intake (per SD increase) and GWG (kg)	Age, parity, pre-pregnancy BMI, maternal education, smoking, energy intake, gestational age at delivery, gender of the baby, height, pre-pregnancy OC use			-5.22 (-6.79, -3.65)[3]	<0.01[4]
Maple-Brown, 2013 (16)	Pearson correlation	Correlation between carbohydrate intake and GWG (kg)				NR	NS
Olafsdottir, 2006 (18)	ANOVA	Difference in carbohydrate intake (E%) between categories of GWG adequacy		BMI <25 BMI ≥ 25		NR -	NS <0.01
Ostachowska-Gasior, 2003 (19)	NR	Difference in carbohydrate intake (E%) between adequate and excessive GWG			T1 T2 T3	null null null	NS NS NS
Papoz, 1980 (20)	Pearson correlation	Correlation between carbohydrate intake (g) and GWG (kg)			T1 cT1[5] cT1-3[5]	0.24 0.17 -0.15	<0.01 <0.05 <0.01
Picone, 1982 (21)	ANOVA	Difference in carbohydrate intake (g) between categories of GWG adequacy				null	NS
Shin, 2014 (23)	Wald F test	Difference in carbohydrate intake (E%) between categories of GWG adequacy	Age, pre-pregnancy BMI, education, family poverty income ratio, ethnicity, smoking during pregnancy, physical activity, trimester of gestation, marital status, daily supplement use			null	0.90

Supplemental Table 2.1.8 (continued) Associations between carbohydrate intake and gestational weight gain (N=18)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
Low- and middle-income countries							
Longitudinal studies							
Changamire, 2014 (28)	GEE	Difference in GWG (g/month) when substituting 5E% from fat with carbohydrate	Parity, pre-pregnancy BMI, maternal education, socio-economic position indicator, energy intake, maternal height, baseline haemoglobin level, marital status, season, trimester of pregnancy, multivitamin regimen assignment , other macronutrients			-1 (-21, 20)	0.96
	GEE	Difference in GWG (g/month) when substituting 5E% from protein with carbohydrate	Parity, pre-pregnancy BMI, maternal education, socio-economic position indicator, energy intake, maternal height, baseline haemoglobin level, marital status, season, trimester of pregnancy, multivitamin regimen assignment , other macronutrients			70 (15, 124)	0.01
Ebrahimi, 2015 (31)	Logistic regression	Carbohydrate intake (g) and the odds of inadequate (vs. adequate) GWG	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			1.00 (<1.00, 1.01)	≥0.05
	Logistic regression	Carbohydrate intake (g) and the odds of inadequate (vs. excessive) GWG	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			1.00 (<1.00, 1.01)	≥0.05
	Logistic regression	Carbohydrate intake (g) and the odds of adequate (vs. excessive) GWG	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			<1.00 (0.99, 1.00)	≥0.05
	Cumulative Logit Model for Ordinal Responses	Odds ratio between carbohydrate intake (g) and adequacy of GWG (inadequate, adequate and excessive GWG)	Age, pre-pregnancy BMI, maternal education, household income, physical activity, gravidity			1.00 (<1.00, 1.01)	0.32
Jaruratanasirikul, 2009 (34)	Logistic regression	Carbohydrate intake (g) and the odds of inadequate (vs. adequate) GWG	Pre-pregnancy BMI, maternal education, energy intake, family income, intake of calcium and iron			0.67 (0.25, 1.72)	0.39
Popa, 2014 (37)	Chi-square test	Difference in carbohydrate intake (E%) between inadequate, adequate and excessive GWG				null	NS

Supplemental Table 2.1.8 (continued) Associations between carbohydrate intake and gestational weight gain (N=18)

First author, year	Statistical analysis	Measure of association	Covariate adjustments	Subgroups	Trimester	Effect estimate[1] (95% CI)	P-value
Rodrigues, 2008 (38)	Linear regression	Association between carbohydrate intake (g/day) and GWG (kg)				-0.00 (-0.01, 0.01)	0.98
Saowakontha, 1992 (39)	Linear regression	Explained variance of GWG (R^2) by carbohydrate intake (g)		Rural[6]	T1	NR	NS
				Rural	T2	NR	NS
				Rural	T3	NR	NS
				Urban[6]	T1	18.8	≤0.05
				Urban	T2	25.8	≤0.05
				Urban	T3	19.0	≤0.05
Zulfiqar, 2011 (43)	Regression	Association between carbohydrate intake (g/day) and GWG (g/week)				0.52 (NR)	0.01
Case control study							
Costa, 2011 (44)	Spearman correlation	Correlation between carbohydrate intake (g) and GWG (kg)				0.13	0.07

[1.] Parameter estimate of the used statistical method, + = positive value, - = negative value, null = no association; [2.] Only descriptive, no statistical analysis. Based on reported numbers and the assumption of a normal distribution of carbohydrate intake, we have a Welch *t*-test performed; [3.] 95% confidence interval calculated using reported mean and standard error; [4.] *p* for trend; [5.] Change of carbohydrate intake as compared with previous dietary assessment (cT1: change during 1st trimester of pregnancy, cT1-3: change during 3rd until 8th month of pregnancy); [6.] Living location of the women (rural vs. urban); **Abbreviations:** ANOVA, Analysis of Variance; BMI, body mass index (kg/m^2); CI, confidence interval; E%, energy percent; GEE, generalized estimating equation; GWG, gestational weight gain; NR, not reported; NS, not significant; OC, oral contraceptive; SD, standard deviation; T, trimester of pregnancy.

References: supplementary material chapter 2.1

1. Carter P, Gray LJ, Troughton J, Khunti K, Davies MJ. Fruit and vegetable intake and incidence of type 2 diabetes mellitus: systematic review and meta-analysis. BMJ 2010;341:c4229.
2. National Collaborating Centre for Methods and Tools. Quality Assessment Tool for Quantitative Studies. Hamilton, ON: McMaster University, 2008.
3. Bompiani GD, Botta RM. Treatment of non insulin-dependent diabetic women during pregnancy. Acta Endocrinol Suppl (Copenh) 1986;277:56-9.
4. Rae A, Bond D, Evans S, North F, Roberman B, Walters B. A randomised controlled trial of dietary energy restriction in the management of obese women with gestational diabetes. Aust N Z J Obstet Gynaecol 2000;40:416-22.
5. Althuizen E, Van Poppel MNM, Seidell JC, Van Mechelen W. Correlates of absolute and excessive weight gain during pregnancy. J Women's Health 2009;18:1559-1566.
6. Ancri G, Morse EH, Clarke RP. Comparison of the nutritional status of pregnant adolescents with adult pregnant women. III. Maternal protein and calorie intake and weight gain in relation to size of infant at birth. Am J Clin Nutr 1977;30:568-572.
7. Anderson AS, Lean ME. Dietary intake in pregnancy. A comparison between 49 Cambridgeshire women and current recommended intake. Hum Nutr Appl Nutr 1986;40:40-48.
8. Bellati U, Pompa P, Liberati M. Evaluation of the influence of a mediterranean diet and of pregravidic body mass on the intra-uterine weight increase. Minerva Ginecol 1995;47:259-262.
9. Bergmann MM, Flagg EW, Miracle-McMahill HL, Boeing H. Energy intake and net weight gain in pregnant women according to body mass index (BMI) status. Int J Obes 1997;21:1010-1017.
10. Blumfield ML, Schreurs M, Rollo ME, MacDonald-Wicks LK, Kokavec A, Collins CE. The association between portion size, nutrient intake and gestational weight gain: a secondary analysis in the WATCH study 2006/7. J Hum Nutr Diet 2015.
11. Chasan-Taber L, Schmidt MD, Pekow P, Sternfeld B, Solomon CG, Markenson G. Predictors of excessive and inadequate gestational weight gain in Hispanic women. Obesity (Silver Spring) 2008;16:1657-66.
12. Gaillard R, Durmus B, Hofman A, Mackenbach JP, Steegers EA, Jaddoe VW. Risk factors and outcomes of maternal obesity and excessive weight gain during pregnancy. Obesity (Silver Spring) 2013;21:1046-55.
13. Heery E, Kelleher CC, Wall PG, McAuliffe FM. Prediction of gestational weight gain - a biopsychosocial model. Public Health Nutr 2015;18:1488-98.
14. Lagiou P, Tamimi RM, Mucci LA, Adami HO, Hsieh CC, Trichopoulos D. Diet during pregnancy in relation to maternal weight gain and birth size. Eur J Clin Nutr 2004;58:231-7.
15. Langhoff-Roos J, Lindmark G, Kylberg E, Gebre-Medhin M. Energy intake and physical activity during pregnancy in relation to maternal fat accretion and infant birthweight. Br J Obstet Gynaecol 1987;94:1178-1185.
16. Maple-Brown LJ, Roman NM, Thomas A, Presley LH, Catalano PM. Perinatal factors relating to changes in maternal body fat in late gestation. J Perinatol 2013;33:934-8.
17. Montpetit AE, Plourde H, Cohen TR, Koski KG. Modeling the impact of prepregnancy BMI, physical activity, and energy intake on gestational weight gain, infant birth weight, and postpartum weight retention. J Phys Act Health 2012;9:1020-1029.
18. Olafsdottir AS, Skuladottir GV, Thorsdottir I, Hauksson A, Steingrimsdottir L. Maternal diet in early and late pregnancy in relation to weight gain. Int J Obes (Lond) 2006;30:492-9.
19. Ostachowska-Gasior A, Janik A. [Dietary assessment of pregnant women with different anthropometric measures] Sposób żywienia kobiet w ciąży a wybrane wskaźniki antropometryczne. Przegl Lek 2003;60 Suppl 6:4-7.
20. Papoz L, Eschwege E, Cubeua J, Pequignot G, Barrat J, Le Lorier G. [Dietary behavior during pregnancy] Comportement alimentaire au cours de la grossesse. Rev Epidemiol Sante Publique 1980;28:155-67.
21. Picone TA, Allen LH, Schramm MM, Olsen PN. Pregnancy outcome in North American women. I. Effects of diet, cigarette smoking, and psychological stress on maternal weight gain. Am J Clin Nutr 1982;36:1205-13.
22. Scholl TO, Hediger ML, Schall JI, Fischer RL, Khoo CS. Low zinc intake during pregnancy: Its association with preterm and very preterm delivery. Am J Epidemiol 1993;137:1115-1124.
23. Shin D, Bianchi L, Chung H, Weatherspoon L, Song WO. Is gestational weight gain associated with diet quality during pregnancy? Matern Child Health J 2014;18:1433-43.
24. Stuebe AM, Oken E, Gillman MW. Associations of diet and physical activity during pregnancy with risk for excessive gestational weight gain. Am J Obstet Gynecol 2009;201:58 e1-8.
25. Uusitalo U, Arkkola T, Ovaskainen ML, Kronberg-Kippila C, Kenward MG, Veijola R, Simell O, Knip M, Virtanen SM. Unhealthy dietary patterns are associated with weight gain during pregnancy among Finnish women. Public Health Nutr 2009;12:2392-9.
26. Ali I, Rehana K, Nisara B. Pregnancy weight gain in relation to various sociomedical factors and perinatal outcome. JK Pract 2002;9:106-109.
27. Castro Pda S, Castro MB, Kac G. [Adherence to dietary recommendations by the Institute of Medicine and the effect on body weight during pregnancy] Aderência às recomendações dietéticas do Institute of Medicine (Estados Unidos) e o seu efeito no peso durante a gestação. Cad Saude Publica 2013;29:1311-21.
28. Changamire FT, Mwiru RS, Msamanga GI, Spiegelman D, Urassa W, Hertzmark E, Fawzi WW, Peterson KE. Macronutrient and sociodemographic determinants of gestational weight gain among HIV-negative women in Tanzania. Food Nutr Bull 2014;35:43-50.
29. Das KB. Weight gain in pregnancy among underprivileged Bengali Hindu women. Indian J Public Health 1976;20:39-47.
30. Drehmer M, Camey S, Schmidt MI, Olinto MTA, Giacomello A, Buss C, Melere C, Hoffmann J, Manzolli P, Soares RM, et al. Socioeconomic, demographic and nutritional factors associated with maternal weight gain in general practices in Southern Brazil. Cad Saude Publica 2010;26:1024-1034.
31. Ebrahimi F, Shariff ZM, Tabatabaei SZ, Fathollahi MS, Mun CY, Nazari M. Relationship between sociodemographics, dietary intake, and physical activity with gestational weight gain among pregnant women in Rafsanjan City, Iran. J Health Popul Nutr 2015;33:168-76.
32. Ho LF, Benzie IF, Lao TT. Relationship between caloric intake and pregnancy outcome in diet-treated gestational diabetes mellitus. Nurs Health Sci 2005;7:15-20.

33. Hsu WY, Wu CH, Hsieh CT, Lo HC, Lin JS, Kao MD. Low body weight gain, low white blood cell count and high serum ferritin as markers of poor nutrition and increased risk for preterm delivery. Asia Pac J Clin Nutr 2013;22:90-9.
34. Jaruratanasirikul S, Sangsupawanich P, Koranantakul O, Chanvitan P, Sriplung H, Patanasin T. Influence of maternal nutrient intake and weight gain on neonatal birth weight: a prospective cohort study in southern Thailand. J Matern Fetal Neonatal Med 2009;22:1045-50.
35. Kardjati S, Kusin JA, Schofield WM, de With C. Energy supplementation in the last trimester of pregnancy in East Java, Indonesia: Effect on maternal anthropometry1-4. Am J Clin Nutr 1990;52:987-994.
36. Lechtig A, Martorell R, Delgado H. Food supplementation during pregnancy, maternal anthropometry and birth weight in a Guatemalan rural population. J Trop Pediatr Environ Child Health 1978;24:217-222.
37. Popa AD, Popescu RM, Botnariu GE. Adequate weight gain in pregnancy: an analysis of its determinants in a cross-sectional study. Srp Arh Celok Lek 2014;142:695-702.
38. Rodrigues PL, Lacerda EM, Schlussel MM, Spyrides MH, Kac G. Determinants of weight gain in pregnant women attending a public prenatal care facility in Rio de Janeiro, Brazil: a prospective study, 2005-2007. Cad Saude Publica 2008;24 Suppl 2:S272-84.
39. Saowakontha S, Pongpaew P, Schelp FP, Rojsathaporn K, Intarakha C, Pipitgool V, Mahaweerawat U, Lumbiganon P, Sriboonlue P, Sanchaisuriya P, et al. Pregnancy, nutrition and parasitic infection of rural and urban women in Northeast Thailand. Nutr Res 1992;12:929-942.
40. Siega-Riz AM, Adair LS. Biological determinants of pregnancy weight gain in a Filipino population. Am J Clin Nutr 1993;57:365-372.
41. Smith C. The effect of maternal nutritional variables on birthweight outcomes of infants born to Sherpa women at low and high altitudes in Nepal. American Journal of Human Biology 1997;9:751-763.
42. Wagner M, Mora JO, De Navarro L. [Nutrition during phases of development in early infancy and its influence on physical and mental growth. I. Influence of food supplements during pregnancy on maternal weight gain and infant birth weight] Die Ernährung während frühkindlicher Entwicklungsabschnitte und ihr Eindfluss auf die körperliche und geistige Untwicklung von kindern. I. Der Einfluss von Nahrungszulagen während der Schwangerschaft auf den Gewichtszuwachs der Mütter und das Geburtsgewicht der Kinder. Ernahrungs Umschau 1975;22:323-325.
43. Zulfiqar T, Rizvi F, Jalali S, Shami SA, Tasnim N, Jahan S. Effects of Maternal Macronutrient intake in 3rd trimester of normal pregnancy on the maternal weight gain and neonatal birth weight of full term neonates. Rawal Med J 2011;36:137-142.
44. Costa BMF, Paulinelli RR, Fornes NS. [Nutritional factors may affect weight gain during pregnancy?] Fatores nutricionais podem interferir no ganho ponderal na gestação? Rev Bras Med 2011;68:329-335.
45. Rasmussen KM, Yaktine AL, Editors Committee to Reexamine IOM Pregnancy Weight Guidelines, Institute of Medicine, National Research Council. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington (DC): National Academies Press (US), 2009.
46. Viegas OA, Scott PH, Cole TJ, Mansfield HN, Wharton P, Wharton BA. Dietary protein energy supplementation of pregnant Asian mothers at Sorrento, Birmingham. I: Unselective during second and third trimesters. Br Med J (Clin Res Ed) 1982;285:589-92.
47. Viegas OA, Scott PH, Cole TJ, Eaton P, Needham PG, Wharton BA. Dietary protein energy supplementation of pregnant Asian mothers at Sorrento, Birmingham. II: Selective during third trimester only. Br Med J (Clin Res Ed) 1982;285:592-5.
48. Adair LS, Pollitt E, Mueller WH. The Bacon Chow study: effect of nutritional supplementation on maternal weight and skinfold thicknesses during pregnancy and lactation. Br J Nutr 1984;51:357-369.
49. Begum N, Hussain T, Afridi B, Hamid A. Effect of supplementary feeding of pregnant women on birth weight of the new born. Plant Foods Hum Nutr 1991;41:329-336.
50. Hussain T, Tontisirin K. Effect of a formulation of supplementary food for pregnant women on birth weight of newborns. J Nutr Sci Vitaminol 1988;34:151-157.
51. Kaseb F, Kimiagar M, Ghafarpoor M, Valaii N. Effect of traditional food supplementation during pregnancy on maternal weight gain and birthweight. Int J Vitam Nutr Res 2002;72:389-393.
52. Nahar S, Mascie-Taylor CGN, Begum HA. Impact of targeted food supplementation on pregnancy weight gain and birth weight in rural Bangladesh: An assessment of the Bangladesh Integrated Nutrition Program (BINP). Public Health Nutr 2009;12:1205-1212.
53. Ortolano SE, Mahmud Z, Kabir AFMI, Levinson FJ. Effect of targeted food supplementation and services in the Bangladesh integrated nutrition project on women and their pregnancy outcomes. J Health Popul Nutr 2003;21:83-89.
54. Qureshi S, Rao NP, Madhavi V. Effect of maternal nutrition supplementation on the birth weight of the newborn. Indian Pediatr 1973;10:541-544.
55. Tontisirin K, Booranasubkajorn U, Hongsumarn A, Thewtong D. Formulation and evaluation of supplementary foods for Thai pregnant women. Am J Clin Nutr 1986;43:931-939.
56. Maslova E, Halldorsson TI, Astrup A, Olsen SF. Dietary protein-to-carbohydrate ratio and added sugar as determinants of excessive gestational weight gain: a prospective cohort study. BMJ Open 2015;5:e005839.
57. Renault KM, Carlsen EM, Norgaard K, Nilas L, Pryds O, Secher NJ, Olsen SF, Halldorsson TI. Intake of Sweets, Snacks and Soft Drinks Predicts Weight Gain in Obese Pregnant Women: Detailed Analysis of the Results of a Randomised Controlled Trial. PLoS One 2015;10:e0133041.
58. Sloan NL, Lederman SA, Leighton J, Himes JH, Rush D. The effect of prenatal dietary protein intake on birth weight. Nutrition Research 2001;21:129-139.
59. Martins APB, Benicio MHD. Influence of dietary intake during gestation on postpartum weight retention. Rev Saude Publica 2011;45:870-877.

Chapter 2.2

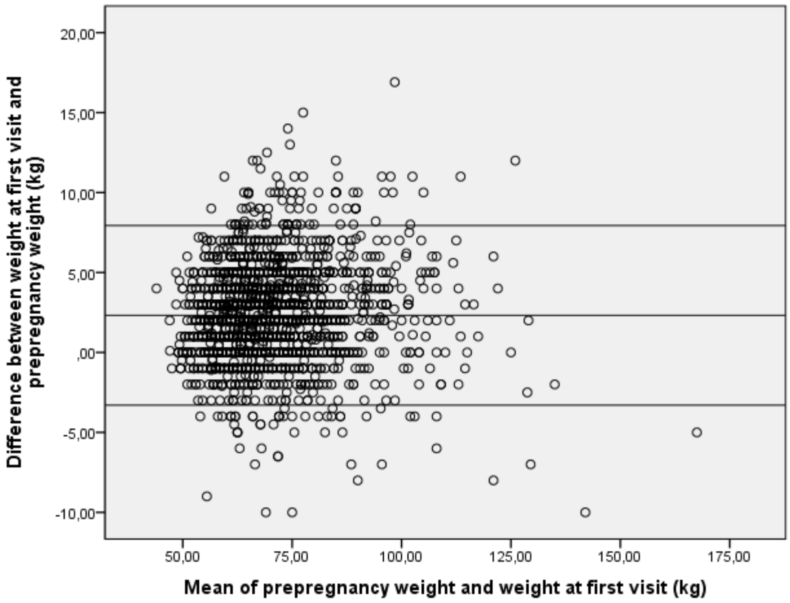
A Priori and *a posteriori* dietary patterns during pregnancy and gestational weight gain: The Generation R Study

Myrte J. Tielemans, Nicole S. Erler, Elisabeth T.M. Leermakers, Marion van den Broek, Vincent W.V. Jaddoe, Eric A.P. Steegers, Jessica C. Kiefte-de Jong, Oscar H. Franco

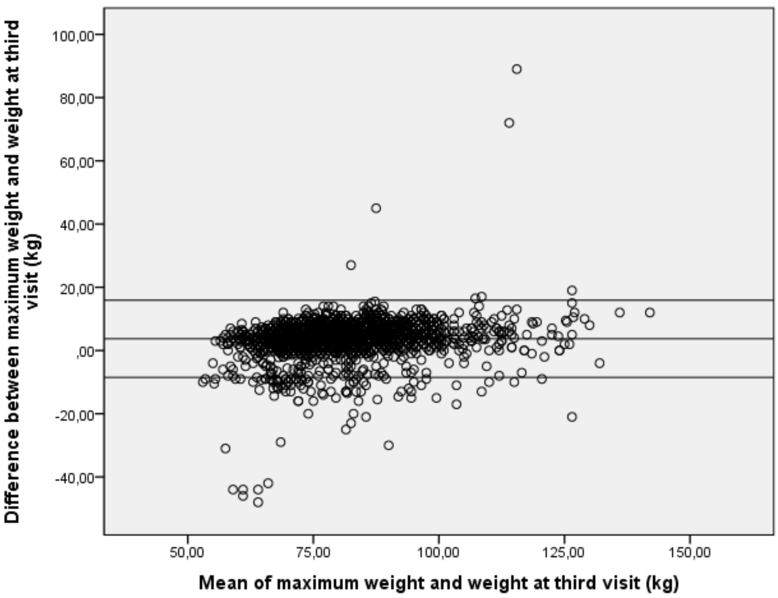
Nutrients. 2015 Nov; 7, 9383-9399

Supplementary Figure 2.2.1. Bland Altman plots for self-reported pre-pregnancy weight and maximum weight in pregnancy.

A. Bland-Altman plot for pre-pregnancy weight and weight during the first visit (n = 2425)



B. Bland-Altman plot for maximum weight in pregnancy and weight during the third visit (n = 2177)



Supplementary Table 2.2.1. Food groups and its food components[1]

Food Group	**Food Components**
Potatoes and other tubers	Potatoes (cooked or fried) and French fries
Vegetables	Endive, purslane, turnip tops, lettuce, chard, spinach, chicory, eggplant, avocado, cucumber, paprika, corn, pickle, tomatoes, beans, snow peas, courgette, tomato sauce, carrots, beetroots, cabbages, mushrooms, green peas, onions, leek, garlic, bean sprouts, celery, atjar tjampoer and crudités
Fruits	Apple, strawberries, apricot, pineapple, red berries, banana, blackberries, lemon, grapes, raspberries, cherries, grapefruit, tangerine, peach, pear, prunes, orange, applesauce, kiwi, mango, rhubarb, melon, nectarine, canned fruit and dried fruit
Dairy products—high fat	Whole milk, full-fat yoghurt drink, full-fat yogurt, cheese 40–60+, cream cheese, full-fat quark, pudding, sour cream, whipped cream and crème fraiche
Dairy products—low fat	Skimmed and semi-skimmed milk, skimmed and semi-skimmed yoghurt drink, skimmed and semi-skimmed yogurt, cheese 20–30+ and low-fat quark
Cereals—high fibre	Brown rice, whole wheat pasta, whole wheat/brown/rye bread, muesli, seitan, oatmeal, wheat germ, and bran
Cereals—low fibre	White rice, couscous, bulgur, white bread, rusk, croissants, corn flakes, crackers, rice cake, toast, pancakes, raisin bread, bami and white pasta
Meat and meat products	Red meat, poultry, organ meat and meat products
Fish and shellfish	Fish, fish products and shellfish
Eggs and egg products	Egg (cooked or fried)
Vegetable oils	Olive oil, nut oil, salad oil, sesame oil, sunflower oil, soybean oil and peanut oil
Margarine and butter	Margarine (solid and liquid) and butter
Sugar and confectionary and cakes	Chocolate, candy, chocolate sprinkles, cake, pastry and biscuits
Snacks	Peanuts, beer nuts, trail mix, pretzels and chips
Coffee and tea	Coffee, cappuccino, espresso, English tea, green tea and herbal tea
Sugar-containing beverages	Coke/Fanta/Sprite soft drinks, isotonic drinks, fruit juices and vegetable juices
Light soft drinks	Coke/Fanta/Sprite light soft drinks and water
Alcoholic beverages	Beer, wine, mixed drinks and liquor
Condiments and sauces	Chili/tomato/barbecue/shaslick/peanut/garlic/whisky/soy/salad sauce, salad dressing, mayonnaise, fish/egg/meat/Russian salad, sandwich spread, marmite, salt, spices/herbs and flavour powder
Soups and bouillon	Soup or bouillon with or without meat, meal soup and lentil soup
Nuts, seeds and olives	Nut butter, tahini, poppy seed, sesame, pumpkin seeds, sunflower seeds, pine nuts, mixed seeds and olives
Soy products	Tofu, tempeh, soymilk, soy chunks, soy dessert, vegetable burgers and Quorn
Legumes	Legumes and tempeh

[1] Reprinted with permission from van den Broek *et al.*, [1]. The food groups were primarily created based on the Dutch National Food Consumption Survey.

Supplementary Table 2.2.2. Modified version of the Dutch Healthy Diet-index[1]

Components of the Dutch Healthy Diet-Index		Minimum Score (0)	Maximum Score (10)
1	Physical activity (daily)	NA	NA
2	Vegetable (g/day)	0	≥200
3	Fruit (g/day) [a]	0	≥200
4	Fiber (g/4.2MJ/day)	0	≥14
5	Fish (g/day)	0	34.3 [b]
6	Saturated fat (E%)	≥16.6	<10
7	*Trans* fatty acid (E%)	NA	NA
8	Acidic drinks and foods (servings/day)	NA	NA
9	Sodium (mg/day)	≥2450	<1680
10	Alcohol (g/day)	NI	NI

[1] Adapted from van Lee *et al.*, [2]; [a] Fruit without fruit juices; [b] Based on two portions of 120 g fish per week [3]; Abbreviations: NA: not available; NI: not included.

Supplementary Table 2.2.3. Sensitivity analyses in normal weight women (*n* = 2141)[1]

Dietary Pattern Quartile	Gestational Weight Gain until Early Third Trimester of Pregnancy	1. Additionally Adjusted for Energy Intake[2]	2. Additional Adjustment for Estimated Foetal Weight	3. Excluding Women with Comorbidities or Pregnancy Complications[3]	4. Excluding Women Vomiting > 1 Times per Week in Previous Three Months	Maximal Gestational Weight Gain[4]
	n = 2141	n = 2141	n = 2120	n = 1937	n = 1890	n = 1492
"Vegetable, Oil and Fish" Pattern						
Q1 (low)	Reference	Reference	Reference	Reference	Reference	Reference
Q2	16 (−0; 31)	14 (−1; 30)	**16 (0; 32)**	**20 (3; 36)**	13 (−4; 30)	14 (−12; 41)
Q3	5 (−11; 21)	2 (−15; 18)	5 (−11; 21)	7 (−10; 23)	2 (−15; 19)	4 (−23; 31)
Q4 (high)	**25 (9; 42) ***	**18 (0; 35)**	**25 (9; 41) ***	**27 (11; 44) ***	**20 (3; 37)**	**29 (2; 57)**
Per SD	***p = 0.02***	*p = 0.29*	***p = 0.02***	***p < 0.01 ****	*p = 0.11*	*p = 0.19*
"Nuts, High-Fibre Cereals and Soy" Pattern						
Q1 (low)	Reference	Reference	Reference	Reference	Reference	Reference
Q2	10 (−6; 26)	7 (−9; 23)	11 (−5; 26)	12 (−4; 29)	11 (−6; 28)	16 (−12; 44)
Q3	−3 (−19; 14)	−6 (−23; 10)	0 (−16; 16)	0 (−17; 17)	−1 (−18; 16)	25 (−3; 54)
Q4 (high)	−5 (−22; 11)	−12 (−29; 5)	−5 (−21; 11)	−2 (−19; 15)	−7 (−24; 10)	10 (−19; 38)
Per SD	*p = 0.51*	*p = 0.14*	*p = 0.36*	*p = 0.66*	*p = 0.48*	*p = 0.20*
"Margarine, Sugar and Snacks" Pattern						
Q1 (low)	Reference	Reference	Reference	Reference	Reference	Reference
Q2	6 (−9; 21)	−1 (−19; 16)	3 (−12; 18)	6 (−10; 22)	4 (−12; 20)	**27 (1; 53)**
Q3	−0 (−16; 16)	−14 (−35; 7)	−2 (−17; 13)	1 (−15; 17)	−3 (−20; 13)	26 (−0; 53)
Q4 (high)	11 (−5; 26)	−11 (−40; 17)	9 (−7; 24)	10 (−6; 26)	7 (−9; 23)	24 (−2; 50)
Per SD	*p = 0.37*	*p = 0.06*	*p = 0.48*	*p = 0.48*	*p = 0.82*	*p = 0.12*
"Dutch Healthy Diet-Index" Pattern						
Q1 (low)	Reference	Reference	Reference	Reference	Reference	Reference
Q2	−9 (−24; 7)	−10 (−25; 6)	−8 (−23; 8)	−13 (−29; 3)	−12 (−28; 4)	−10 (−35; 16)
Q3	−2 (−18; 13)	−3 (−19; 12)	−3 (−18; 13)	−4 (−20; 12)	−6 (−22; 10)	4 (−22; 29)
Q4 (high)	−11 (−27; 5)	−11 (−27; 5)	−9 (−25; 6)	−16 (−33; 1)	−13 (−29; 4)	**−28 (−55; −1)**
Per SD	*p = 0.13*	*p = 0.13*	*p = 0.19*	*p =0.06*	*p = 0.08*	*p = 0.05*

[1] Values (regression coefficients with 95%-confidence interval) reflect the difference in gestational weight gain until early-third trimester (g/week) for quartile 2 until 4 relative to quartile 1 in normal weight women. *p*-Values correspond to the effect of 1SD increase in dietary pattern score. Adjusted for pre-pregnancy BMI, median gestational age at follow-up, age, educational level, household income, parity, smoking during pregnancy, alcohol consumption during pregnancy, stress during pregnancy, and fetal sex. [2] Further adjusted for energy intake (kcal/day). [3] Women excluded with pre-existing comorbidities (diabetes mellitus, hypercholesterolemia, hypertension, heart disease, thyroid disease, and systemic lupus erythematosus) and with pregnancy complications (pregnancy-induced hypertension, preeclampsia or gestational diabetes). [4] Gestational weight gain calculated from self-reported pre-pregnancy weight and maximum weight in pregnancy. Significant results are presented in bold (*p*-value < 0.05) and results with a *p*-value < 0.0125 with an asterisk (*).

Supplementary Table 2.2.4. Sensitivity analyses in overweight women (n = 674)[1]

Dietary Pattern Quartile	Gestational Weight Gain until Early Third Trimester of Pregnancy	1. Additionally Adjusted for Energy Intake[2]	2. Additional Adjustment for Estimated Foetal Weight	3. Excluding Women with Comorbidities or Pregnancy Complications[3]	4. Excluding Women Vomiting > 1 Times per Week in Previous Three Months	Maximal Gestational Weight Gain[4]
	n = 674	n = 674	n = 665	n = 532	n = 560	n = 425
"Vegetable, Oil and Fish" Pattern						
Q1 (low)	Reference	Reference	Reference	Reference	Reference	Reference
Q2	30 (−8; 68)	29 (−8; 67)	28 (−9; 65)	27 (−13; 66)	27 (−14; 68)	11 (−40; 62)
Q3	**40 (1; 79)**	38 (−2; 77)	**41 (2; 80)**	40 (−2; 81)	**44 (3; 86)**	25 (−27; 77)
Q4 (high)	26 (−15; 67)	22 (−21; 65)	25 (−15; 66)	19 (−23; 61)	38 (−6; 82)	1 (−54; 55)
Per SD	*p = 0.15*	*p = 0.22*	*p = 0.13*	*p = 0.18*	*p = 0.07*	*p = 0.87*
"Nuts, High-Fibre Cereals and Soy" Pattern						
Q1 (low)	Reference	Reference	Reference	Reference	Reference	Reference
Q2	1 (−38; 39)	0 (−38; 39)	−0 (−38; 38)	−23 (−63; 17)	6 (−38; 49)	10 (−46; 67)
Q3	−14 (−53; 25)	−14 (−54; 25)	−19 (−58; 19)	−8 (−50; 33)	−14 (−57; 29)	47 (−9; 102)
Q4 (high)	−9 (−50; 32)	−10 (−53; 32)	−12 (−52; 28)	−12 (−55; 31)	−11 (−55; 33)	15 (−41; 72)
Per SD	*p = 0.49*	*p = 0.45*	*p = 0.38*	*p = 0.48*	*p = 0.38*	*p = 0.70*
"Margarine, Sugar and Snacks" Pattern						
Q1 (low)	Reference	Reference	Reference	Reference	Reference	Reference
Q2	11 (−26; 48)	19 (−24; 61)	10 (−27; 46)	1 (−39; 40)	7 (−33; 48)	−1 (−50; 48)
Q3	18 (−20; 55)	31 (−21; 83)	16 (−21; 53)	26 (−12; 65)	9 (−31; 49)	8 (−42; 59)
Q4 (high)	30 (−8; 68)	51 (−17; 120)	28 (−9; 66)	38 (−2; 79)	27 (−15; 69)	22 (−31; 75)
Per SD	*p = 0.36*	*p =0.89*	*p = 0.41*	*p = 0.20*	*p = 0.49*	*p = 0.51*
"Dutch Healthy Diet-Index" Pattern						
Q1 (low)	Reference	Reference	Reference	Reference	Reference	Reference
Q2	−3 (−40; 34)	−4 (−41; 34)	1 (−36; 38)	−6 (−46; 34)	8 (−32; 47)	−28 (−76; 21)
Q3	16 (−22; 54)	15 (−22; 53)	15 (−23; 52)	11 (−29; 52)	28 (−13; 68)	−5 (−55; 44)
Q4 (high)	9 (−30; 48)	9 (−30; 48)	9 (−30; 48)	11 (−30; 52)	−3 (−46; 40)	−9 (−62; 44)
Per SD	*p = 0.84*	*p = 0.83*	*p = 0.82*	*p = 0.89*	*p = 0.50*	*p = 0.84*

[1] Values (regression coefficients with 95%-confidence interval) reflect the difference in gestational weight gain until early third trimester (g/week) for quartile 2 until 4 relative to quartile 1 in overweight women. *p*-Values correspond to the effect of 1SD increase in dietary pattern score. Adjusted for pre-pregnancy BMI, median gestational age at follow-up, age, educational level, household income, parity, smoking during pregnancy, alcohol consumption during pregnancy, stress during pregnancy, and fetal sex. [2] Further adjusted for energy intake (kcal/day). [3] Women excluded with pre-existing comorbidities (diabetes mellitus, hypercholesterolemia, hypertension, heart disease, thyroid disease, and systemic lupus erythematosus) and with pregnancy complications (pregnancy-induced hypertension, preeclampsia or gestational diabetes). [4] Gestational weight gain calculated from self-reported pre-pregnancy weight and maximum weight in pregnancy. Significant results are presented in bold (*p*-value < 0.05) and results with a *p*-value < 0.0125 with an asterisk (*).

Supplementary Table 2.2.5. Gestational weight trajectories in normal weight and overweight women (*n* = 3374)[1]

Normal Weight Women (n=2564)	**Mean**	**95%CI**
"Vegetable, oil and fish" pattern	0.217	−0.010; 0.443
"Nuts, high-fibre cereals and soy" pattern	0.151	−0.084; 0.395
"Margarine, sugar and snacks" pattern	**0.300**	**0.074; 0.520 ***
Gestational age (at measurement in weeks)	**0.131**	**0.121; 0.142 ***
Gestational age × gestational age	**0.008**	**0.007; 0.008 ***
"Vegetable, oil and fish" pattern × gestational age	-0.001	−0.007; 0.005
"Nuts, high-fibre cereals and soy" pattern × gestational age	**−0.010**	**−0.016; −0.004 ***
"Margarine, sugar and snacks" pattern × gestational age	0.006	−0.000; 0.012
Overweight women (n=810)	**Mean**	**95%CI**
"Vegetable, oil and fish" pattern	0.263	−0.180; 0.717
"Nuts, high-fibre cereals and soy" pattern	−0.306	−0.767; 0.140
"Margarine, sugar and snacks" pattern	0.319	−0.074; 0.714
Gestational age (at measurement in weeks)	**0.099**	**0.081; 0.118 ***
Gestational age × gestational age	**0.008**	**0.007; 0.008 ***
"Vegetable, oil and fish" pattern × gestational age	0.005	−0.006; 0.016
"Nuts, high-fibre cereals and soy" pattern × gestational age	0.007	−0.004; 0.018
"Margarine, sugar and snacks" pattern × gestational age	0.005	−0.005; 0.015

[1] The table shows the posterior mean and 95% credible intervals (95%CI) of the longitudinal analysis of *a posteriori*-derived dietary patterns and weight development in pregnancy in normal weight and overweight women using Bayesian linear mixed models. The model included the following variables: the *a posteriori*-derived dietary patterns, gestational age at measurement, gestational age at measurement × gestational age at measurement, interaction terms of the dietary patterns with gestational age at measurement, age, educational level, household income, parity, smoking during pregnancy, alcohol consumption during pregnancy, stress during pregnancy, and fetal sex. Significant results are presented in bold (*p*-value < 0.05) and results with a *p*-value <0.0125 with an asterisk (*).

Supplementary Table 2.2.6. Association of dietary patterns with adequacy of weekly gestational weight gain (n=2745)[1]

Dietary Pattern Quartile	Inadequate Weekly GWG (n=437) OR (95%CI)	Adequate Weekly GWG (n=753)	Excessive Weekly GWG (n=1555) OR (95%CI)
		"Vegetable, Oil and Fish" Pattern	
Q1 (low)	Reference	Reference	Reference
Q2	0.81 (0.57; 1.16)	Reference	0.99 (0.76; 1.29)
Q3	0.83 (0.58; 1.18)	Reference	0.89 (0.68; 1.16)
Q4 (high)	0.97 (0.67; 1.41)	Reference	0.85 (0.64; 1.13)
Per SD	*p = 0.92*		*p = 0.11*
		"Nuts, High-Fibre Cereals and Soy" Pattern	
Q1 (low)	Reference	Reference	Reference
Q2	1.12 (0.79; 1.59)	Reference	1.16 (0.89; 1.51)
Q3	0.86 (0.59; 1.24)	Reference	0.99 (0.76; 1.30)
Q4 (high)	1.10 (0.76; 1.61)	Reference	1.16 (0.87; 1.55)
Per SD	*p = 0.83*		*p = 0.20*
		"Margarine, Sugar and Snacks" Pattern	
Q1 (low)	Reference	Reference	Reference
Q2	1.17 (0.83; 1.65)	Reference	1.13 (0.88; 1.47)
Q3	0.92 (0.65; 1.32)	Reference	1.10 (0.85; 1.43)
Q4 (high)	**1.49 (1.05; 2.11)**	Reference	**1.32 (1.01; 1.72)**
Per SD	*p = 0.19*		*p = 0.29*
		"Dutch Healthy Diet-Index" Pattern	
Q1 (low)	Reference	Reference	Reference
Q2	0.79 (0.56;1.11)	Reference	0.93 (0.72;1.20)
Q3	0.88 (0.62;1.25)	Reference	1.10 (0.85;1.42)
Q4 (high)	1.00 (0.69;1.43)	Reference	1.02 (0.77;1.34)
Per SD	*p = 0.84*		*p = 0.63*

[1] Results from multivariable multinomial logistic regression analyses, based on imputed data. Low dietary pattern adherence (Q1) is the reference category for diet and adequate weekly GWG is the reference category for weekly GWG in the multinomial regression model. *p*-Values correspond to the effect of 1SD increase in dietary pattern score. Adjusted for pre-pregnancy BMI, gestational age at measurements, age, educational level, household income, parity, smoking during pregnancy, alcohol consumption during pregnancy, stress during pregnancy, and fetal sex. Significant results are presented in bold (*p*-value < 0.05) and results with a *p*-value <0.0125 with an asterisk (*). Abbreviations: CI: confidence interval; GWG: gestational weight gain; OR: odds ratio; SD: standard deviation; Q: quartile.

References chapter 2.2

1. Van den Broek, M.; Leermakers, E.T.; Jaddoe, V.W.; Steegers, E.A.; Rivadeneira, F.; Raat, H.; Hofman, A.; Franco, O.H.; Kiefte-de Jong, J.C. Maternal dietary patterns during pregnancy and body composition of the child at age 6 y: The generation R study. *Am. J. Clin. Nutr.* **2015**, *102*, 873–880.
2. Van Lee, L.; Geelen, A.; van Huysduynen, E.J.; de Vries, J.H.; van't Veer, P.; Feskens, E.J. The Dutch healthy diet index (DHD-index): An instrument to measure adherence to the Dutch guidelines for a healthy diet. *Nutr. J.* **2012**, *11*, doi:10.1186/1475-2891-11-49.
3. Donders-Engelen, M.; van der Heijden, L. *Maten, Gewichten en Codenummers 2003 (Measures, Weights and Code Numbers 2003)*; Wageningen UR, Vakgroep Humane Voeding Wageningen and TNO Voeding: Zeist, the Netherlands, 2003.

Chapter 2.3

Dietary acid load and blood pressure development in pregnancy: The Generation R Study

Myrte J. Tielemans, Nicole S. Erler, Oscar H. Franco, Vincent W.V. Jaddoe, Eric A.P. Steegers, Jessica C. Kiefte-de Jong

Submitted for publication

Statistical analysis – Modelling choices for the linear mixed models

In the following, we provide details on the modelling choices for the linear mixed models to evaluate the association between dietary acid load measurements and the development of diastolic blood pressure (DBP) and systolic blood pressure (SBP) during pregnancy.

1. **Determining the random effects structure**
   First, an extensive fixed effects structure was used to compare a model containing only a random intercept with models containing a random intercept and slope using an adapted likelihood ratio test. This analysis showed that a random intercept model was adequate for DBP, whereas for SBP a model with a random intercept and slope was more appropriate.

2. **Simplifying the fixed effects structure**
   Second, we evaluated the models with different numbers of *df* in the spline for gestational age and compared the fit using the Akaike's Information Criterion (AIC). For DBP, the AIC indicated that a model with 2 *df* in the natural cubic spline for gestational age was the best fit for all exposures. For SBP, the AIC had no clear preference for a specific number of *df.* Plots of the non-linear effect of time showed that in the model for SBP at least 4 *df* were required to allow for enough flexibility to represent the expected physiological development of blood pressure, and we therefore chose to use 4 *df* in the model for SBP. Analogous comparisons showed that there was no evidence for non-linear effects of the exposures on either DBP or SBP.

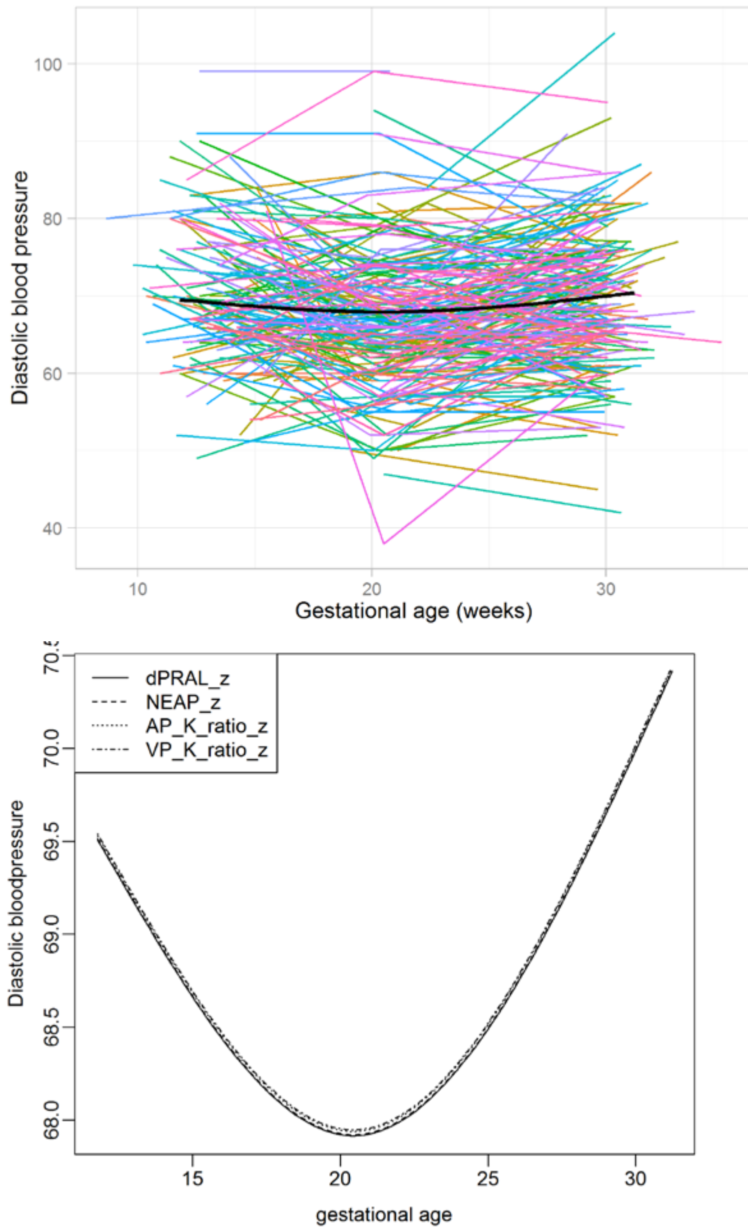
3. **Testing for interaction**
   We tested whether including interaction terms between the exposure and gestational age and between the exposure and smoking would significantly improve the fit of any of the models. Likelihood ratio tests showed that none of the interaction terms significantly improved the model fit.

4. **Final models**
   The models for the main analysis include

   Final model DBP: a random intercept, a natural cubic spline with 2 *df* for gestational age, linear effects of the exposure (i.e. dPRAL, NEAP, animal protein/potassium ratio, or vegetable protein/potassium ratio), covariates (namely maternal age, educational level, household income, pre-pregnancy BMI, parity, maternal alcohol consumption and maternal smoking), and no interaction terms.

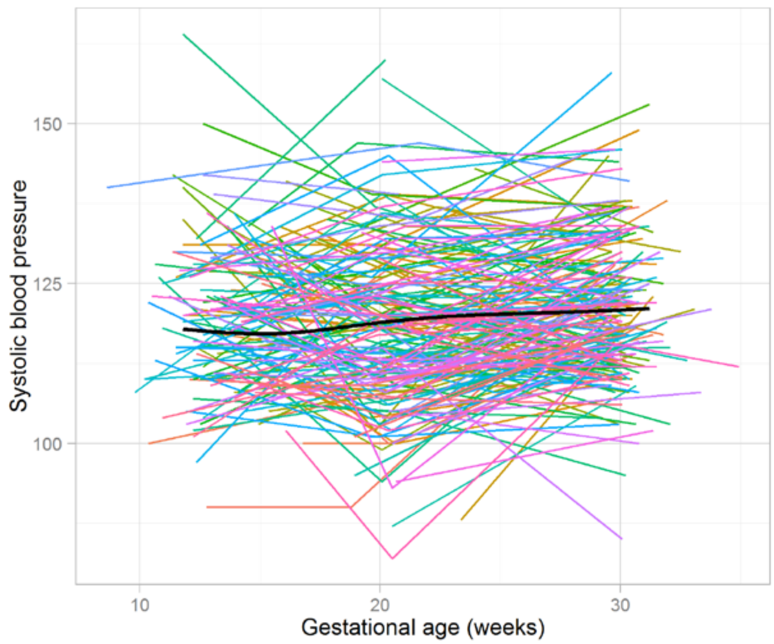
   Final model SBP: a random intercept and a random slope, a natural cubic spline with 4 *df* for gestational age, linear effects of the exposure (i.e. dPRAL, NEAP, animal protein/potassium ratio, or vegetable protein/potassium ratio), covariates (namely maternal age, educational level, household income, pre-pregnancy BMI, parity, maternal alcohol consumption and maternal smoking), and no interaction terms.

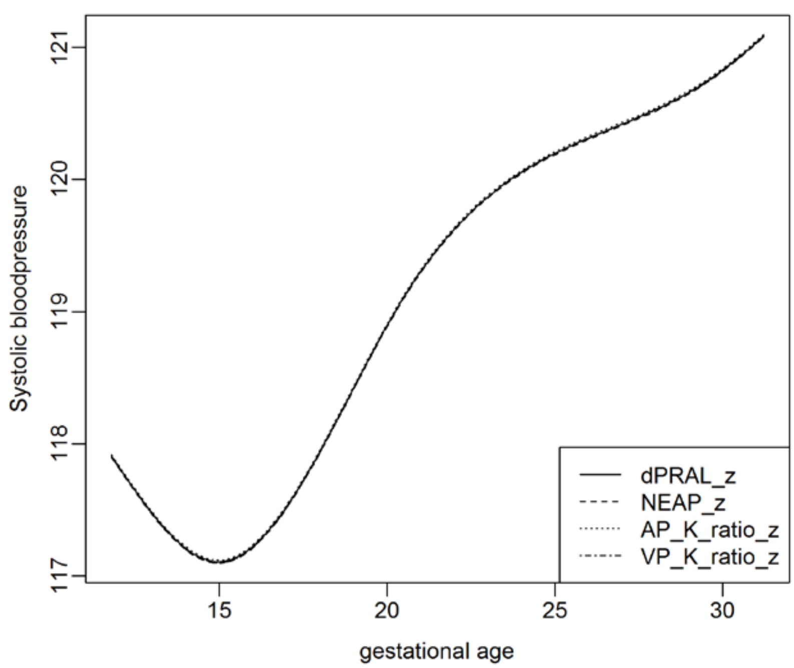
Supplementary Figure 2.3.1. Development of diastolic blood pressure during pregnancy



The upper panel shows the estimated average profile of diastolic blood pressure (mmHg) of a subgroup of 200 randomly selected participants. The mean value is presented in black and individual trajectories in color. The lower panel shows a zoomed-in version of the mean diastolic blood pressure during pregnancy in all participants.

Supplementary Figure 2.3.2. Development of systolic blood pressure during pregnancy





The upper panel shows the estimated average profile of systolic blood pressure (mmHg) of a subgroup of 200 randomly selected participants. The mean value is presented in black and individual trajectories in color. The lower panel shows a zoomed-in version of the mean systolic blood pressure during pregnancy in all participants.

Supplementary Table 2.3.1. Details of the multiple imputation process

	Multiple imputation
Software used	IBM SPSS statistics version 21
Imputation method and key settings	Fully conditional specification (Markov chain Monte Carlo method); maximum iterations: 10
No. of imputed data sets created	10
Variables included in the imputation procedure as both predictor variable as a variable to be imputed	Age mother at enrolment; Gravidity at enrolment; Parity at enrolment; Nausea during pregnancy; Vomiting during pregnancy; Pre-pregnancy weight; Pre-pregnancy BMI; Gestational weight gain: Height at enrolment; Maternal educational level at enrolment; Maternal alcohol consumption during pregnancy; Maternal smoking during pregnancy; Folic acid supplementation during pregnancy; Age partner at enrolment; BMI partner; Education level partner at enrolment; Household income at enrolment; Maternal stress during pregnancy; Foetal sex; Gestational age at birth; Preterm birth.
Variables added as predictors (not used in the main analysis) of missing data to increase plausibility of missing at random assumption	Dietary potential renal acid load (dPRAL); net endogenous acid production (NEAP); Animal protein/potassium ratio (AP/K ratio); Dutch Healthy Diet-Index; Maternal energy intake during pregnancy; Maternal serum folate level <18 weeks of gestation; Height at 2nd and 3rd visit; Weight at 1st, 2nd and 3rd visit; Birthweight; Standardized birth weight (Niklasson);Maternal educational level 6 years after enrolment; Household income 6 years after enrolment; Hypertensive complications in pregnancy; Gestational age at first, second and third visit; Systolic blood pressure during first, second, and third visit; Diastolic blood pressure during first, second, and third visit.
Treatment of not normally distributed variables	Predictive mean matching
Treatment of binary/categorical variables	Logistic regression models
Population	For the multiple imputation we included those mothers of Dutch ancestry, enrolled during pregnancy and with available dietary information (n=3558)

Supplementary Table 2.3.2. Differences between the population of analysis and eligible women not included in the analysis (n=4096)[1]

	Included (n=3411)	**Not included** (n=685)	**p-value**[2]
Age (years)	31.4 ± 4.4	30.7 ± 5.1	**0.001**
Missing	*0 (0)*	*0 (0)*	
Educational level			**<0.001**
Low and midlow	505 (15.0)	173 (25.9)	
Midhigh	1712 (50.8)	322 (48.2)	
High	1150 (34.2)	173 (25.9)	
Missing	*44 (1.3)*	*17 (2.5)*	
Household income (Euros/month)			**<0.001**
< 2,200	769 (25.2)	182 (34.9)	
≥ 2,200	2281 (74.8)	340 (65.1)	
Missing	*361 (10.6)*	*163 (23.8)*	
Parity			0.40
0	2038 (59.9)	396 (58.1)	
≥1	1365 (40.1)	285 (41.9)	
Missing	*8 (0.2)*	*4 (0.6)*	
Pre-pregnancy body mass index (kg/m^2)	22.2 (20.6 – 24.6)	22.5 (20.5 – 25.2)	0.16
Missing	*467 (13.7)*	*119 (17.4)*	
Smoking			**<0.001**
Never during pregnancy	2346 (74.2)	415 (66.6)	
Until pregnancy was known	280 (8.9)	68 (10.9)	
Continued throughout pregnancy	536 (17.0)	140 (22.5)	
Missing	*249 (7.3)*	*62 (9.1)*	
Alcohol consumption			**0.006**
Never during pregnancy	1059 (33.8)	241 (38.9)	
Until pregnancy was known	509 (16.2)	112 (18.1)	
Continued throughout pregnancy	1569 (50.0)	267 (43.1)	
Missing	*274 (8.0)*	*65 (9.5)*	
Folic acid supplementation			**<0.001**
Started periconceptional	1569 (56.1)	267 (48.6)	
Started first 10 weeks	923 (33.0)	191 (34.8)	
No supplementation	304 (10.9)	91 (16.6)	
Missing	*615 (18.0)*	*136 (19.9)*	
Gestational age at enrolment (weeks)	13.5 (12.4 – 16.1)	13.8 (12.4 – 17.6)	**0.04**
Missing	*0 (0)*	*0 (0)*	
Diastolic blood pressure at enrolment (mmHg)	68 ± 9	70 ± 11	**<0.001**
Missing	*28 (0.8)*	*11 (1.6)*	
Systolic blood pressure at enrolment (mmHg)	117 ± 12	120 ± 14	**<0.001**
Missing	*28 (0.8)*	*11 (1.6)*	
Pregnancy-induced hypertension	173 (5.3)	34 (5.0)	0.64
Missing	*140 (4.1)*	*95 (13.9)*	
Pre-eclampsia	59 (1.9)	19 (3.3)	**0.03**
Missing	*254 (7.4)*	*110 (16.1)*	

[1] Values represent n (%), mean ± SD, median (interquartile range). [2.] Differences between continuous variables tested using independent student *t*-test or Mann Whitney U test, and between categorical variables were tested using Chi-square statistics.

Supplementary Table 2.3.3. Pooled results of dietary acid load with systolic blood pressure and with diastolic blood pressure, additionally adjusted for the Dutch Healthy Diet-index (n=3411)

Dietary acid load		Diastolic blood pressure Difference in mmHg (95% CI)	Systolic blood pressure Difference in mmHg (95% CI)
dPRAL			
	Adjusted (per SD)	-0.07 (-0.32; 0.19)	0.14 (-0.18; 0.46)
NEAP			
	Adjusted (per SD)	-0.13 (-0.39; 0.13)	0.12 (-0.21; 0.44)
Animal protein/potassium ratio			
	Adjusted (per SD)	0.06 (-0.19; 0.32)	0.31 (-0.01; 0.63)
Vegetable protein/potassium ratio			
	Adjusted (per SD)	**-0.28 (-0.52; 0.04)***	-0.28 (-0.58; 0.03)

[1.] Results (coefficients with 95% confidence interval (CI)) from linear mixed model analysis. The coefficient reflects the difference in systolic blood pressure (mmHg) or diastolic blood pressure (mmHg) per one standard deviation (SD) increase in dietary acid load. The models include the natural cubic splines for gestational age (2 *df* for DBP and 4 *df* for SBP), a random intercept for DBP and a random intercept and slope for SBP, maternal age, pre-pregnancy BMI, parity, educational level, household income, alcohol consumption during pregnancy, smoking behavior during pregnancy, and Dutch Health Diet-index. Significant associations (p-value <0.05) are presented with an asterisk (*). **Abbreviations**: DBP: diastolic blood pressure, dPRAL: dietary potential renal acid load, NEAP: net endogenous acid production, SBP: systolic blood pressure.

Supplementary Table 2.3.4. Analysis in women without pre-existing comorbidities (n=3290)[1]

Dietary acid load		Diastolic blood pressure Difference in mmHg (95% CI)	Systolic blood pressure Difference in mmHg (95% CI)
dPRAL			
	Adjusted (per SD)	-0.13 (-0.37; 0.11)	0.07 (-0.24; 0.37)
NEAP			
	Adjusted (per SD)	-0.17 (-0.41; 0.07)	0.06 (-0.24; 0.37)
Animal protein/potassium ratio			
	Adjusted (per SD)	-0.01 (-0.25; 0.23)	0.23 (-0.07; 0.54)
Vegetable protein/potassium ratio			
	Adjusted (per SD)	**-0.30 (-0.54; -0.05)***	-0.28 (-0.59; 0.02)

[1.] Results (coefficients with 95% confidence interval (CI)) from linear mixed model analysis. The coefficient reflects the difference in systolic blood pressure or diastolic blood pressure (mmHg) per one standard deviation (SD) increase in dietary acid load. The models include the natural cubic splines for gestational age (2 *df* for DBP and 4 *df* for SBP), a random intercept for DBP and a random intercept and slope for SBP, maternal age, pre-pregnancy BMI, parity, educational level, household income, alcohol consumption during pregnancy and smoking behavior during pregnancy. Significant associations (p-value <0.05) are presented with an asterisk (*). **Abbreviations**: DBP: diastolic blood pressure, dPRAL: dietary potential renal acid load, NEAP: net endogenous acid production, SBP: systolic blood pressure.

Chapter 3.1

Maternal fish consumption, fatty acid levels and angiogenic factors: The Generation R Study

Myrte J. Tielemans*, Paula K. Bautista Niño*, Sarah Schalekamp-Timmermans, Jolien Steenweg-de Graaff, Albert Hofman, Henning Tiemeier, Vincent W. Jaddoe, Eric A.P.Steegers, Janine F.Felix, Oscar H.Franco

* Contributed equally

Placenta. 2015 Oct;36(10):1178-84

Supplementary Table 3.1.1. Characteristics of participants (n = 3134)[a]

Maternal characteristics	**Unimputed dataset**	**Imputed dataset**
Age (years)	31.4 ± 4.3	31.4 ± 4.3
Gestational age at enrolment (weeks)	13.2 (9.9-21.6)	No missing
BMI at enrolment (kg/m^2)	24.1 ± 3.9	24.1 ± 3.9
Parity, *% (n)*		
Nullipara	60.1 (1880)	60.1 (1883)
Multipara	39.9 (1247)	39.9 (1251)
Highest education finished, *% (n)*		
Primary	3.1 (97)	3.2 (100)
Secondary	36.4 (1133)	36.4 (1140)
Higher	60.5 (1885)	60.5 (1894)
Smoking during pregnancy, *% (n)*		
Yes	25.9 (755)	28.5 (894)
No	74.1 (2160)	71.5 (2240)
Alcohol use during pregnancy, *% (n)*		
Yes	67.1 (1944)	67.2 (2105)
No	32.9 (952)	32.8 (1029)
Folic acid supplementation use, *% (n)*		
Yes	89.5 (2310)	89.0 (2789)
No	10.5 (272)	11.0 (345)
Pregnancy-induced hypertension, *% (n)*		
Yes	5.3 (164)	Not imputed
No	94.7 (2914)	
Preeclampsia, *% (n)*		
Yes	1.9 (56)	Not imputed
No	98.1 (2914)	
Season of conception, *% (n)*		
Winter	28.3 (888)	28.3 (888)
Spring	23.6 (738)	23.6 (738)
Summer	21.8 (684)	21.8 (684)
Fall	26.3 (823)	26.3 (823)
Total daily energy intake (kJ/day)	8972 ± 2127[b]	No missing
Total fish intake (gram/week)[c]	75 (0-318)	No missing
Lean fish intake (gram/week)[c]	24 (0-149)	No missing
Fatty fish intake (gram/week)[c]	30 (0-150)	No missing
Shellfish intake (gram/week)[c]	0 (0-34.5)	No missing
Plasma fatty acids		
Docosahexaenoic acid (mg/L)	80.1 ± 20.0	Not imputed
Eicosapentaenoic acid (mg/L)	13.0 ± 4.2	Not imputed
Alpha-Linolenic acid (mg/L)	5.5 ± 1.8	Not imputed
Linoleic acid (mg/L)	352.3 ± 59.5	Not imputed

Supplementary Table 3.1.1. (continued) Characteristics of participants (n = 3134)[a]

Maternal characteristics	Unimputed dataset	Imputed dataset
Arachidonic acid (mg/L)	154.5 ± 31.2	Not imputed
Omega-3/omega-6 ratio	0.2 ± 0.05	Not imputed
EPA/AA ratio	0.06 ± 0.04	Not imputed
DHA/AA ratio	0.5 ± 0.14	Not imputed
Angiogenic factors levels		
First trimester		
PlGF (pg/mL)	37.8 (14.4-154.7)	Not imputed
sFlt-1 (ng/mL)	4.9 (1.9-12.8)	Not imputed
sFlt-1/PlGF ratio	0.13 (0.02-0.43)	Not imputed
Second trimester		
PlGF (pg/mL)	185.9 (73.2-569.3)	Not imputed
sFlt-1 (ng/mL)	4.7 (1.5-16.0)	Not imputed
sFlt-1/PlGF ratio	0.02 (0.01-0.11)	Not imputed
Cord blood		
PlGF (pg/mL)	8.6 (0.0-20.7)	Not imputed
sFlt-1 (ng/mL)	0.45 (0.08-4.01)	Not imputed
sFlt-1/PlGF ratio	0.05 (0.01-0.42)	Not imputed
Child characteristics		
Sex, *% (n)*		
Boy	50.8 (1592)	50.8 (1592)
Girl	49.2 (1541)	49.2 (1542)
Gestational age at birth (weeks)	40.3 (36.0-42.4)	40.3 (36.0-42.4)
Birth weight (grams)	3497 ± 549	3497 ± 550

[a.] Values are mean ± SD when normally distributed or median (95% range) when not normally distributed for continuous variables and percentages (n) for categorical outcomes. The number of missings were 0.03% (n = 1) for maternal age, 0.4% (n = 14) for BMI at enrolment, 0.2% (n = 7) for parity, 0.6% (n = 19) for maternal education, 7.0% (n = 219) for smoking, 7.6% (n = 238) for alcohol use, 17.6% (n = 552) for folic acid supplementation use, 1.8% (n = 56) for pregnancy-induced hypertension, 5.2% (n = 164) for preeclampsia, 0.03% (n = 1) for season of conception, 13.9% (n = 435) for plasma fatty acids, 0.03% (n = 1) for child sex, 0.03% (n = 1) gestational age at birth and 0.2 % (n = 5) for birth weight. AA: Arachidonic acid, DHA: Docosahexanoic acid, EPA: Eicosapentanoic acid, PlGF: Placental growth factor, sFlt-1: Soluble Flt-1. [b.] Value corresponds to a daily energy intake of 2143 ± 508 kcal/day. [c.] Absolute values of fish consumption.

Supplementary Table 3.1.2. Associations between weekly maternal fatty fish consumption and levels of angiogenic factors[a]

Fatty fish consumption (energy-adjusted g/week)	First Trimester			Second Trimester			Cord Blood		
	n	Beta	95% CI	n	Beta	95% CI	n	Beta	95% CI
	Ln-PlGF pg/mL (n=2515)			**Ln-PlGF pg/mL** (n=2845)			**Ln-PlGF pg/mL** (n=1552)		
0	222		Reference	256		Reference	135		Reference
1-34	1098	0.003	-0.065, 0.071	1242	0.010	-0.059, 0.078	642	-0.062	-0.420, 0.297
35-69	720	-0.020	-0.089, 0.050	797	-0.024	-0.095, 0.046	460	-0.123	-0.480, 0.233
>70	475	0.002	-0.071, 0.076	550	-0.017	-0.090, 0.057	315	-0.023	-0.218, 0.173
P for trend			*0.77*			*0.22*			*0.94*
	Ln-sFlt-1 ng/mL (n=2513)			**Ln-sFlt-1 ng/mL** (n=2844)			**Ln-sFlt-1 ng/mL** (n=1695)		
0	222		Reference	256		Reference	145		Reference
1-34	1096	0.022	-0.057, 0.100	1242	0.064	-0.023, 0.150	706	0.013	-0.191, 0.218
35-69	719	-0.023	-0.104, 0.058	797	0.036	-0.054, 0.125	496	0.022	-0.187, 0.231
>70	476	-0.005	-0.089, 0.079	549	0.049	-0.044, 0.143	348	0.076	-0.142, 0.295
P for trend			*0.30*			*0.62*			*0.38*
	Ln-sFlt-1/PlGF ratio (n=2505)			**Ln-sFlt-1/PlGF ratio** (n=2844)			**Ln-sFlt-1/PlGF ratio** (n=1469)		
0	222		Reference	256		Reference	127		Reference
1-34	1093	0.018	-0.078, 0.113	1242	0.054	-0.048, 0.156	605	0.074	-0.123, 0.271
35-69	718	-0.004	-0.102, 0.094	797	0.060	-0.046, 0.165	435	0.074	-0.128, 0.276
>70	472	-0.013	-0.115, 0.090	549	0.066	-0.045, 0.176	302	0.177	-0.033, 0.388
P for trend			*0.44*			*0.22*			*0.09*

Results from multivariable linear regression model, based on imputed data. P for trend was conducted by including fatty fish consumption categories in the multivariable linear regression model. † $P < 0.05$, * $P < 0.01$. **Abbreviations:** CI: confidence interval, n: number of participants, PlGF: placental growth factor, sFlt-1: soluble Flt-1. [a.] Adjusted for total energy intake, maternal age, gestational age at measurement, BMI at enrolment, foetal sex, parity, maternal education, smoking, and season of conception.

Supplementary Table 3.1.3. Associations between weekly maternal lean fish consumption and levels of angiogenic factors[a]

Lean fish consumption (energy-adjusted g/week)	First Trimester			Second Trimester			Cord Blood		
	n	Beta	95% CI	n	Beta	95% CI	n	Beta	95% CI
	Ln-PlGF pg/mL (n=2515)			**Ln-PlGF pg/mL** (n=2845)			**Ln-PlGF pg/mL** (n=1552)		
0	657	Reference		744	Reference		422	Reference	
1-34	932	**-0.049†**	**-0.095, -0.004**	1052	**-0.054†**	**-0.100, -0.008**	556	-0.122	-0.361, 0.117
35-69	613	-0.023	-0.073, 0.027	680	-0.002	-0.053, 0.049	370	0.062	-0.200, 0.325
>70	313	-0.006	-0.066, 0.054	369	-0.025	-0.085, 0.035	204	-0.003	-0.314, 0.308
P for trend			*0.94*			*0.90*			*0.64*
	Ln-sFlt-1 ng/mL (n=2513)			**Ln-sFlt-1 ng/mL** (n=2844)			**Ln-sFlt-1 ng/mL** (n=1695)		
0	661	Reference		744	Reference		459	Reference	
1-34	928	0.039	-0.014, 0.091	1052	0.020	-0.038, 0.078	616	0.010	-0.125, 0.145
35-69	610	0.028	-0.030, 0.085	680	0.027	-0.037, 0.092	400	0.061	-0.089, 0.210
>70	314	-0.025	-0.093, 0.044	368	-0.034	-0.110, 0.043	220	0.052	-0.125, 0.229
P for trend			*0.67*			*0.66*			*0.40*
	Ln-sFlt-1/PlGF ratio (n=2505)			**Ln-sFlt-1/PlGF ratio** (n=2844)			**Ln-sFlt-1/PlGF ratio** (n=1469)		
0	657	Reference		744	Reference		401	Reference	
1-34	926	**0.086***	**0.023, 0.150**	1052	**0.074†**	**0.005, 0.143**	520	0.097	-0.035, 0.228
35-69	610	0.051	-0.019, 0.121	680	0.030	-0.047, 0.106	357	**0.165†**	**0.022, 0.308**
>70	312	-0.020	-0.104, 0.064	368	-0.009	-0.099, 0.081	191	0.042	-0.130, 0.213
P for trend			*0.76*			*0.76*			*0.24*

Results from multivariable linear regression model, based on imputed data. P for trend was conducted by including lean fish consumption categories in the multivariable linear regression model. † P<0.05, * P < 0.01. **Abbreviations:** CI: confidence interval, n: number of participants, PlGF: placental growth factor, sFlt-1: soluble Flt-1. [a.] Adjusted for total energy intake, maternal age, gestational age at measurement, BMI at enrolment, foetal sex, parity, maternal education, smoking, and season of conception.

Supplementary Table 3.1.4. Associations between weekly maternal shellfish consumption and levels of angiogenic factors[a]

Shellfish consumption (energy-adjusted g/week)	First Trimester			Second Trimester			Cord Blood		
	n	Beta	95% CI	n	Beta	95% CI	n	Beta	95% CI
	Ln-PlGF pg/mL (n=2515)			**Ln-PlGF pg/mL** (n=2845)			**Ln-PlGF pg/mL** (n=1552)		
0	1569	Reference		1769	Reference		996	Reference	
1-13	462	-0.020	-0.066, 0.025	509	-0.002	-0.049, 0.045	276	-0.014	-0.257, 0.229
>14	484	0.021	-0.025, 0.066	567	0.004	-0.041, 0.050	280	-0.030	-0.272, 0.213
P for trend			*0.56*			*0.88*			*0.81*
	Ln-sFlt-1 ng/mL (n=2513)			**Ln-sFlt-1 ng/mL** (n=2844)			**Ln-sFlt-1 ng/mL** (n=1695)		
0	1569	Reference		1769	Reference		1077	Reference	
1-13	458	-0.027	-0.079, 0.026	509	-0.003	-0.062, 0.056	301	0.080	-0.057, 0.218
>14	486	-0.003	-0.055, 0.049	566	-0.026	-0.084, 0.032	317	-0.094	-0.231, 0.043
P for trend			*0.72*			*0.41*			*0.37*
	Ln-sFlt-1/PlGF ratio (n=2505)			**Ln-sFlt-1/PlGF ratio** (n=2844)			**Ln-sFlt-1/PlGF ratio** (n=1469)		
0	1565	Reference		1769	Reference		942	Reference	
1-13	457	-0.007	-0.071, 0.057	509	-0.001	-0.071, 0.069	262	0.113	-0.020, 0.246
>14	483	-0.026	-0.089, 0.038	566	-0.031	-0.099, 0.038	265	-0.084	-0.219, 0.051
P for trend			*0.44*			*0.42*			*0.53*

Results from multivariable linear regression model, based on imputed data. P for trend was conducted by including shellfish consumption categories in the multivariable linear regression model. † P < 0.05, * P < 0.01. **Abbreviations:** CI: confidence interval, n: number of participants, PlGF: placental growth factor, sFlt-1: soluble Flt-1. [a.] Adjusted for total energy intake, maternal age, gestational age at measurement, BMI at enrolment, foetal sex, parity, maternal education, smoking, and season of conception.

Chapter 3.2

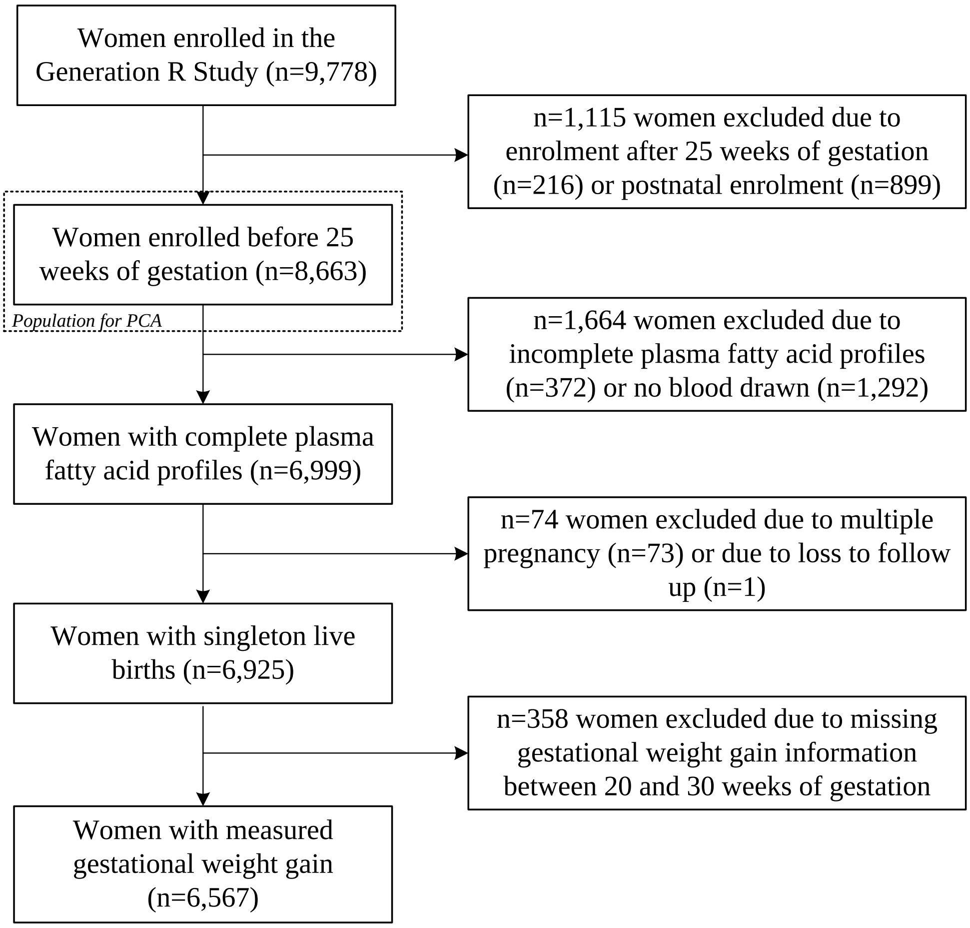
Circulating fatty acid patterns, gestational weight gain and hypertensive complications in pregnancy: The Generation R Study

Myrte J. Tielemans, Trudy Voortman*, Josje D. Schoufour*, Jolien Steenweg-de Graaff, Vincent W.V. Jaddoe, Oscar H. Franco, Eric A.P. Steegers, Henning Tiemeier, Jessica C. Kiefte-de Jong

* Contributed equally

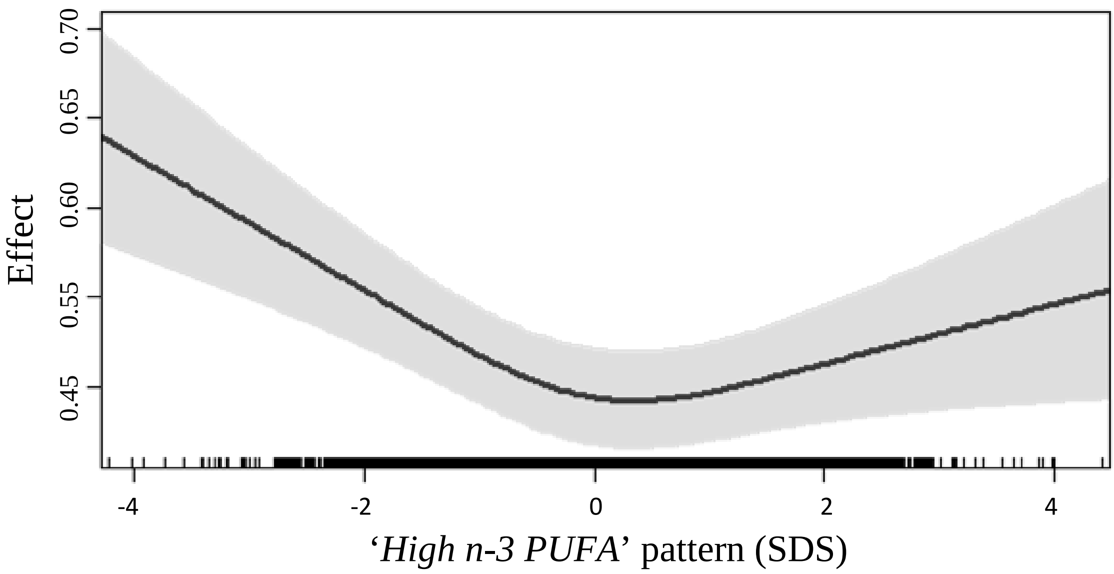
Submitted for publication

Supplementary Figure 3.2.1. Selection of participants: the Generation R Study, Rotterdam, the Netherlands (2002 – 2006)



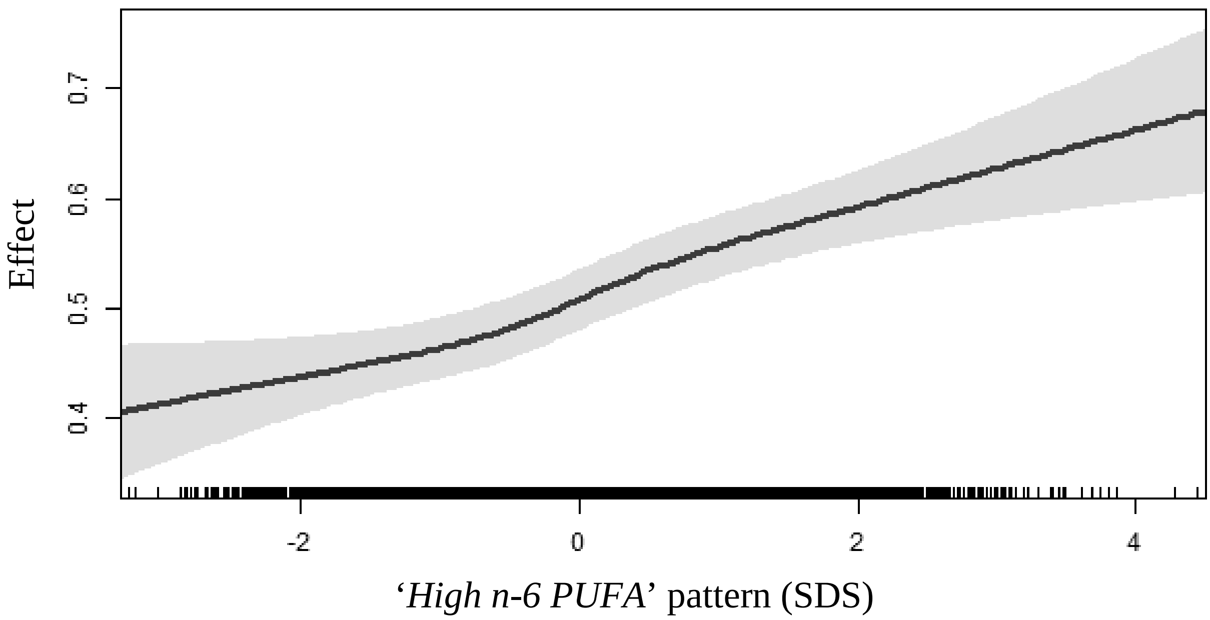
Abbreviation: PCA, principal component analysis

Supplementary Figure 3.2.2. Evaluation of non-linear associations of the '*High n-3 PUFA*' pattern with gestational weight gain (n=6567)



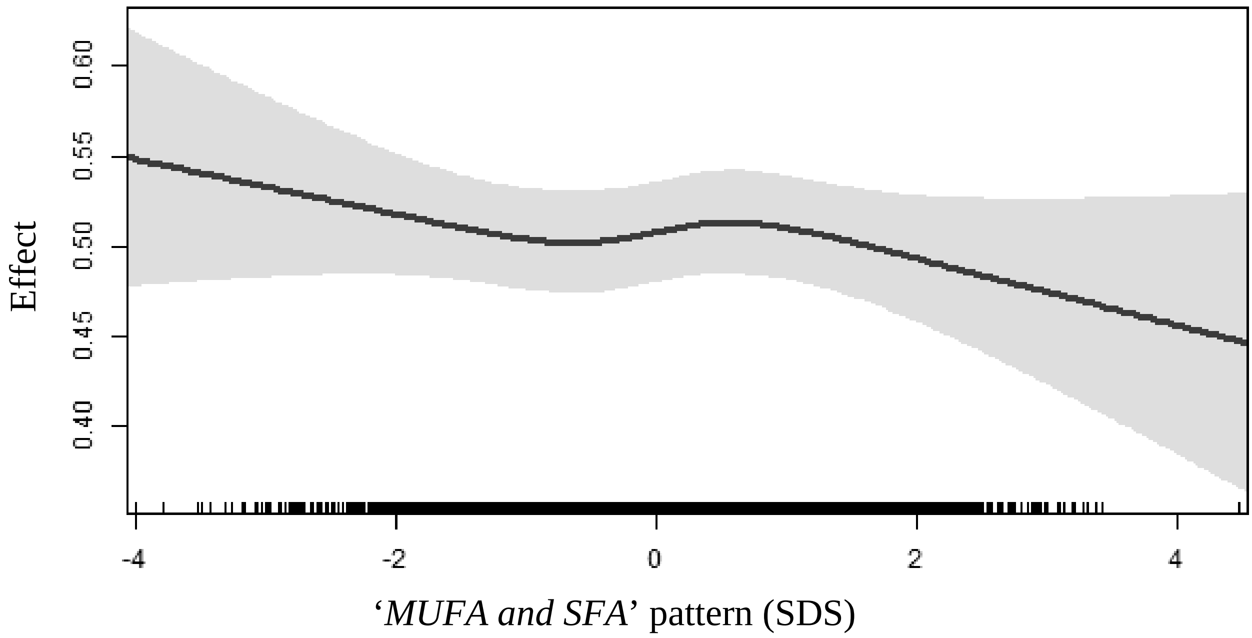
Multivariable linear regression using natural cubic splines (*df* = 2) improved the fit of the model significantly for the association of the '*High n-3 PUFA*' pattern with gestational weight gain (X^2=15.8, *P*<0.001). Adjusted for fetal sex, gestational age at birth, gestational age at fatty acid measurement, other fatty acid patterns, maternal age, ethnicity, educational level, household income, pre-pregnancy BMI, parity, alcohol consumption during pregnancy, maternal smoking during pregnancy, and folic acid supplementation. SDS: standard deviation score.

Supplementary Figure 3.2.3. Evaluation of non-linear association of the '*High n-6 PUFA*' pattern with gestational weight gain (n=6567)



Multivariable linear regression using natural cubic splines (*df* = 3) did not improve the fit of the model for the association of the '*High n-6 PUFA*' pattern with weekly gestational weight gain (X^2=2.3, *P*=0.32). Adjusted for gestational age at fatty acid measurement, other fatty acid patterns, maternal age, ethnicity, educational level, household income, pre-pregnancy BMI, parity, alcohol consumption during pregnancy, maternal smoking during pregnancy, folic acid supplementation and fetal sex. SDS: standard deviation score.

Supplementary Figure 3.2.4. Evaluation of non-linear association of the '*MUFA and SFA*' pattern with gestational weight gain (n=6567)



Multivariable linear regression using natural cubic splines (*df* = 3) did not improve the fit of the model for the association of the '*MUFA and SFA*' pattern with weekly gestational weight gain (X^2=3.0, *P*=0.22). Adjusted for gestational age at fatty acid measurement, other fatty acid patterns, maternal age, ethnicity, educational level, household income, pre-pregnancy BMI, parity, alcohol consumption during pregnancy, maternal smoking during pregnancy, folic acid supplementation and fetal sex. SDS: standard deviation score.

Supplementary Table 3.2.1. Spearman correlations between individual plasma fatty acids (in percentage of total plasma fatty acids) (n=6999)

14:0	1																					
P-value																						
16:0	**0.34**	1																				
P-value	<0.01																					
17:0	**0.05**	**-0.33**	1																			
P-value	<0.01	<0.01																				
18:0	**-0.19**	**-0.66**	**0.17**	1																		
P-value	<0.01	<0.01	<0.01																			
15:1n-5	**0.44**	**0.08**	**0.51**	**-0.15**	1																	
P-value	<0.01	<0.01	<0.01	<0.01																		
16:1n-7	**0.55**	**0.61**	**-0.24**	**-0.43**	**0.20**	1																
P-value	<0.01	<0.01	<0.01	<0.01	<0.01																	
18:1n-7	**-0.15**	0.02	0.01	**-0.30**	**0.09**	**0.16**	1															
P-value	<0.01	0.16	0.54	<0.01	<0.01	<0.01																
18:1n-9	**0.28**	**0.25**	**-0.11**	**-0.28**	**0.22**	**0.46**	**0.30**	1														
P-value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01															
20:1n-9	**-0.27**	**-0.42**	**0.26**	**0.06**	**0.05**	**-0.37**	**0.42**	**0.10**	1													
P-value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01														
18:3n-3	**0.30**	**0.07**	**-0.08**	**-0.12**	**0.16**	**0.19**	**0.10**	**0.33**	**0.09**	1												
P-value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01													
20:3n-3	**0.03**	**-0.06**	**0.09**	**-0.04**	**0.19**	-0.01	**0.33**	**0.10**	**0.19**	**0.17**	1											
P-value	<0.05	<0.01	<0.01	<0.01	<0.01	0.40	<0.01	<0.01	<0.01	<0.01												
20:5n-3	**0.22**	**0.17**	**0.14**	**-0.12**	**0.37**	**0.22**	**0.10**	**0.23**	0.02	**0.28**	**0.19**	1										
P-value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.05	<0.01	<0.01											
22:5n-3	**0.20**	**0.11**	**0.07**	**-0.14**	**0.21**	**0.24**	**0.15**	**0.22**	0.01	**0.26**	**0.20**	**0.53**	1									
P-value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.36	<0.01	<0.01	<0.01										
22:6n-3	**-0.08**	0.00	**0.20**	**-0.08**	**0.15**	**-0.09**	**0.21**	**-0.03**	**0.16**	-0.00	**0.17**	**0.61**	**0.39**	1								
P-value	<0.01	0.82	<0.01	<0.01	<0.01	<0.01	<0.01	<0.05	<0.01	0.68	<0.01	<0.01	<0.01									
18:2n-6	**-0.28**	**-0.47**	**0.06**	**0.25**	**-0.21**	**-0.59**	**-0.26**	**-0.46**	**0.19**	**-0.03**	**-0.18**	**-0.49**	**-0.42**	**-0.38**	1							
P-value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.05	<0.01	<0.01	<0.01	<0.01								
18:3n-6	**0.47**	**0.23**	**-0.05**	-0.02	**0.15**	**0.54**	**-0.27**	**0.16**	**-0.41**	**0.06**	**-0.07**	**0.11**	**0.11**	**-0.14**	**-0.36**	1						
P-value	<0.01	<0.01	<0.01	0.07	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01							
20:2n-6	-0.01	**-0.18**	**0.13**	**0.05**	-0.02	**-0.09**	**0.12**	**-0.17**	**0.33**	0.02	**0.03**	**-0.31**	**-0.19**	**-0.19**	**0.36**	**-0.16**	1					
P-value	0.30	<0.01	<0.01	<0.01	0.16	<0.01	<0.01	<0.01	<0.01	0.10	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01						
20:3n-6	**0.31**	**0.34**	**-0.18**	**-0.17**	**0.12**	**0.55**	**-0.07**	**0.19**	**-0.28**	**0.04**	-0.02	0.01	**0.06**	**-0.25**	**-0.35**	**0.34**	**0.15**	1				
P-value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.06	0.54	<0.01	<0.01	<0.01	<0.01	<0.01					
20:4n-6	**-0.28**	**-0.14**	**0.06**	**0.14**	**-0.17**	**-0.16**	**0.06**	**-0.33**	**-0.10**	**-0.40**	**0.08**	**-0.07**	**-0.10**	**0.09**	**-0.30**	**0.09**	**-0.32**	**-0.18**	1			
P-value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01				
22:4n-6	**0.10**	**0.08**	**-0.14**	-0.01	**-0.16**	**0.29**	**-0.04**	-0.01	**-0.28**	**-0.17**	0.01	**-0.30**	**0.12**	**-0.31**	**-0.28**	**0.35**	-0.00	**0.31**	**0.38**	1		
P-value	<0.01	<0.01	<0.01	0.33	<0.01	<0.01	<0.01	0.34	<0.01	<0.01	0.23	<0.01	<0.01	<0.01	<0.01	<0.01	0.97	<0.01	<0.01			
22:5n-6	**0.13**	**0.08**	**-0.02**	-0.02	-0.01	**0.20**	**-0.05**	**0.03**	**-0.19**	**-0.19**	0.01	**-0.37**	**-0.05**	**-0.33**	**-0.28**	**0.31**	0.00	**0.30**	**0.39**	**0.78**	1	
P-value	<0.01	<0.01	<0.05	0.06	0.52	<0.01	<0.01	<0.05	<0.01	<0.01	0.51	<0.01	<0.01	<0.01	<0.01	<0.01	0.73	<0.01	<0.01	<0.01		
20:3n-9	**0.30**	**0.27**	0.01	**-0.13**	**0.30**	**0.46**	**0.12**	**0.46**	**-0.11**	**0.13**	**0.18**	**0.29**	**0.35**	-0.01	**-0.56**	**0.34**	**-0.21**	**0.32**	**0.04**	**0.23**	**0.29**	1
P-value	<0.01	<0.01	0.39	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.26	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	
	14:0	**16:0**	**17:0**	**18:0**	**15:1n-5**	**16:1n-7**	**18:1n-7**	**18:1n-9**	**20:1n-9**	**18:3n-3**	**20:3n-3**	**20:5n-3**	**22:5n-3**	**22:6n-3**	**18:2n-6**	**18:3n-6**	**20:2n-6**	**20:3n-6**	**20:4n-6**	**22:4n-6**	**22:5n-6**	**20:3n-9**

Supplementary Table 3.2.2. Details of the multiple imputation process

	Multiple imputation
Software used	IBM SPSS statistics version 21
Imputation method and key settings	Fully conditional specification (Markov chain Monte Carlo method); maximum iterations: 10
No. of imputed data sets created	10
Variables included in the imputation procedure as both predictor variable as a variable to be imputed	Age at enrolment, ethnicity, gravidity, parity, educational level at enrolment, marital status, household income at enrolment, gestational age at enrolment, pre-pregnancy BMI, alcohol consumption during pregnancy, smoking during pregnancy, folic acid supplementation during pregnancy, maternal stress during pregnancy, nausea during 1st trimester, vomiting during 1st trimester, gestational age at birth, birth weight, standardized birth weight (Niklasson) and fetal sex.
Variables added as predictors (not used in the main analysis) of missing data to increase plausibility of missing at random assumption	'*High n-6 PUFA'* pattern, '*MUFA and SFA*' pattern, '*High n-3 PUFA'* pattern, ethnicity father of the child, educational level 6 years after enrolment, paternal education at enrolment, paternal education 6 years after enrolment, household income 6 years after enrolment, pre-pregnancy weight, weight at enrolment, gestational age at 1st visit, weight at 1st visit, height at 1st visit, gestational age at 2nd visit, weight at 2nd visit, height at 2nd visit, gestational age at 3rd visit, weight at 3rd visit, height at 3rd visit, smoking during 1st trimester, smoking during 2nd trimester, smoking during 3rd trimester, alcohol consumption during 1st trimester, alcohol consumption during 2nd trimester, alcohol consumption during 3rd trimester, energy intake, combined 4 items of the Dutch Healthy Diet-index, serum folate levels < 18 weeks of gestation, gestational weight gain between 1st and 2nd visit, gestational weight gain between 2nd and 3rd visit, weekly weight gain between 2nd and 3rd visit
Treatment of not normally distributed variables	Predictive mean matching
Treatment of binary/categorical variables	Logistic regression models
Population	For the multiple imputation we included those mothers with complete plasma fatty acid profiles (n=6,999)

Supplementary Table 3.2.3. Differences between population of analysis and eligible women not included in the analysis (n=8663)[1]

Subject characteristics	**Included** (n=6567)	**Excluded** (n=2096)	***P*-value**[2]
Age (years)	29.8 ± 5.2	29.3 ± 5.5	**0.002**
Missing	0	1 (0.0)	
Ethnicity			
Western	3716 (58.9)	1031 (54.6)	**0.001**
Non western	2598 (41.1)	858 (45.4)	
Missing	253 (3.9)	276 (9.9)	
Educational level			
Low and midlow	1571 (25.8)	557 (30.9)	**<0.001**
Midhigh	3090 (50.7)	856 (47.4)	
High	1436 (23.6)	392 (21.7)	
Missing	470 (7.2)	291 (13.9)	
Household income (Euro/month)			
< 2,200	2365 (45.1)	607 (47.3)	0.15
≥ 2,200	2880 (54.9)	675 (52.7)	
Missing	1322 (20.1)	814 (38.8)	
Parity			
0	3685 (56.6)	1079 (53.0)	**0.005**
≥1	2831 (43.4)	957 (47.0)	
Missing	51 (0.8)	60 (2.9)	
Pre-pregnancy BMI (kg/m^2)	23.6 ± 4.3	23.7 ± 4.5	0.42
Missing	1172 (17.8)	504 (24.1)	
Alcohol			
Never during pregnancy	2783 (48.2)	904 (52.8)	**0.001**
Until pregnancy was known	798 (13.8)	241 (14.1)	
Continued throughout pregnancy	2191 (38.0)	566 (33.1)	
Missing	795 (12.1)	385 (18.4)	
Smoking			
Never during pregnancy	4250 (72.6)	1259 (72.8)	0.93
Until pregnancy was known	517 (8.8)	148 (8.6)	
Continued throughout pregnancy	1085 (18.5)	323 (18.7)	
Missing	715 (10.9)	366 (17.5)	
Folic acid supplementation			
Started periconceptional	2011 (40.5)	552 (37.8)	**0.01**
Started first 10 weeks	1566 (31.5)	443 (30.3)	
No supplementation	1391 (28.0)	467 (31.9)	
Missing	1599 (24.3)	634 (30.2)	
Energy intake (kcal/day)	2041 ± 568	2028 ± 572	0.48
Missing	1582 (24.1)	759 (36.2)	
DHD-index (maximum score: 40)	22.4 ± 5.7	22.1 ± 6.0	0.13
Missing	1582 (24.1)	759 (36.2)	

[1] Values represent n (%), mean ± SD, median (interquartile range). [2.] Differences between continuous variables tested using independent student t-test and between categorical variables were tested using Chi-square statistics. **Abbreviations**: BMI: body mass index; DHD-index: Dutch Healthy Diet-index; GWG: gestational weight gain.

Supplementary Table 3.2.4. Association of plasma fatty acid patterns with mid-pregnancy adequacy of gestational weight gain (n=6567)[1]

	Mid-pregnancy adequacy of GWG				
	Inadequate GWG (n=1490)		**Adequate GWG** (n=1405)	**Excessive GWG** (n=3672)	
	Crude[1]	**Multivariable**[2]		**Crude**[1]	**Multivariable**[2]
Plasma fatty acid patterns	OR (95%CI)	OR (95%CI)		OR (95%CI)	OR (95%CI)
'High n-6 PUFA' (per SD)	0.80 (0.74, 0.86)*	0.78 (0.72, 0.85)*	1.00	1.13 (1.06, 1.20)*	1.11 (1.04, 1.19)*
'MUFA and SFA' (per SD)	0.99 (0.91, 1.06)	1.01 (0.93, 1.09)	1.00	1.04 (0.97, 1.11)	1.00 (0.93, 1.07)
'High n-3 PUFA' (per SD)	0.97 (0.90, 1.04)	1.03 (0.95, 1.11)	1.00	0.96 (0.90, 1.07)	0.95 (0.88, 1.01)

Results from multinomial logistic regression analyses. Odds ratios reflect difference in odds to have an inadequate or excessive GWG as compared with adequate mid-pregnancy GWG. [1.] Adjusted for gestational age at measurements and other fatty acid patterns. [2.]Crude model additionally adjusted for maternal age, ethnicity, educational level, household income, pre-pregnancy BMI, parity, alcohol consumption during pregnancy, maternal smoking during pregnancy, folic acid supplementation and fetal sex. * Statistical significant result (*P*-value <0.05). **Abbreviations**: CI: confidence interval, GWG: gestational weight gain, MUFA: mono-unsaturated fatty acids, OR: odds ratio, PUFA: poly-unsaturated fatty acids, SD: standard deviation, SFA: saturated fatty acids

Supplementary Table 3.2.5. Association of plasma fatty patterns with mid-pregnancy gestational weight gain, stratified by pre-pregnancy BMI and ethnicity (n=6567)[1]

	Gestational weight gain (g/week) between 20-30 weeks of gestation			
	BMI < 25 kg/m²		**BMI ≥ 25 kg/m²**	
	Western (n=2986)	**Non-Western** (n=1810)	**Western** (n=876)	**Non-Western** (n=895)
Plasma fatty acid patterns	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
'High n-6 PUFA' (per SD)	28 (18, 38)*	40 (26, 53)*	60 (36, 83)*	75 (52, 98)*
'MUFA and SFA' (per SD)	-3 (-13, 8)	6 (-7, 20)	-16 (-40, 8)	-4 (-25, 16)
'High n-3 PUFA' (per SD)	-3 (-13, 8)	-12 (-25, 1)	-6 (-29, 17)	-23 (-43, -2)

Results from multivariable linear regression analyses. Beta-coefficients reflect the change in gestational weight gain (g/week) per standard deviation increase in plasma fatty acid pattern. [1.] Adjusted for gestational age at both measurements, other fatty acid patterns, maternal age, educational level, household income, pre-pregnancy BMI, parity, alcohol consumption during pregnancy, smoking during pregnancy, folic acid supplementation and fetal sex. * Statistical significant result (*P*-value <0.05). **Abbreviations**: BMI: body mass index, CI: confidence interval, MUFA: mono-unsaturated fatty acids, PUFA: poly-unsaturated fatty acids, SD: standard deviation, SFA: saturated fatty acids

Supplementary Table 3.2.6. Association of plasma fatty patterns with pregnancy-induced hypertension, stratified by ethnicity (n=6224)[1]

	Pregnancy-induced hypertension (cases n=226)	
	Western (cases n=167)	**Non-Western** (cases n=59)
Plasma fatty acid patterns	OR (95% CI)	OR (95% CI)
'High n-6 PUFA' (per SD)	1.09 (0.92, 1.31)	0.91 (0.70, 1.19)
'MUFA and SFA' (per SD)	1.01 (0.85, 1.20)	0.94 (0.72, 1.23)
'High n-3 PUFA' (per SD)	0.91 (0.76, 1.10)	1.42 (1.08, 1.87)*

Results from multivariable logistic regression. Odds ratios reflect the odds of having pregnancy-induced hypertension per SD higher score on that fatty acid pattern. [1.] Adjusted for gestational age at both measurements, maternal age, educational level, household income, pre-pregnancy BMI, parity, alcohol consumption during pregnancy, smoking during pregnancy, folic acid supplementation and fetal sex. * Statistical significant result (*P*-value <0.05). **Abbreviations**: CI: confidence interval, MUFA: mono-unsaturated fatty acids, OR: odds ratio, PUFA: poly-unsaturated fatty acids, SD: standard deviation, SFA: saturated fatty acids

Supplementary Table 3.2.7. Association of plasma fatty acid patterns with mid-pregnancy gestational weight gain, when taking into account early-pregnancy gestational weight gain (n=5131)

	GWG (g/week) between 20 – 30 weeks of gestation (n = 5131)	
	Adjusted[1]	**Additionally adjusted for early GWG[2]**
Plasma fatty acid patterns	β (95%CI)	β (95%CI)
'High n-6 PUFA' (per SD)	40 (33, 48)*	41 (33, 48)*
'MUFA and SFA' (per SD)	0 (-8, 8)	-1 (-8, 7)
'High n-3 PUFA' (per SD)	-10 (-18, -2)*	-11 (-18, -3)*

Results from multivariable linear regression analyses. Beta-coefficient reflects the change in gestational weight gain (g/week) per standard deviation increase in plasma fatty acid pattern. [1.] Adjusted for gestational age at measurements, other fatty acid patterns, maternal age, ethnicity, educational level, household income, pre-pregnancy BMI, parity, alcohol consumption during pregnancy, maternal smoking during pregnancy, folic acid supplementation, and fetal sex. [2.] Adjusted model that was additionally adjusted for early GWG between 12 and 20 weeks of gestation. **Abbreviations**: CI: confidence interval, MUFA: mono-unsaturated fatty acids, PUFA: poly-unsaturated fatty acids, SD: standard deviation, SFA: saturated fatty acids

Supplementary Table 3.2.8. Association of plasma fatty acid patterns with mid-pregnancy gestational weight gain in women with available fetal ultrasound measurements (n=6380)

	GWG (g/week) between 20 – 30 weeks of gestation (n = 6380)		
	Crude[1]	**Multivariable**[2]	**Model 2**[3]
Plasma fatty acid patterns	β (95%CI)	β (95%CI)	β (95%CI)
'High n-6 PUFA' (per SD)	42 (35, 49)*	42 (35, 49)*	41 (35, 48)*
'MUFA and SFA' (per SD)	-1 (-8, 6)	-2 (-9, 5)	-3 (-10, 4)
'High n-3 PUFA' (per SD)	-3 (-10, 4)	-9 (-16, -2)*	-9 (-16, -1)*

Results from multivariable linear regression analyses. Beta-coefficient reflects the change in gestational weight gain (g/week) per standard deviation increase in plasma fatty acid pattern. [1.] Adjusted for gestational age at measurements and other fatty acid patterns. [2.] Crude model additionally adjusted for maternal age, ethnicity, educational level, household income, pre-pregnancy BMI, parity, alcohol consumption during pregnancy, maternal smoking during pregnancy, folic acid supplementation, and foetal sex. [3.] Multivariable model, additionally adjusted for change in estimated fetal weight. * Statistical significant result (*P*-value <0.05). **Abbreviations**: CI: confidence interval, MUFA: mono-unsaturated fatty acids, PUFA: poly-unsaturated fatty acids, SD: standard deviation, SFA: saturated fatty acids

Supplementary Table 3.2.9. Association of plasma fatty acid patterns with gestational weight gain between 20 and 39 weeks of gestation in women with available information on birthweight and placental weight (n=2478)

	GWG (g/week) between 20 – 39 weeks of gestation (n = 2478)		
	Crude[1]	**Multivariable**[2]	**Model 2**[3]
Plasma fatty acid patterns	β (95%CI)	β (95%CI)	β (95%CI)
'High n-6 PUFA' (per SD)	24 (-9, 57)	28 (-7, 62)	28 (-7, 62)
'MUFA and SFA' (per SD)	-15 (-49, 20)	-17 (-53, 18)	-16 (-52, 19)
'High n-3 PUFA' (per SD)	11 (-23, 45)	-4 (-40, 31)	-5 (-40, 31)

Results from multivariable linear regression analyses. Beta-coefficient reflects the change in gestational weight gain (g/week) per standard deviation increase in plasma fatty acid pattern. [1.] Adjusted for gestational age at measurements and other fatty acid patterns. [2.] Crude model, additionally adjusted for maternal age, ethnicity, educational level, household income, pre-pregnancy BMI, parity, alcohol consumption during pregnancy, maternal smoking during pregnancy, folic acid supplementation, and fetal sex. [3.] Multivariable model additionally adjusted for birthweight and placental weight. All results were non-significant. **Abbreviations**: CI: confidence interval, MUFA: mono-unsaturated fatty acids, PUFA: poly-unsaturated fatty acids, SD: standard deviation, SFA: saturated fatty acids

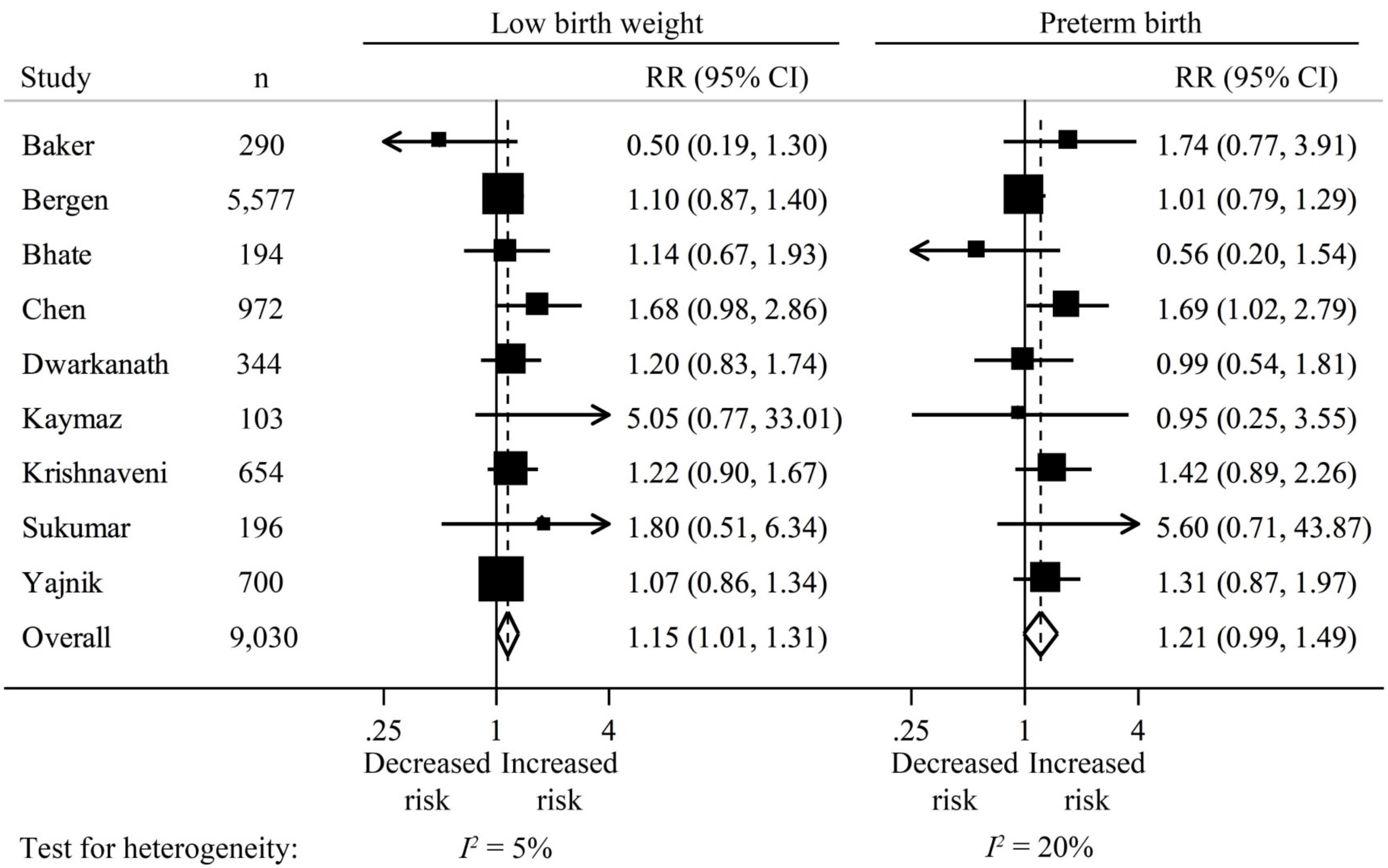
Chapter 3.3

Maternal vitamin B12 in pregnancy and risk of preterm birth and low birth weight: A systematic review and individual participant data meta-analysis

Tormod Rogne, Myrte J. Tielemans, Mary Foong-Fong Chong, Chittaranjan S. Yajnik, Ghattu V. Krishnaveni, Lucilla Poston, Vincent W.V. Jaddoe, Eric A.P. Steegers, Suyog Joshi, Yap-Seng Chong, Keith M. Godfrey, Fabian Yap, Raquel Yahyaoui, Tinku Thomas, Gry Hay, Marije Hogeveen, Ahmet Demir, Ponnusamy Saravanan, Eva Skovlund, Marit P. Martinussen, Geir W. Jacobsen, Oscar H. Franco, Michael B. Bracken, Kari R. Risnes

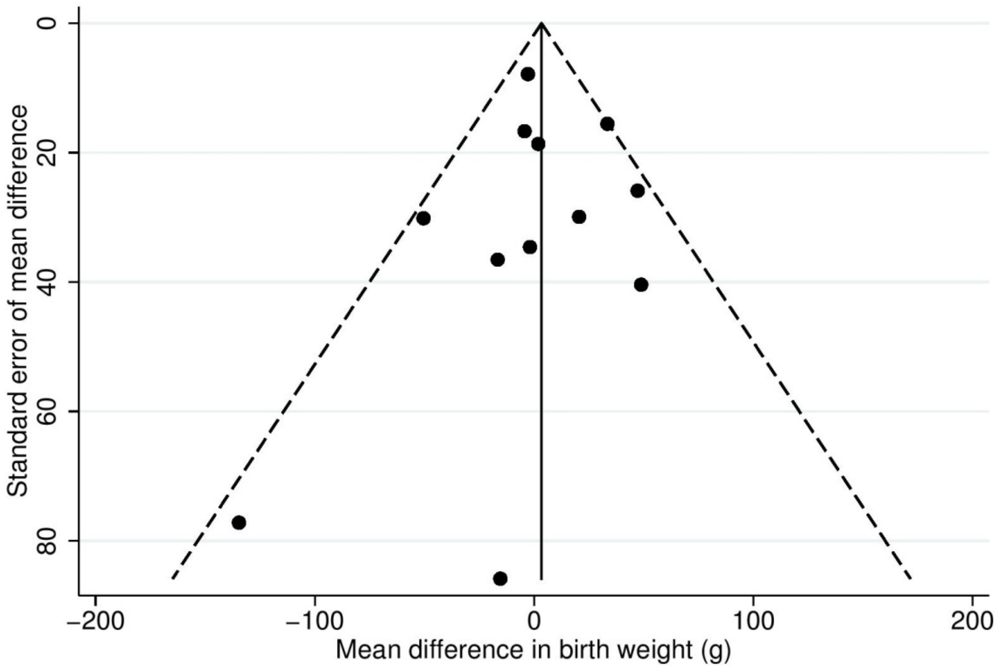
Submitted for publication

Supplementary Figure 3.3.1. Forest plot presenting the association between B12-deficiency and the risk of low birth weight (left panel) and preterm birth (right panel)



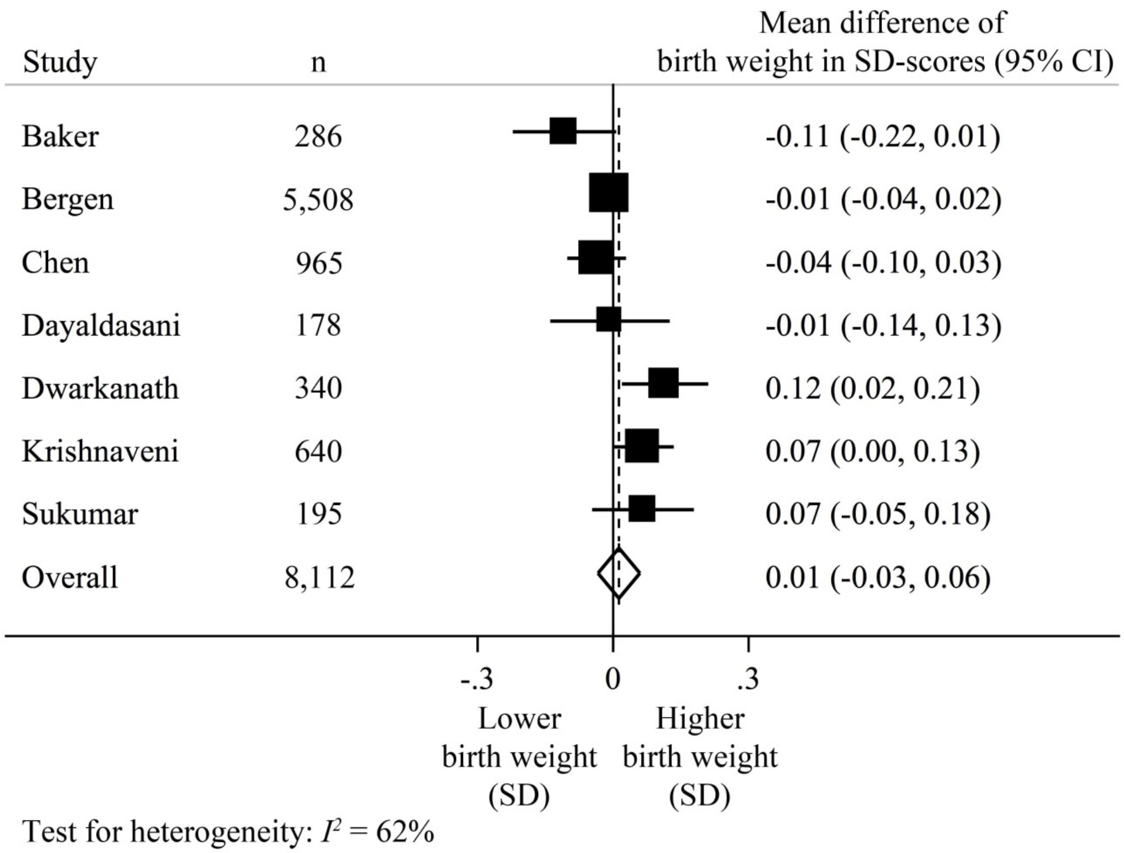
Meta-analysis of studies of the association between vitamin B12-deficiency and the risk of low birth weight (left panel) and preterm birth (right panel) after adjustment for maternal age, parity and body mass index or weight. Effect estimate expressed as risk ratio of the outcome comparing B12 deficient to non-deficient. CI, confidence interval; n, number pregnancies; RR, risk ratio.

Supplementary Figure 3.3.2. Funnel plot of studies evaluating the association between B12 and birth weight



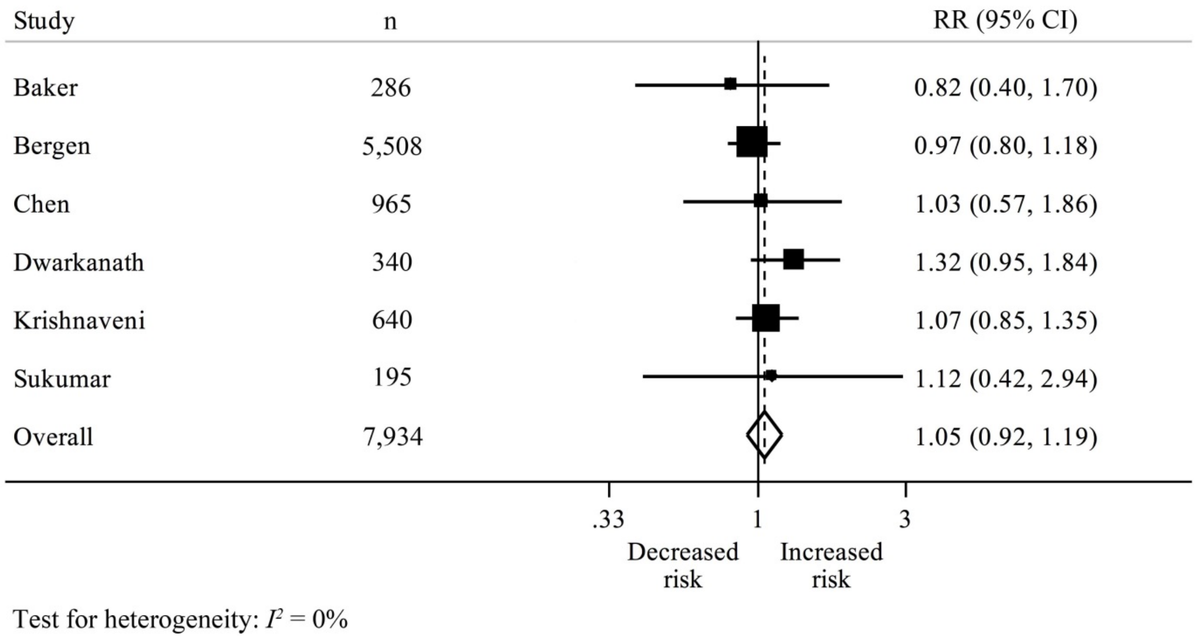
Funnel plot of studies evaluating the association between vitamin B12 and birth weight after adjustment for maternal age, parity and body mass index or weight. Individual studies are represented by solid dots, and the pseudo-95% confidence interval by broken lines.

Supplementary Figure 3.3.3. Forest plot presenting the association between B12 and birth weight SD score



Meta-analysis of studies of the association between vitamin B12 and birth weight standard deviation scores (i.e. accounting for length of gestation and sex) after adjustment for maternal age, parity and body mass index or weight. Effect estimate expressed as change in birth weight standard deviation score per one standard deviation increase of vitamin B12. CI, confidence interval; n, number pregnancies.

Supplementary Figure 3.3.4. Forest plot presenting the association between B12-deficiency and the risk of small-for-gestational-age birth



Meta-analysis of studies of the association between vitamin B12-deficiency and the risk of small-for-gestational-age birth after adjustment for maternal age, parity and body mass index or weight. Effect estimate expressed as risk ratio of small-for-gestational-age birth comparing B12-deficient to non-deficient. CI, confidence interval; n, number pregnancies; RR, risk ratio.

Supplementary Table 3.3.1 Study characteristics of eligible studies not included in the meta-analysis[a]

Study	n	Country	Study years	B12 analysis method	Week of B12 measurement, range, median	Main objectives
Karakantza 2008[36]	392	Greece	2004-2006	NA	6-8	Studied three thrombophilic mutations in relation to pregnancy outcomes (including IUGR).
Lee 2014[38]	T2: 83 T3: 42	USA	2006-2012	RIA	T2: 24·4 ± 2·2[b] T3: 29·7 ± 1·8[b]	Studied changes in iron status in pregnant adolescents, and iron status in relation to hepcidin and inflammatory markers.
López-Quesada 2004[37]	94	Spain	2000-2001	ECL	24-24, median 24	Studied uterine artery Doppler velocimetry in relation to pregnancy outcomes and homocysteine, folate and B12.
Neumann 2013[39]	138	Kenya	1984-1986	NA	NA	Studied B12 dietary intake during pregnancy and lactation in relation to pregnancy outcome, breast milk B12 concentration and infant growth and development.

Studies are referred to according to their citation number in the text. **Abbreviations:** ECL, electroluminescence; IUGR, intrauterine growth restriction; n, number of pregnancies; NA, not available; RIA, radioimmunoassay; T2, 2nd trimester; T3, 3rd trimester. [a.] Eligible studies were not included in the systematic review or the meta-analyses when individual participant data or results from requested reanalyses were not provided, appropriate data and results were not available in the original report, and when no association between B12 and birth weight or length of gestation was presented; [b.] mean ± SD.

Supplementary Table 3.3.2 Risk of bias of studies included in the meta-analysis

Study	1	2	3	4	5	6	7	Total
Baker 2009[18]	1	1	1	0	1	1	0	5
Bergen 2012[19]	1	1	1	1	1	1	1	7
Bhate 2012[32]	1	1	1	1	1	1	1	7
Chen 2015[20]	1	1	1	1	1	1	1	7
Dayaldasani 2014[33]	1	1	1	1	1	?	1	6
Dwarkanath 2013[21]	1	1	1	1	1	1	0	6
Furness 2013[22]	1	1	1	0	1	1	1	6
Halicioglu 2012[23]	1	0	0	1	1	1	1	5
Hay 2010[34]	1	1	1	0	1	1	0	5
Hogeveen 2010[24]	1	0	1	1	1	1	0	5
Kaymaz 2011[35]	1	1	1	1	1	1	?	6
Krishnaveni 2013[25]	1	1	1	1	1	1	0	6
Mamabolo 2006[26]	1	0	0	1	1	1	1	5
Relton 2005[27]	1	0	0	1	?	1	0	3
Sukumar 2011[28]	1	1	1	1	1	1	0	6
Takimoto 2007[29]	1	1	1	1	1	1	0	6
Wu 2013[30]	1	0	0	?	1	1	?	3
Yajnik 2008[31]	1	1	1	1	1	1	1	7

Each item was scored "1" (i.e. "yes"), "0" (i.e. "no") or "?" (i.e. "uncertain"), where only the answer "1" scored 1 point. The following questions were evaluated: 1: Was B12 ascertained irrespective of the risk of low birth weight birth or preterm birth, and otherwise not prone to selection bias?; 2: Was the study controlled for maternal body mass index or weight either by matching or by statistical methods?; 3: Was the study controlled for previous low birth weight birth or preterm birth, or maternal age, parity, socioeconomic status, smoking habits, ethnicity, vegetarian status or B12 supplement use (at least two of these) either by matching or by statistical methods? In addition, because of potential over-adjustment, if a study adjusted for levels of folate, homocysteine or methylmalonic acid, they earned no point on this item (even if they had adjusted for two or more of the mentioned confounders); 4: Was the exposed cohort truly or somewhat representative of the average pregnant population in the community?; 5: Did the women with B12-deficiency receive the same follow-up and interventions as the non-deficient women?; 6: Was the outcome assessed by independent or blind assessment, or by secure records or record linkage?; 7: Was follow-up >80% or was any description provided for those lost to follow-up? Studies are referred to according to their citation number in the text.

Supplementary Table 3.3.3 Pooled results from subgroup and sensitivity analyses of B12 SD score on birth weight

Analysis	Number of studies	Number of pregnancies	Birth weight (g) per 1 SD increase in B12 (95% CI)	I^2
Alternative models				
Crude	12[18-21,24,25,28,31-35]	9,819	-4·9 (-15·7, 5·8)	0
Adjusting for BMI or weight[a]	9[18-21,25,28,33-35]	8,505	7·8 (-9·0, 24·6)	28
Adjusting for maternal age,[b] parity,[c] and BMI or weight[a] ("main model")	12[18-21,25,28,29,31-35]	9,406	5·1 (-10·9, 21·0)	30
Adjusting for maternal age,[b] parity,[c] BMI or weight,[a] and smoking[d]	10[18-20,25,28,31-35]	8,420	0·7 (-15·5, 16·9)	29
Adjusting for maternal age,[b] parity,[c] BMI or weight,[a] smoking[d] and education[e] ("extended model")	4[18,19,25,34]	5,948	-1·9 (-40·5, 36·6)	76
Adjusted main model among those with data on smoking	10[18-20,25,28,31-35]	8,420	2·4 (-8·8, 13·6)	0
Adjusted main model among those with data on the extended model	4[18,19,25,34]	5,948	4·1 (-27·8, 35·9)	65
Adjusting for BMI[b] among those with weight	4[19,20,25,33]	7,416	6·3 (-10·5, 23·1)	26
Adjusting for weight[b] among those with BMI	4[19,20,25,33]	7,416	8·2 (-6·2, 22·5)	13
Fixed effects model	12[18-21,25,28,29,31-35]	9,406	3·4 (-7·4, 14·1)	30
Trimester of B12 measurement				
1st trimester	4[19,21,28,33]	1,461	19·1 (-13·1, 51·4)	0
2nd trimester	8[19-21,25,28,33-35]	6,217	11·5 (-11·4, 34·5)	34
1st and 2nd trimester	10[19-21,25,28,29,31,33-35]	8,325	12·1 (-9·7, 33·8)	47
3rd trimester	6[18,20,21,25,28,29]	1,140	-0·1 (-31·0, 30·8)	14
Measurement technique[f]				
Radioimmunoassay	2[18,28]	459	-16·1 (-84·9, 52·7)	61
Electroluminescence assay	7[19-21,28,29,33,35]	7,256	0·0 (-18·3, 18·4)	14
Microbiologic assay	4[25,31,32,34]	1,691	20·4 (-0·9, 41·7)	0
Country income category				
High income	7[18-20,28,29,33,34]	7,411	-5·5 (-24·8, 13·7)	23
Middle or low income	5[21,25,31,32,35]	1,995	22·2 (2·1, 42·4)	0
Maternal BMI				
BMI <25 kg/m^2	6[19,20,25,28,33,35]	4,728	-1·9 (-16·4, 12·5)	0
BMI ≥25 kg/m^2	6[19,20,25,28,33,35]	2,945	17·5 (-17·6, 52·5)	41

Pooled results of the mean difference (95% CI) in birth weight (g) per 1 SD increase in maternal B12. All analyses are linear regression analyses with random effects, and adjusted for the main model (i.e. maternal age, BMI (weight if missing BMI), and parity (nulliparous yes/no)) unless otherwise specified. Studies included in the analyses are referred to according to their citation number in the text. BMI, body mass index; CI, confidence interval; SD, standard deviation. [a.] BMI and weight (if missing BMI) as continuous covariates; [b.] continuous covariate; [c.] nulliparous (yes/no); [d.] smoking during pregnancy (yes/no); [e.] completed high school (yes/no); [f.] Sukumar 2011[28] measured n=182 by radioimmunoassay and n=27 by electroluminescence assay.

Supplementary Table 3.3.4. B12-deficiency and B12 tertiles in relation to birth weight

Analysis	Number of studies	Number of pregnancies	Number of exposed	Mean difference in birth weight (g) in exposed versus non-exposed (95% CI)	I^2
B12-deficiency					
IPD, crude	9[18-21,24,25,28,34,35]	8,735	3,006	9·3 (-14·9, 33·5)	0
IPD, main model[a]	8[18-21,25,28,34,35]	8,279	2,846	-14·5 (-39·1, 10·2)	0
Aggregate, crude[b]	4[23,30-32]	1,323	695	63·8 (-32·6, 159·9)	69
Aggregate, main model[a]	2[31,32]	894	542	-1·36 (-53·5, 50·8)	0
IPD + aggregate, crude	13[18-21,23-25,28,30-32,34,35]	10,058	3,701	23·3 (-6·7, 53·4)	24
IPD + aggregate, main model[a]	10[18-21,25,28,31,32,34,35]	9,173	3,388	-14·0 (-36·3, 8·3)	0
B12 tertiles[c]					
IPD, crude	10[18-21,24,25,28,33-35]	5,942	3,179	18·9 (-15·8, 53·8)	8
IPD, main model[a]	9[18-21,25,28,33-35]	5,633	2,997	-16·6 (-54·5, 21·2)	11

Pooled results of the mean difference in birth weight (g) in exposed versus non-exposed pregnancies. All analyses are random effects models and crude, unless otherwise specified. Studies included in the analyses are referred to according to their citation number in the text. CI, confidence interval; IPD, individual participant data. [a.] adjusted for maternal age, body mass index (weight if missing body mass index), and parity (nulliparous yes/no); [b.] B12-deficiency defined as <148 pmol/L except for Halicioglu 2012[23] (<118 pmol/L); [c.] lowest tertile (i.e. exposed) versus highest tertile.

Supplementary Table 3.3.5 Pooled results from subgroup and sensitivity analyses of B12 SD score and the risk of preterm birth

Analysis	Number of studies	Number of pregnancies	Number of preterm births	Risk ratio of preterm birth per 1 SD increase in B12 (95% CI)	I^2
Alternative models					
Crude	11[18-21,24,25,28,31-33,35]	9,747	643	0·90 (0·81, 1·00)	15
Adjusting for BMI or weight[a]	8[18-21,25,28,33,35]	8,362	510	0·89 (0·81, 0·98)	0
Adjusting for maternal age,[b] parity,[c] and BMI or weight[a] ("main model")	10[18-21,25,28,31-33,35]	9,291	615	0·89 (0·82, 0·97)	0
Adjusting for maternal age,[b] parity,[c] BMI or weight,[a] and smoking[d]	9[18-20,25,28,31-35]	8,365	531	0·90 (0·82, 0·99)	0
Adjusting for maternal age,[b] parity,[c] BMI or weight,[a] smoking[d] and education[e] ("extended model")	3[18,19,25]	5,813	304	0·92 (0·82, 1·03)	0
Adjusted main model among those with data on smoking	9[18-20,25,28,31-33,35]	8,365	531	0·89 (0·81, 0·98)	0
Adjusted main model among those with data on the extended model	3[18,19,25]	5,813	304	0·91 (0·81, 1·02)	0
Adjusting for BMI[b] among those with data on weight	4[19,20,25,33]	7,416	424	0·91 (0·82, 1·01)	0
Adjusting for weight[b] among those with data on BMI	4[19,20,25,33]	7,416	424	0·90 (0·81, 1·00)	0
Fixed effects model	10[18-21,25,28,31-33,35]	9,291	615	0·89 (0·82, 0·97)	0
Non-robust error variance	10[18-21,25,28,31-33,35]	9,291	615	0·90 (0·82, 0·99)	0
Logistic regression	10[18-21,25,28,31-33,35]	9,285	615	0·88 (0·80, 0·97)[f]	0
Trimester of B12 measurement					
1st trimester	3[19,21,33]	1,453	107	1·01 (0·84, 1·20)	0
2nd trimester	6[19-21,25,28,35]	6,061	344	0·85 (0·67, 1·07)	57
1st and 2nd trimesters	8[19-21,25,28,31,33,35]	8,190	522	0·86 (0·71, 1·05)	45
3rd trimester	5[18,20,21,25,28]	1,058	86	0·86 (0·70, 1·06)	4
Measurement technique					
Radioimmunoassay	2[18,28]	459	29	0·60 (0·33, 1·07)	56
Electroluminescence assay	5[19-21,33,35]	7,178	418	0·93 (0·83, 1·04)	0
Microbiologic assay	3[25,31,32]	1,627	168	0·86 (0·73, 1·02)	0
Country income category					
High income	5[18-20,28,33]	7,217	391	0·87 (0·74, 1·02)	19
Middle or low income	5[21,25,31,32,35]	2,074	224	0·88 (0·76, 1·02)	0
Maternal BMI					
BMI <25 kg/m^2	6[19,20,25,28,33,35]	4,728	241	0·90 (0·81, 1·01)	0
BMI ≥25 kg/m^2	5[19,20,25,28,33]	2,913	200	0·81 (0·63, 1·05)	44

Pooled results of the risk ratio (95% CI) of preterm birth per 1 SD increase in maternal B12. All analyses are Poisson regression analyses with random effects, robust error variance and adjusted for the main model (maternal age, BMI (weight if missing BMI), and parity (nulliparous yes/no)) unless otherwise specified. Studies included in the analyses are referred to according to their citation number in the text. BMI, body mass index; CI, confidence interval; SD, standard deviation. [a.] BMI and weight (if missing BMI) as continuous covariates; [b.] continuous covariate; [c.] nulliparous (yes/no); [d.] smoking during pregnancy (yes/no); [e.] completed high school (yes/no); [f.] odds ratio.

Supplementary Table 3.3.6 Level of B12 in small-for-gestational-age and non-small-for-gestational-age pregnancies

Analysis	Number of studies	Number of pregnancies	Number of SGA[a] births	Mean difference in B12 (pmol/L) in SGA versus non-SGA (95% CI)	I^2
IPD	8[18-21,24,25,28,33]	8,561	882	3·3 (-3·4, 9·9)	0
Aggregate	2[22,26]	303	87	-11·7 (-47·4, 24·1)	49
IPD + aggregate	10[18-22,24-26,28,33]	8,864	969	2·4 (-3·9, 8·7)	0

Pooled results of the mean difference in maternal B12 (pmol/L) in SGA versus non-SGA pregnancies. All analyses are random effects models and crude. Studies included in the analyses are referred to according to their citation number in the text. CI, confidence interval; IPD, individual participant data; SGA, small-for-gestational-age. [a], SGA defined as birth weight <10th centile after taking sex and length of gestation into account, with the following exceptions: In Furness 2013,[22] SGA was defined as "serial tapering of growth in abdominal circumference and of estimated fetal weight below the 10th centile of population-based growth charts", and in Mamabolo 2006,[26] SGA was defined as birth weight in the 1st tertile (mean 2,940 g).

Chapter 4.1

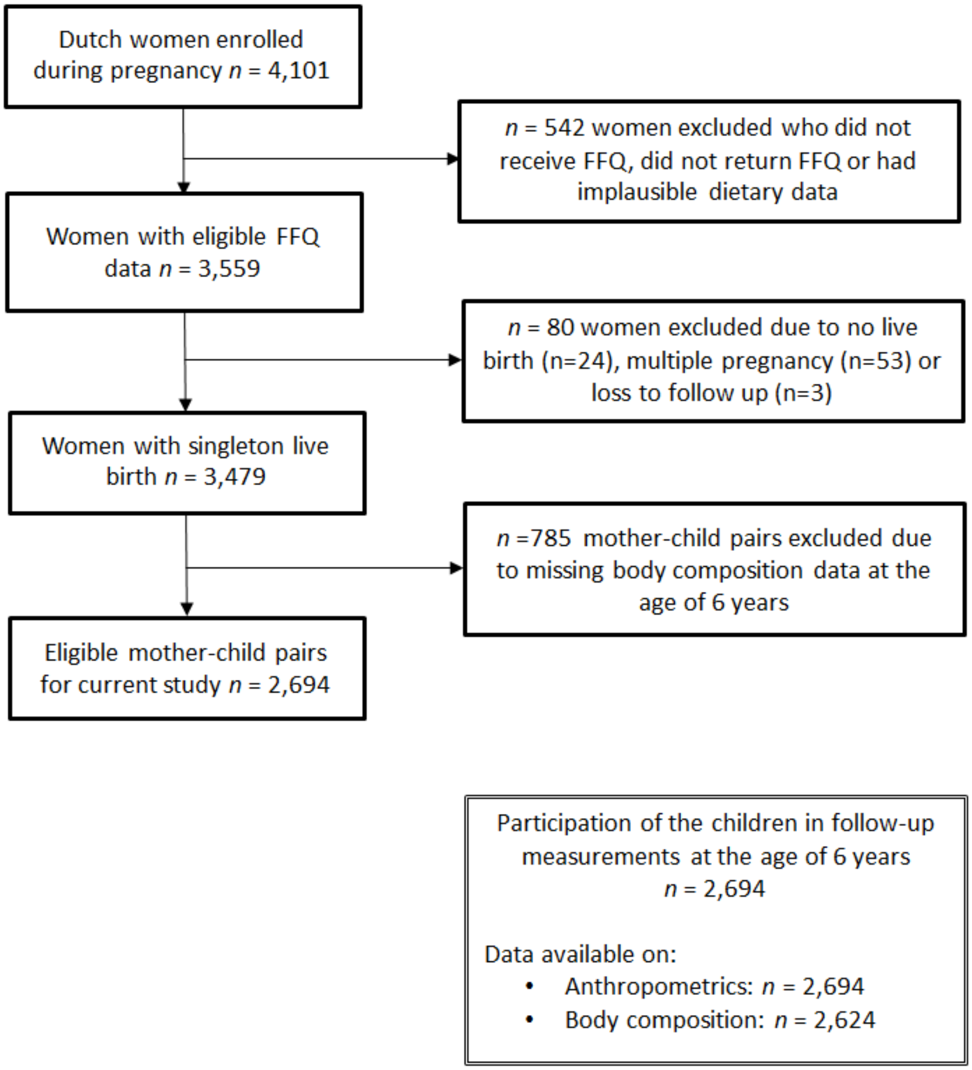
Protein intake during pregnancy and offspring body composition at 6 years: The Generation R Study

Myrte J. Tielemans, Eric A.P. Steegers*, Trudy Voortman*, Vincent W.V. Jaddoe, Fernando Rivadeneira, Oscar H. Franco, Jessica C. Kiefte-de Jong

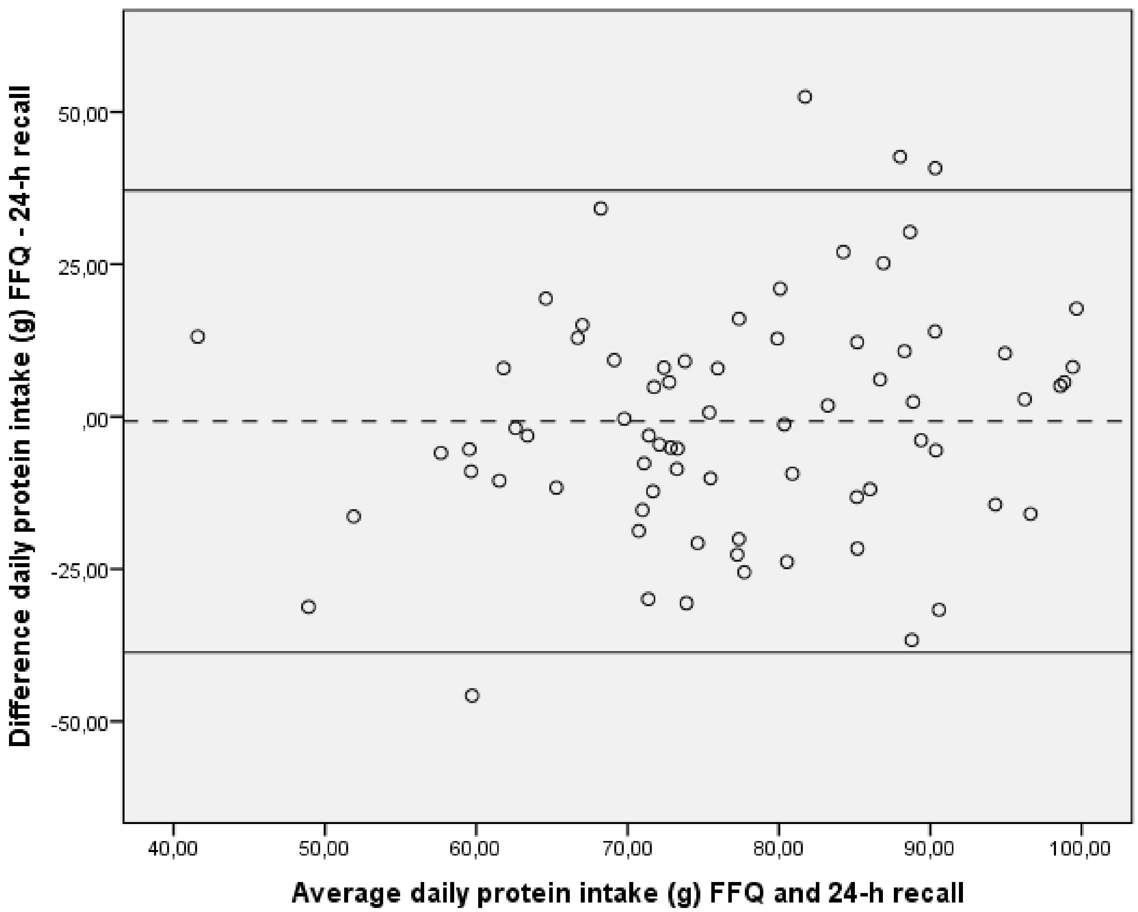
* Contributed equally

In revision (European Journal of Nutrition)

Supplementary Figure 4.1.1. Flow chart of the study population: the Generation R Study, Rotterdam, the Netherlands



Supplementary Figure 4.1.2. Bland-Altman plot validation of protein intake comparing FFQ and 24-hour dietary recall method (n=71)



Supplementary Table 4.1.1. Details of the multiple imputation process[a]

	Multiple imputation [1,2]
Software used	IBM SPSS statistics version 21
Imputation method and key settings	Fully conditional specification (Markov chain Monte Carlo method); maximum iterations: 10
No. of imputed data sets created	10
Variables included in the imputation procedure as both predictor variable as a variable to be imputed	Age mother at enrolment; Gravidity at enrolment; Parity at enrolment; Maternal educational level at enrolment; Pre-pregnancy maternal BMI; Maternal BMI at intake; Maternal alcohol consumption during pregnancy; Maternal smoking during pregnancy; Maternal folic acid use during pregnancy; Measured gestational weight gain; Gestational weight gain based on self-reported pre-pregnancy weight; Age partner at enrolment; BMI partner; Educational level partner at enrolment; Household income at enrolment; Gender child; Birth weight; Gestational age at birth; Standardized birth weight (Niklasson); Breastfeeding practice at the age of 2 months; Age of the children at follow-up; Height of the children at follow-up; Screen time of the children at the age of 6 years; Participation in sports of the children at the age of 6 years.
Variables added as predictors (not used in the main analyses) of missing data to increase plausibility of missing at random assumption	Maternal energy-adjusted protein intake during pregnancy; Maternal energy intake during pregnancy; Maternal serum folate level <18 weeks of gestation; Breastfeeding practice (ever versus never); Maternal educational level 6 years after enrolment; Household income 6 years after enrolment; Total energy intake of the children at the age of 14 months; Weight of the children at DXA measurement; Android/gynoid fat mass ratio of the children at follow-up (measured by DXA); Total fat percentage of the children at follow-up (measured by DXA); Fat-free mass index of the children at follow-up (measured by DXA); Fat mass index of the children at follow-up (measured by DXA); BMI-for-age of the children between 10-13 months; BMI-for-age of the children between 13-17 months; BMI-for-age of the children between 17-23 months; BMI-for-age of the children between 23-35 months; BMI-for-age of the children between 35-44 months; BMI-for-age of the children between 44-56 months; BMI of the children at follow-up; Overweight status of the children at follow-up.
Treatment of not normally distributed variables	Predictive mean matching
Treatment of binary/categorical variables	Logistic regression models
Population	For the multiple imputation we included those mothers with a Dutch ancestry, available dietary information, and those who visited the research center with their children at the age of 6 years (n=2,777)

[a] The missing values of the covariate 'hypertensive complications during pregnancy' were not imputed as a result of lacking predictive variables.
Abbreviations: BMI: body mass index, DXA: dual-energy X-ray absorptiometry.

References table 4.1.1.

1. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR (2009) Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338:b2393
2. Rubin DB, Schenker N (1991) Multiple imputation in health-care databases: an overview and some applications. Stat Med 10 (4):585-598

Supplementary Table 4.1.2. Maternal and children's characteristics presented per quartile of energy-adjusted maternal protein intake (n=2694)[a]

		Quartile 1 n=673	Quartile 2 n=674	Quartile 3 n=674	Quartile 4 n=673	P value
Crude values of protein intake (g/day)[b]		65 (16,110)	74 (38,115)	81 (49,120)	95 (55,145)	**<0.001**
Energy-adjusted values of protein intake[b]		-12 (-43,-8)	-4 (-8,-0)	3 (-0,7)	13 (7,41)	**<0.001**
Maternal Characteristics						
Gestational age at enrolment (weeks)		13.4 (12.2-15.8)	13.5 (12.4-15.7)	13.4 (12.2-15.2)	13.2 (12.2-15.4)	
Age (years)		30.8 ±4.5	31.6 ± 4.3	32.0 ± 3.9	32.2 ± 4.0	**<0.001**
Maternal education (%)	Low and midlow (%)	21.3	10.5	8.4	7.5	**<0.001**
	Midhigh (%)	55.2	55.5	51.6	49.9	
	High (%)	23.5	34.1	40.0	42.7	
	Missing (%)	*1.5*	*2.1*	*1.0*	*0.7*	
Nulliparity (%)		63.1	59.7	63.1	61.6	0.53
	Missing (%)	*0.1*	*0.3*	*0.0*	*0.1*	
Body mass index at enrolment (kg/m^2)		23.4 (21.2-26.2)	23.3 (21.3-25.8)	23.4 (21.9-25.8)	23.7 (22.1-26.2)	0.15
	Missing (%)	*0.6*	*0.4*	*0.4*	*0.4*	
Gestational weight gain[c] (g/week)		498 ±208	509 ± 188	495 ± 193	509 ± 197	0.50
	Missing (%)	*18.1*	*19.1*	*16.5*	*16.6*	
Smoking during pregnancy	Never (%)	71.5	75.8	79.2	77.2	**0.004**
	Until pregnancy was known (%)	10.1	9.0	8.5	10.5	
	Continued (%)	18.4	15.3	12.3	12.4	
	Missing (%)	*7.3*	*10.5*	*5.8*	*7.6*	
Alcohol during pregnancy	Never (%)	42.1	29.9	26.9	26.8	**<0.001**
	Until pregnancy was known (%)	16.8	16.9	16.3	17.0	
	Continued (%)	41.1	53.2	56.7	56.2	
	Missing (%)	*8.2*	*11.3*	*6.4*	*8.0*	
Alcohol consumption (g/day)						
Folic acid supplementation	No (%)	11.7	10.4	7.6	7.0	**0.02**
	Started < 10 wk of gestation (%)	88.3	89.6	92.4	93.0	
	Missing (%)	*18.9*	*20.3*	*16.3*	*15.3*	
Energy intake (kcal/day)		2178 ±560	2104 ± 507	2128 ± 472	2200 ± 462	**0.001**
Protein intake (g/day)	Total protein	66 ±16	74 ± 15	82 ± 14	96 ± 16	**<0.001**
	Animal protein	37 ±11	44 ± 10	51 ± 9	63 ± 11	**<0.001**
	Vegetable protein	30 ±9	31 ± 9	31 ± 8	32 ± 9	**<0.001**
Protein intake (E%)	Total protein	12 ±1	14 ± 1	16 ± 1	18 ± 2	**<0.001**
	Animal protein	7 ±1	8 ± 1	10 ± 1	12 ± 2	**<0.001**
	Vegetable protein	5 ±1	6 ± 1	6 ± 1	6 ± 1	**<0.001**
Pregnancy outcomes						
Hypertensive complications (%)		8.3	6.0	6.4	8.4	0.18
	Missing (%)	*3.9*	*2.8*	*2.7*	*3.3*	
Gender, boy (%)		50.5	51.6	47.9	50.4	0.58
Birth weight (g)		3473 ±536	3500 ± 537	3509 ± 553	3530 ±536	0.27
	Missing (%)	*0.4*	*0.0*	*0.0*	*0.0*	
Gestational age at birth (weeks)		39.9 ±1.7	40.0 ± 1.8	40.0 ± 1.7	40.1 ±1.5	0.11
Preterm birth (%)		4.8	4.6	4.6	2.8	0.24
Breastfeeding at 2 months (%)		60.7	70.1	73.1	74.9	**<0.001**
	Missing (%)	*19.2*	*13.8*	*13.9*	*13.1*	
Dietary intake of the children aged 13 months						
Energy intake (kcal/day)		1326 ± 365	1273 ± 335	1310 ± 340	1293 ± 326	0.15
	Missing (%)	*42.6*	*38.3*	*40.9*	*41.9*	
Protein intake (g/day)		41 ± 12	40 ± 11	42 ± 11	43 ± 11	**0.001**
Protein intake (E%)		12 ± 2	13 ± 2	13 ± 2	14 ± 2	**<0.001**
	Missing (%)	*42.6*	*38.3*	*40.9*	*41.9*	

Supplementary Table 4.1.2. (continued) Maternal and children's characteristics presented per quartile of energy-adjusted maternal protein intake (n=2694)[a]

Children's characteristics aged 6 years		**Quartile 1** n=673	**Quartile 2** n=674	**Quartile 3** n=674	**Quartile 4** n=673	**P value**
Age (years)		6.1 ±0.5	6.1 ± 0.4	6.1 ± 0.5	6.1 ± 0.4	0.39
Playing sports (%)		48.1	48.1	50.6	52.9	0.26
	Missing (%)	*6.7*	*8.2*	*5.3*	*5.1*	
≥ 2h/day screen time (%)		25.8	19.9	17.7	16.5	**<0.001**
	Missing (%)	*16.3*	*18.0*	*13.1*	*13.4*	
Height of the children (cm)		120 ±6	119 ± 6	119 ± 6	120 ± 6	0.41
Overweight/obese (%)		13.0	9.7	11.1	11.5	0.30
	Missing (%)	*0.3*	*0.1*	*0.0*	*0.3*	
Body mass index (kg/m^2)		15.6 (14.9-16.6)	15.6 (14.9-16.6)	15.7 (15.0-16.6)	15.7 (15.0-16.6)	0.75
Fat mass index (kg/m^2)		3.6 (3.2-4.3)	3.5 (3.0-4.3)	3.6 (3.2-4.3)	3.5 (3.1-4.1)	0.12
	Missing (%)	*2.8*	*2.7*	*1.9*	*3.0*	
Fat-free mass index (kg/m^2)		11.8 ± 0.8	11.9 ± 0.8	11.9 ± 0.8	12.0 ± 0.8	**0.03**
	Missing (%)	*2.8*	*2.7*	*1.9*	*3.0*	
Total fat percentage (%)		23.7 (21.0-27.0)	23.2 (20.0-26.6)	23.5 (20.8-26.8)	23.1 (20.3-26.2)	**0.02**
	Missing (%)	*2.8*	*2.7*	*1.9*	*3.0*	
Android/gynoid fat mass ratio		0.24 (0.21-0.27)	0.24 (0.20-0.27)	0.24 (0.21-0.27)	0.24 (0.21-0.27)	0.21
	Missing (%)	*2.8*	*2.7*	*1.9*	*3.0*	

[a.] The values represent for continuous measures mean ± SD or median (interquartile range), and for dichotomous values the percentage of participants per category are presented. The missing values are also presented in percentages. The p-values were calculated using Analysis of Variance (ANOVA). [b.] Results for protein intake are presented as median and total range. [c.] Weekly gestational weight gain (g/week) between enrolment around 13 weeks of pregnancy and early-third trimester (around 30 weeks). **Abbreviations:** CI: confidence interval, E%: energy percent.

Supplementary Table 4.1.3. Association of maternal protein intake during pregnancy with childhood body composition at the age of 6 years, in non-imputed data

	Childhood body mass index (SDS)		**Fat-free mass index** (SDS)		**Fat mass index** (SDS)	
	Model 1[a]	***Model 2***[b]	***Model 1***[a]	***Model 2***[b]	***Model 1***[a]	***Model 2***[b]
	n=2694	n=1611	n=2624	n=1566	n=2624	n=1566
Total protein intake[c]	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Quartile 1	reference	reference	reference	reference	reference	reference
Quartile 2	-0.03 (-0.14, 0.07)	-0.00 (-0.14, 0.14)	**0.10 (0.00, 0.20)**	0.06 (-0.07, 0.20)	-0.10 (-0.20, 0.00)	-0.05 (-0.18, 0.08)
Quartile 3	-0.00 (-0.11, 0.11)	0.07 (-0.07, 0.21)	**0.12 (0.02, 0.22)**	**0.13 (0.00, 0.26)**	-0.08 (-0.18, 0.02)	0.00 (-0.12, 0.13)
Quartile 4	0.02 (-0.08, 0.13)	0.06 (-0.08, 0.21)	**0.17 (0.07, 0.27)**	0.12 (-0.01, 0.26)	-0.10 (-0.20, 0.00)	-0.02 (-0.16, 0.11)
p for trend	*0.56*	*0.25*	***0.001***	*0.05*	*0.09*	*1.00*
Animal protein intake[c]						
Quartile 1	reference	reference	reference	reference	reference	reference
Quartile 2	0.03 (-0.07, 0.14)	0.07 (-0.07, 0.20)	0.10 (-0.00, 0.20)	0.10 (0.03, 0.23)	0.01 (-0.09, 0.11)	0.07 (-0.06, 0.19)
Quartile 3	0.04 (-0.07, 0.14)	0.08 (-0.07, 0.22)	**0.11 (0.01, 0.21)**	0.13 (-0.00, 0.27)	-0.02 (-0.12, 0.08)	0.03 (-0.10, 0.16)
Quartile 4	0.07 (-0.04, 0.18)	0.15 (-0.00, 0.29)	**0.18 (0.08, 0.28)**	**0.20 (0.06, 0.34)**	-0.03 (-0.14, 0.07)	0.07 (-0.07, 0.20)
p for trend	*0.23*	*0.06*	***0.001***	***0.007***	*0.45*	*0.50*
Vegetable protein intake[c]						
Quartile 1	reference	reference	reference	reference	reference	reference
Quartile 2	-0.07 (-0.18, 0.04)	-0.06 (-0.20, 0.08)	0.06 (-0.04, 0.16)	-0.07 (-0.20, 0.06)	-0.10 (-0.20, 0.01)	-0.01 (0.14, 0.12)
Quartile 3	-0.03 (-0.13, 0.08)	0.01 (-0.14, 0.15)	**0.14 (0.04, 0.24)**	0.03 (-0.11, 0.16)	**-0.11 (-0.21, -0.01)**	0.01 (-0.12, 0.14)
Quartile 4	-0.03 (-0.14, 0.08)	0.05 (-0.10, 0.20)	**0.22 (0.12, 0.32)**	0.10 (-0.05, 0.24)	**-0.19 (-0.30, -0.09)**	0.01 (-0.12, 0.15)
p for trend	*0.75*	*0.30*	***<0.001***	*0.06*	***0.001***	*0.78*

Results from multivariable linear regression analyses in non-imputed data. The regression coefficients (95% CI) reflect the difference in age- and sex-specific SDS of childhood body mass index, fat-free mass index and fat mass index relative to the first quartile of energy-adjusted protein intake. Trend tests were conducted by using the quartiles of protein intake as a continuous variable in the model. [a.] *Model 1*: Vegetable and animal protein intake were additionally adjusted for each other. [b.] *Model 2*: *Model 1* further adjusted for maternal age, educational level, smoking and alcohol use and folic acid supplementation during pregnancy, energy and carbohydrate intake during pregnancy, gestational age at birth, breastfeeding 2 months postpartum and screen time of the children at 6 years of age. [c.] Energy-adjusted protein intake using the nutritional residual method. **Abbreviations** CI: confidence interval, SDS: standard deviation score.

Supplementary Table 4.1.4. Association between protein intake during pregnancy and childhood total fat percentage and android/gynoid fat mass ratio at the age of 6 years

	Total fat percentage (SDS) n=2,624		**Android/gynoid fat mass ratio** (SDS) n=2,624	
	Model 1[a]	***Model 2***[b]	***Model 1***[a]	***Model 2***[b]
Total protein intake[c]	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Quartile 1	reference	reference	reference	reference
Quartile 2	**-0.13 (-0.22, -0.03)**	-0.05 (-0.15, 0.04)	-0.10 (-0.20, 0.01)	-0.03 (-0.14, 0.08)
Quartile 3	-0.09 (-0.18, 0.01)	0.03 (-0.07, 0.13)	-0.02 (-0.13, 0.09)	0.07 (-0.04, 0.18)
Quartile 4	**-0.15 (-0.24, -0.05)**	-0.01 (-0.12, 0.09)	-0.08 (-0.19, 0.03)	0.02 (-0.10, 0.14)
p for trend	***0.009***	*0.77*	*0.36*	*0.35*
Animal protein intake[c]				
Quartile 1	reference	reference	reference	reference
Quartile 2	-0.01 (-0.10, 0.09)	0.05 (-0.05, 0.14)	0.06 (-0.05, 0.16)	0.11 (-0.01, 0.22)
Quartile 3	-0.04 (-0.13, 0.06)	0.06 (-0.04, 0.15)	0.04 (-0.07, 0.15)	0.11 (-0.01, 0.22)
Quartile 4	-0.08 (-0.18, 0.01)	0.04 (-0.06, 0.15)	-0.01 (-0.12, 0.10)	0.08 (-0.04, 0.20)
p for trend	*0.08*	*0.45*	*0.75*	*0.24*
Vegetable protein intake[c]				
Quartile 1	reference	reference	reference	reference
Quartile 2	**-0.12 (-0.22, -0.03)**	-0.03 (-0.13, 0.06)	-0.11 (-0.21, 0.00)	-0.03 (-0.14, 0.08)
Quartile 3	**-0.12 (-0.22, -0.03)**	0.02 (-0.08, 0.12)	**-0.12 (-0.23, -0.01)**	0.00 (-0.11, 0.12)
Quartile 4	**-0.23 (-0.32, -0.13)**	-0.04 (-0.15, 0.06)	**-0.18 (-0.29, -0.07)**	-0.03 (-0.15, 0.09)
p for trend	***<0.001***	*0.68*	***0.003***	*0.74*

Results from multivariable linear regression analyses, based on imputed data. The regression coefficients (95% CI) reflect the difference in age- and sex-specific SDS of total fat percentage and android/gynoid fat mass ratio of the child relative to the first quartile of energy-adjusted protein intake. Trend tests were conducted by using the quartiles of protein intake as a continuous variable in the model. [a.] *Model 1:* Adjusted for height of the child aged 6 years. The vegetable and animal protein intake were additionally adjusted for each other. [b.] *Model 2*: *Model 1* additionally adjusted for maternal age, educational level, smoking and alcohol use and folic acid supplementation during pregnancy, energy and carbohydrate intake during pregnancy, gestational age at birth, breastfeeding 2 months postpartum and screen time of the children at 6 years of age. [c.] Energy-adjusted protein intake using the nutritional residual method. **Abbreviations:** CI: confidence interval. SDS: standard deviation score.

Supplementary Table 4.1.5. Association between protein intake during pregnancy and childhood BMI and fat-free mass index at the age of 6 years, stratified by maternal overweight status at enrollment[a]

	Childhood Body Mass Index (SDS) n = 2694		**Childhood Fat-Free Mass Index** (SDS) n = 2624	
	Maternal BMI <25 kg/m² n=1807	**Maternal BMI ≥25 kg/m²** n= 887	**Maternal BMI <25 kg/m²** n= 1761	**Maternal BMI ≥25 kg/m²** n=863
Total protein intake[b]	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Quartile 1	reference	reference	reference	reference
Quartile 2	0.01 (-0.11, 0.13)	0.05 (-0.17, 0.26)	0.07 (-0.05, 0.19)	0.15 (-0.04, 0.34)
Quartile 3	0.03 (-0.10, 0.15)	0.17 (-0.05, 0.39)	0.06 (-0.06, 0.19)	0.18 (-0.01, 0.37)
Quartile 4	0.03 (-0.11, 0.16)	**0.28 (0.05, 0.51)**	0.07 (-0.06, 0.20)	**0.32 (0.11, 0.52)**
p for trend	*0.67*	***0.01***	*0.36*	***0.003***
Animal protein intake[b]				
Quartile 1	reference	reference	reference	reference
Quartile 2	**0.12 (0.01, 0.24)**	-0.05 (-0.27, 0.17)	0.09 (-0.03, 0.21)	0.08 (-0.12, 0.28)
Quartile 3	0.06 (-0.06, 0.19)	0.14 (-0.08, 0.36)	0.07 (-0.05, 0.20)	0.13 (-0.06, 0.33)
Quartile 4	0.10 (-0.03, 0.24)	0.21 (-0.03, 0.45)	0.11 (-0.02, 0.25)	**0.27 (0.06, 0.48)**
p for trend	*0.28*	***0.02***	*0.15*	***0.01***
Vegetable protein intake[b]				
Quartile 1	reference	reference	reference	reference
Quartile 2	0.08 (-0.04, 0.20)	-0.08 (-0.29, 0.13)	0.09 (-0.03, 0.21)	0.01 (-0.17, 0.20)
Quartile 3	0.08 (-0.04, 0.21)	0.16 (-0.06, 0.37)	**0.15 (0.02, 0.27)**	0.13 (-0.06, 0.32)
Quartile 4	0.08 (-0.05, 0.22)	0.19 (-0.04, 0.42)	**0.16 (0.03, 0.29)**	**0.33 (0.13, 0.54)**
p for trend	*0.27*	***0.04***	***0.01***	***0.001***

[a] Results from multivariable linear regression analyses, based on imputed data. The regression coefficients (95% CI) reflect the difference in age- and sex-specific SDS of childhood body mass index and fat-free mass index relative to the first quartile of energy-adjusted protein intake. Trend tests were conducted by using the quartiles of protein intake as a continuous variable in the model. The analyses were adjusted for maternal age, educational level, smoking and alcohol use and folic acid supplementation during pregnancy, energy and carbohydrate intake during pregnancy, gestational age at birth, breastfeeding 2 months postpartum and screen time of the children at 6 years of age. Vegetable and animal protein intake were additionally adjusted for each other. [b] Energy-adjusted protein intake using the nutritional residual method. **Abbreviations:** CI: confidence interval, SDS: standard deviation score.

Supplementary Table 4.1.6. Association between protein intake during pregnancy and childhood fat-free mass index at the age of 6 years, in the population with available protein intake of the children at 14 months of age (n=1558)

	Fat-free mass index (SDS) n=1558		
	Model 1[a]	***Model 2***[b]	***Model 2****[c]
Total protein intake[d]	β (95% CI)	β (95% CI)	β (95% CI)
Quartile 1	reference	reference	reference
Quartile 2	0.04 (-0.09, 0.17)	0.02 (-0.11, 0.15)	0.02 (-0.11, 0.15)
Quartile 3	0.12 (-0.01, 0.24)	0.11 (-0.03, 0.24)	0.10 (-0.04, 0.23)
Quartile 4	**0.14 (0.02, 0.27)**	0.14 (-0.01, 0.28)	0.11 (-0.03, 0.26)
p for trend	***0.01***	***0.03***	*0.06*
Animal protein intake[d]			
Quartile 1	reference	reference	reference
Quartile 2	0.06 (-0.06, 0.19)	0.07 (-0.06, 0.20)	0.06 (-0.07, 0.19)
Quartile 3	0.09 (-0.03, 0.22)	0.10 (-0.03, 0.23)	0.09 (-0.05, 0.22)
Quartile 4	**0.17 (0.04, 0.31)**	**0.20 (0.06, 0.34)**	**0.18 (0.03, 0.32)**
p for trend	***0.009***	***0.007***	***0.02***
Vegetable protein intake[d]			
Quartile 1	reference	reference	reference
Quartile 2	-0.05 (-0.18, 0.08)	-0.05 (-0.19, 0.08)	-0.06 (-0.19, 0.08)
Quartile 3	0.04 (-0.09, 0.17)	0.04 (-0.10, 0.18)	0.03 (-0.11, 0.17)
Quartile 4	**0.17 (0.03, 0.31)**	**0.16 (0.01, 0.30)**	**0.15 (0.00, 0.30)**
p for trend	***0.003***	***0.009***	***0.01***

Results from multivariable linear regression analyses, based on imputed data. The regression coefficients (95% CI) reflect the difference in age- and sex-specific SDS of the fat-free mass index of the child relative to the first quartile of energy-adjusted protein intake. Trend tests were conducted by using the quartiles of protein intake as a continuous variable in the model. [a.] *Model 1*: The vegetable and animal protein intake were additionally adjusted for each other. [b.] *Model 2*: *Model 1* additionally adjusted for maternal age, educational level, smoking and alcohol use during pregnancy, folic acid supplementation, energy and carbohydrate intake during pregnancy, gestational age at birth, breastfeeding 2 months postpartum and screen time of the children at 6 years of age. [c.] *Model 2**: *Model 2* additionally adjusted for protein intake of the children at 14 months of age. [d.] Energy-adjusted protein intake using the nutritional residual method. **Abbreviations:** CI: confidence interval, SDS: standard deviation score.

Supplementary Table 4.1.7. Association between protein intake during pregnancy and childhood lean mass index at the age of 6 years (n= 2624)

	Lean mass index (SDS) n=2624	
	Model 1[a]	**Model 2**[b]
Total protein intake[c]	β (95% CI)	β (95% CI)
Quartile 1	reference	reference
Quartile 2	**0.10 (0.00, 0.20)**	0.10 (-0.00, 0.20)
Quartile 3	**0.12 (0.02, 0.21)**	**0.11 (0.01, 0.22)**
Quartile 4	**0.17 (0.07, 0.27)**	**0.16 (0.05, 0.27)**
p for trend	***0.001***	***0.005***
Animal protein intake[c]		
Quartile 1	reference	reference
Quartile 2	0.09 (-0.01, 0.19)	**0.10 (0.00, 0.21)**
Quartile 3	**0.10 (0.00, 0.20)**	**0.11 (0.01, 0.22)**
Quartile 4	**0.18 (0.07, 0.28)**	**0.19 (0.08, 0.31)**
p for trend	***0.001***	***0.002***
Vegetable protein intake[c]		
Quartile 1	reference	reference
Quartile 2	0.05 (-0.05, 0.15)	0.06 (-0.04, 0.16)
Quartile 3	**0.14 (0.04, 0.24)**	**0.15 (0.04, 0.25)**
Quartile 4	**0.22 (0.12, 0.32)**	**0.22 (0.11, 0.33)**
p for trend	***0.001***	***<0.001***

Results from multivariable linear regression analyses, based on imputed data. The regression coefficients (95% CI) reflect the difference in age- and sex-specific SDS of lean mass index of the child relative to the first quartile of energy-adjusted protein intake. Trend tests were conducted by using the quartiles of protein intake as a continuous variable in the model. [a.] *Model 1*: The vegetable and animal protein intake were additionally adjusted for each other. [b.] *Model 2*: *Model 1* further adjusted for maternal age, maternal educational level, maternal smoking and alcohol use during pregnancy, folic acid supplementation, maternal energy and carbohydrate intake, gestational age at birth, gender of the child, breastfeeding practice 2 months postpartum, and screen time of the children at 6 years of age; [c.] Energy-adjusted protein intake using the nutritional residual method. **Abbreviations:** CI: confidence interval. SDS: standard deviation score.

Supplementary Table 4.1.8. Association between protein intake during pregnancy and childhood fat-free mass index at the age of 6 years in mothers without hypertensive complications in pregnancy, preterm child birth, or those who gave birth to a new-born with a birth weight outside ±2 SD (n=2242)

	Fat-free mass index (SDS) n=2242	
	Model 1[a]	***Model 2***[b]
Total protein intake[c]	β (95% CI)	β (95% CI)
Quartile 1	reference	reference
Quartile 2	**0.11 (0.06, 0.17)**	**0.11 (0.00, 0.22)**
Quartile 3	**0.11 (0.05, 0.16)**	0.11 (-0.00, 0.22)
Quartile 4	**0.20 (0.14, 0.25)**	**0.20 (0.08, 0.32)**
p for trend	***0.001***	***0.002***
Animal protein intake[c]		
Quartile 1	reference	reference
Quartile 2	**0.08 (0.03, 0.13)**	0.10 (-0.01, 0.21)
Quartile 3	**0.11 (0.05, 0.17)**	**0.13 (0.01, 0.24)**
Quartile 4	**0.17 (0.12, 0.23)**	**0.19 (0.07, 0.32)**
p for trend	***0.002***	***0.002***
Vegetable protein intake[c]		
Quartile 1	reference	reference
Quartile 2	**0.06 (0.01, 0.12)**	0.07 (-0.04, 0.18)
Quartile 3	**0.14 (0.09, 0.20)**	**0.16 (0.04, 0.27)**
Quartile 4	**0.25 (0.19, 0.30)**	**0.25 (0.13, 0.37)**
p for trend	***<0.001***	***<0.001***

Results from multivariable linear regression analyses, based on imputed data. The regression coefficients (95% CI) reflect the difference in age- and gender-specific SDS of the fat-free mass index of the child relative to the first quartile of energy-adjusted protein intake. Trend tests were conducted by using the quartiles of protein intake as a continuous variable in the model. [a.] *Model 1:* The vegetable and animal protein intake were additionally adjusted for each other. [b.] *Model 2*: *Model 1* further adjusted for maternal age, maternal educational level, maternal smoking and alcohol use during pregnancy, folic acid supplementation, maternal energy and carbohydrate intake during pregnancy, gestational age at birth, gender of the child, breastfeeding practice 2 months postpartum, and screen time of the children at 6 years of age; [c.] Energy-adjusted protein intake using the nutritional residual method. **Abbreviations:** CI: confidence interval, SDS: standard deviation score.

Chapter 4.2

Maternal dietary patterns during pregnancy and offspring cardiometabolic health at age 6 years: The Generation R Study

Elisabeth T.M. Leermakers , Myrte J. Tielemans, Marion van den Broek, Vincent W.V. Jaddoe, Oscar H. Franco, Jessica C. Kiefte-de Jong

Clinical nutrition, 2016 jan [Epub ahead of print]

Supplementary Table 4.2.1. Comparison of a selection of the subject characteristics of the study population (n=2695, unimputed data) and the excluded mothers and children (n=1402, unimputed data): The Generation R Study Cohort, Rotterdam, The Netherlands[1]

	Participants in analysis (n=2695)	**Participants not in analysis** (n=1402)
Maternal characteristics		
Age (years)	31.7 ± 4.2	30.5 ± 5.1
Pre-pregnancy BMI (kg/m^2)	23.3 ± 3.9	23.1 ± 4.0
Gestational age at enrolment (weeks)	13.4 (9.9; 22.8)	13.5 (9.5-27.8)
Education level		
Primary or secondary	1019 (37.8%)	697 (50.7%)
Higher	1640 (61.7%)	679 (49.3%)
Missing	*36 (1.3%)*	*26 (1.9%)*
Household income		
<2200 (Euros/month)	591 (23.8%)	360 (33.1%)
>2200 (Euros/month)	1893 (76.2%)	728 (51.9%)
Missing	*211 (7.8%)*	*314 (22.4%)*
Parity		
0	1665 (61.9%)	769 (55.2%)
≥1	1026 (38.1%)	623 (44.8%)
Missing	*4 (0.1%)*	*10 (0.1%)*
Smoking		
Never during pregnancy	1,886 (75.9%)	875 (67.3%)
Until pregnancy was known	236 (9.5%)	113 (8.7%)
Continued throughout pregnancy	363 (14.6%)	313 (24.1%)
Missing	*210 (7.8%)*	*101 (7.2%)*
Alcohol		
Never during pregnancy	776 (28.8%)	525 (40.7%)
Until pregnancy was known	413 (15.3%)	208 (16.1%)
Continued throughout pregnancy	1,278 (51.8%)	558 (43.2%)
Missing	*228 (8.5%)*	*111 (8.5%)*
Folic acid use		
No	203 (9.2%)	192 (13.7%)
Start first 10 weeks	734 (33.1%)	380 (33.7%)
Start periconceptional	1,281 (57.8%)	555 (49.2%)
Missing	*477 (17.7%)*	*275 (19.6%)*
Total energy intake, FFQ (kcal/day)	2153 ± 503	2125 ± 539
Stress during pregnancy, global severity index	0.12 (0.00-0.77)	0.12 (0.00-0.77)

[1] Values represent n (%), mean ± SD, or median (95% range). BMI: body mass index. FFQ: food-frequency questionnaire. Missing values for continuous variables for the population in the analysis were 373 (14%) for pre-pregnancy BMI and 284 (11%) for stress during pregnancy. Missing values for continuous variables in the population not in the analysis were 214 (15%), 538 (38%) for total energy intake and 322 (23%) for stress during pregnancy.