SUPPLEMENTARY MATERIAL: STUDY SUMMARIES

THYROID AND DIABETES-RELATED DISORDERS

IDENTIFYING RESEARCH NEEDS FOR ASSESSING
SAFE USE OF HIGH INTAKES OF FOLIC ACID

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Office of Health Assessment and Translation

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Glycemic Control in Type 2 Diabetics, Meta-analysis

Thyroid and Diabetes-related Disorders, Human Studies

1. SUDCHADA, 2012

Full citation: Sudchada P, Saokaew S, Sridetch S, Incampa S, Jaiyen S, Khaithong W. 2012. Effect of folic acid supplementation on plasma total homocysteine levels and glycemic control in patients with type 2 diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract 98(1): 151-158.
Funding: none reported

1.1. Folic acid supplementation and glycemic control in patients with type 2 diabetes

Protocol: Folic acid supplementation and glycemic control in patients with type 2 diabetes	
Literature Search Strategy: Systematic	**Protocol type:** Meta-analysis
Relevant randomized controlled trials (RCTs) were identified by searching the electronic databases updated to March 2012. PubMed, Scopus and Embase databases were systematically searched using the Medical Subject Headings (MeSH) terms and explored the key words ''folic acid'' and ''diabetes mellitus'' with slight modifications based on the sources for search strategy without language restriction. The articles with following selection criteria were retrieved: (1) study design as an RCT, (2) patients with type 2 diabetes who receiving folic acid, and (3) outcomes were measured as an effect on tHcy levels and/or glycemic control (HbA1c).	**Inclusion Criteria:** outcomes were measured as glycemic control (HbA1c), patients with type 2 diabetes who receiving folic acid, randomized controlled trial **Exclusion Criteria:**
Starting date:	**Ending date:** 2012-03-01
Total references from search: 1887	**References Included:** 4

Additional Notes: meta-analysis also considered impact on total homocysteine level

1.2. Result(s)

1.2.A <u>Folic acid supplementation and glycemic control in patients with type 2 diabetes</u>
Studies (3), Total Subjects (142)

Exposure	Assessed Outcome	mean change	95% CI (low, high)	Test of Heterogeneity
folic acid supplementaion	glycemic control (HbA1c)	-0.37	(-1.1, -0.35)	I2 = 83.8%, p=0.002

Notes: p=0.309 for weighted mean difference using random effect model. No publication bias was found as determined by funnel plot (Egger's test for bias: p = 0.140, Begg's test for bias: p = 0.117).

1.3. Statistical Method(s)

Results: Folic acid supplementation and glycemic control in patients with type 2 diabetes
Adjustment factors:

Statistical metric description: To compare the effect of folic acid with interested outcomes, DerSimmonian and Laird random-effect models were used to pool mean differences estimated for tHcy levels, and HbA1c. Presence of heterogeneity was assessed using Q-statistic. A p-value <0.10 was considered as evidence of heterogeneity. Heterogeneity was also presented as I2 which determined the degree of variation across studies that resulted from heterogeneity rather than by chance. I2 can be calculated as I2 = 100% * (Q - df)/Q (Q, Cochrane's heterogeneity statistics; df, degree of freedom). A percentage of around 25% (I2 = 25%), 50% (I2 = 50%) and 75% (I2 = 75%) indicates low, medium and high heterogeneity, respectively. In the case where heterogeneity existed, an attempt to explore sources of heterogeneity was made. Publication bias was assessed using Begg's test with visual inspection of the funnel plot (asymmetrical shape indicates an existence of bias) and Egger's regression asymmetry test. The p-value <0.05 in publication bias tests was suggestive of publication bias.

2. ADAIKALAKOTESWARI, 2012

Full citation: Adaikalakoteswari A, Rabbani N, Waspadji S, Tjokroprawiro A, Kariadi SH, Adam JM, Thornalley PJ. 2012. Disturbance of B-vitamin status in people with type 2 diabetes in Indonesia--link to renal status, glycemic control and vascular inflammation. Diabetes Res Clin Pract 95(3): 415-424.

TYPE 2 DIABETES IN INDONESIA

Age: 56.0 (mean), from 45.0-65.0 years	**Study design:** Cross-sectional (**n = 152**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Indonesia **Region:** **State:** Jakarta
Inclusion criteria: type 2 diabetes with albuminuria, type 2 diabetes with microalbuminuria, type 2 diabetes with normoalbuminuria	**Exclusion critieria:** allergy or intolerance to thiamine, pyridoxine or cobalamin, anemia, chronic renal insufficiency, liver diseases (abnormal liver function tests – serum albumin, alanine transaminase, aspartate transaminase, participation in another clinical study within the last 30 days, severe CVD (angina, myocardial infarction and normal electrocardiogram within 2 months of enrollment), tuberculosis, women who were pregnant, breast feeding or of child bearing potential not using adequate contraceptive precautions

2.1. Exposure: Plasma folate

Method	Description	Analysis
serum assay	Total plasma folate.. determined by electrochemiluminescent immunoassay using a Roche Elecsys E170 analyzer	n/a

Outcomes

	Outcome	Diagnostic Description
A	Type 2 diabetes with Normoalbuminuria vs Microalbuminuria vs Albuminuria (medical professional or test)	Classification of renal function status implemented in the study is defined by the Asian-Pacific Type 2 Diabetes Policy Group and endorsed by the International Diabetes Federation. diabetic patients – type 2 diabetes with normoalbuminuria (albumin/ creatinine ratio ACR < 22 and <31 mg/g for men and women, respectively), microalbuminuria (ACR 22–220 and 31–220 mg/g for men and women, respectively) and albuminuria (ACR >220 mg/g and plasma creatinine <2 mg/dl)

Results

2.1.A   Type 2 diabetes with Normoalbuminuria vs Microalbuminuria vs Albuminuria

Population: Type 2 Diabetics in Indonesia, ages 45-65
Exposure: Plasma folate
Outcome: Type 2 diabetes with Normoalbuminuria vs Microalbuminuria vs Albuminuria
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Plasma folate	152	-	0.05

Statistical Method(s)

Endpoints: Type 2 diabetes with Normoalbuminuria vs Microalbuminuria vs Albuminuria
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Data are mean +/- SD for parametric data. Significance of difference between mean changes was assessed by Student's t test and one-way ANOVA. Factors linked to markers of B-vitamin dysfunction in patients with type 2 diabetes were explored by multiple linear regression analysis....

3. ASEMI, 2014

Full citation: Asemi Z, Karamali M, Esmaillzadeh A. 2014. Metabolic response to folate supplementation in overweight women with polycystic ovary syndrome: a randomized double-blind placebo-controlled clinical trial. Mol Nutr Food Res 58(7): 1465-1473.

OVERWEIGHT WOMEN WITH POLYCYSTIC OVARY SYNDROME

Age: 18.0-40.0 years	**Study design:** Controlled trial (**n** = 81)
Gender: Female **Ethnicities:**	**Country:** Iran, Islamic Republic Of **Region:** Kashan **State:**
Inclusion criteria: Females diagnosed with Polycystic Ovary Syndrome (PCOS)	**Exclusion critieria:**

3.1. Exposure: Folate supplementation

Method	Description	Analysis
intervention	Group 1: 1 mg/day folate supplement for 8 weeks (n=27) Group 2: 5 mg/day folate 8 weeks (n=27) Group 3: Placebo 8 weeks (n=27)	n/a

Outcomes

	Outcome	Diagnostic Description
A	Homeostatic model of assessment for insulin resistance (HOMA-IR) (medical professional or test)	HOMA-IR calculated based on the methods outlined in this study: Pisprasert, V, et al. Limitations in the use of indices using glucose and insulin levels to predict insulin sensitivity: impact of race and gender and superiority of the indices derived from oral glucose tolerance test in African Americans. Diabetes Care 2013, 36, 845–853.
B	Homeostatic model of assessment for insulin resistance (HOMA-IR): Adjusted Model (medical professional or test)	HOMA-IR calculated based on the methods outlined in this study: Pisprasert, V, et al. Limitations in the use of indices using glucose and insulin levels to predict insulin sensitivity: impact of race and gender and superiority of the indices derived from oral glucose tolerance test in African Americans. Diabetes Care 2013, 36, 845–853.
C	Insulin (medical professional or test)	Serum insulin measured by assay (ELISA kit) in uIU/mL. The intra- and interassay CVs for serum insulin were 2.7 and 5.6%, respectively
D	Insulin: Adjusted model (medical professional or test)	Serum insulin measured by assay (ELISA kit) in uIU/mL. The intra- and interassay CVs for serum insulin were 2.7 and 5.6%, respectively
E	Quantitative insulin sensitivity check index (QUICKI)	Calculated based on methods from following study: Pisprasert, V, et al. Limitations in the use of indices using glucose and insulin levels to

	Outcome	Diagnostic Description
	(medical professional or test)	predict insulin sensitivity: impact of race and gender and superiority of the indices derived from oral glucose tolerance test in African Americans. Diabetes Care 2013, 36, 845–853.
F	Quantitative insulin sensitivity check index (QUICKI): Adjusted Model (medical professional or test)	Calculated based on methods from following study: Pisprasert, V, et al. Limitations in the use of indices using glucose and insulin levels to predict insulin sensitivity: impact of race and gender and superiority of the indices derived from oral glucose tolerance test in African Americans. Diabetes Care 2013, 36, 845–853.

Results

3.1.A   Homeostatic model of assessment for insulin resistance (HOMA-IR)

Population: Overweight Women with Polycystic Ovary Syndrome (PCOS)
Exposure: Folate supplementation
Outcome: Homeostatic model of assessment for insulin resistance (HOMA-IR)
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Placebo Control	27	-	
Group 1 (1 mg/day)	27	-	
Group 2 (5 mg/day)	27	-	0.05

3.1.B   Homeostatic model of assessment for insulin resistance (HOMA-IR): Adjusted Model

Population: Overweight Women with Polycystic Ovary Syndrome (PCOS)
Exposure: Folate supplementation
Outcome: Homeostatic model of assessment for insulin resistance (HOMA-IR): Adjusted Model
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Placebo Control	27	-	
Group 1 (1 mg/day)	27	-	
Group 2 (5 mg/day)	27	-	

3.1.C   Insulin

Population: Overweight Women with Polycystic Ovary Syndrome
Exposure: Folate supplementation
Outcome: Insulin
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Placebo Control	27	-	
Group 1 (1 mg/day)	27	-	
Group 2 (5 mg/day)	27	-	0.05

3.1.D   Insulin: Adjusted model

Population: Overweight Women with Polycystic Ovary Syndrome
Exposure: Folate supplementation
Outcome: Insulin: Adjusted model
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Placebo Control	27	-	
Group 1 (1 mg/day)	27	-	
Group 2 (5 mg/day)	27	-	

3.1.E   Quantitative insulin sensitivity check index (QUICKI)

Population: Overweight Women with Polycystic Ovary Syndrome (PCOS)
Exposure: Folate supplementation
Outcome: Quantitative insulin sensitivity check index (QUICKI)
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Placebo Control	27	-	
Group 1 (1 mg/day)	27	-	
Group 2 (5 mg/day)	27	-	

3.1.F   Quantitative insulin sensitivity check index (QUICKI): Adjusted Model

Population: Overweight Women with Polycystic Ovary Syndrome (PCOS)
Exposure: Folate supplementation
Outcome: Quantitative insulin sensitivity check index (QUICKI): Adjusted Model
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Placebo Control	27	-	
Group 1 (1 mg/day)	27	-	
Group 2 (5 mg/day)	27	-	

Statistical Method(s)

Endpoints: Insulin
Adjustment factors:
Statistical metric: mean change
Statistical metric description: To determine the effects of folate supplementation on glucose metabolism and lipid profiles, we used one-way repeated measures analysis of variance. In this analysis, the treatment was regarded as between-subject factor and time with two time-points (baseline and week 8 of intervention) was considered as within-subject factor. To assess if the magnitude of the change depended on the baseline values, we adjusted all analyses for the baseline values, age, and baseline BMI to avoid the potential bias that might have resulted. $p < 0.05$ was considered as statistically significant

Endpoints: Homeostatic model of assessment for insulin resistance (HOMA-IR): Adjusted Model; Quantitative insulin sensitivity check index (QUICKI): Adjusted Model
Adjustment factors: age, baseline BMI
Statistical metric: mean change
Statistical metric description: To determine the effects of folate supplementation on glucose metabolism and lipid profiles, we used one-way repeated measures analysis of variance. In this analysis, the treatment was regarded as between-subject factor and time with two time-points (baseline and week 8 of intervention) was considered as within-subject factor. To assess if the magnitude of the change depended on the baseline values, we adjusted all analyses for the baseline values, age, and

baseline BMI to avoid the potential bias that might have resulted. p < 0.05 was considered as statistically significant.

Endpoints: Insulin: Adjusted model
Adjustment factors: age, baseline BMI
Statistical metric: mean change
Statistical metric description: To determine the effects of folate supplementation on glucose metabolism and lipid profiles, we used one-way repeated measures analysis of variance. In this analysis, the treatment was regarded as between-subject factor and time with two time-points (baseline and week 8 of intervention) was considered as within-subject factor. To assess if the magnitude of the change depended on the baseline values, we adjusted all analyses for the baseline values, age, and baseline BMI to avoid the potential bias that might have resulted. p < 0.05 was considered as statistically significant

Endpoints: Quantitative insulin sensitivity check index (QUICKI); Homeostatic model of assessment for insulin resistance (HOMA-IR)
Adjustment factors:
Statistical metric: mean change
Statistical metric description: To determine the effects of folate supplementation on glucose metabolism and lipid profiles, we used one-way repeated measures analysis of variance. In this analysis, the treatment was regarded as between-subject factor and time with two time-points (baseline and week 8 of intervention) was considered as within-subject factor. To assess if the magnitude of the change depended on the baseline values, we adjusted all analyses for the baseline values, age, and baseline BMI to avoid the potential bias that might have resulted. p < 0.05 was considered as statistically significant.

4. ATABEK, 2006

Full citation: Atabek ME, Pirgon O, Karagozoglu E. 2006. Plasma homocysteine levels in children and adolescents with type 1 diabetes. Indian Pediatr 43(5): 401-407.

Funding: "None" (as reported in paper)

CHILDREN AND ADOLESCENTS IN TYPE I DIABETES

Age: 11.1 (mean), from 4.0-17.0 years	**Study design:** Case-control (**n** = 54)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Turkey **Region:** **State:**
Inclusion criteria: >1 year period from diagnosis of type 1 diabetes which was detected	**Exclusion critieria:** hypertension, hyperlipidemia, and other cardiovascular disease, taking medication

4.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	serum folate measured by competitive immunoassay and IMMULITE 2000 Analyzer	normal range for folate was 3-17 ng/mL

Outcomes

	Outcome	Diagnostic Description
A	Type 1 Diabetes (medical professional or test)	Type 1 Diabetes (DM) diagnosed according to the World Health Organization (WHO) definition

Results

4.1.A   Type 1 Diabetes

Population: Children and Adolescents in Type I Diabetes
Exposure: Serum folate
Outcome: Type 1 Diabetes
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	54	-	0.02

Statistical Method(s)

Endpoints: Type 1 Diabetes
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Differences between data were studied using Student's t test

5. BAHMANI, 2014

OVERWEIGHT WOMEN WITH POLYCYSTIC OVARY SYNDROME (PCOS)

Age: 18.0-40.0 years	**Study design:** Controlled trial (**n =** 69)
Gender: Female **Ethnicities:**	**Country:** Iran, Islamic Republic Of **Region:** Kashan **State:**
Inclusion criteria: Females diagnosed with Polycystic Ovary Syndrome (PCOS)	**Exclusion critieria:**

5.1. Exposure: Folate supplementation

Method	Description	Analysis
Folate supplementation trial	Placebo (n=23) for 8 weeks Group 1: 1 mg/day (n=23) folate for 8 weeks Group 2: 5 mg/day folate (n=23) for 8 weeks	n/a

Outcomes

	Outcome	Diagnostic Description
A	High-sensitivity C-reactive Protein (Hs-CRP) (medical professional or test)	Serum high-sensitivity C-reactive protein (hs-CRP) was quantified using an ELISA kit
B	High-sensitivity C-reactive Protein (Hs-CRP): Adjusted Model (medical professional or test)	Serum high-sensitivity C-reactive protein (hs-CRP) was quantified using an ELISA kit
C	The homeostatic model assessment for beta-cell function (HOMA-B) (medical professional or test)	calculated based on methods from: Pisprasert, V, et al. Limitations in the use of indices using glucose and insulin levels to predict insulin sensitivity: impact of race and gender and superiority of the indices derived from oral glucose tolerance test in African Americans. Diabetes Care 2013, 36, 845–853.
D	The homeostatic model assessment for beta-cell function (HOMA-B): Adjusted Model (medical professional or test)	calculated based on methods from: Pisprasert, V, et al. Limitations in the use of indices using glucose and insulin levels to predict insulin sensitivity: impact of race and gender and superiority of the indices derived from oral glucose tolerance test in African Americans. Diabetes Care 2013, 36, 845–853.

Results

5.1.A   High-sensitivity C-reactive Protein (Hs-CRP)

Population: Overweight Women with Polycystic Ovary Syndrome (PCOS)
Exposure: Folate supplementation
Outcome: High-sensitivity C-reactive Protein (Hs-CRP)
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Placebo, Control	23	-	
Group 1 (1 mg/day)	23	-	
Group 2 (5 mg/day)	23	-	0.05

5.1.B   High-sensitivity C-reactive Protein (Hs-CRP): Adjusted Model

Population: Overweight Women with Polycystic Ovary Syndrome (PCOS)
Exposure: Folate supplementation
Outcome: High-sensitivity C-reactive Protein (Hs-CRP): Adjusted Model
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Placebo, Control	23	-	
Group 1 (1 mg/day)	23	-	
Group 2 (5 mg/day)	23	-	

5.1.C   The homeostatic model assessment for beta-cell function (HOMA-B)

Population: Overweight Women with Polycystic Ovary Syndrome (PCOS)
Exposure: Folate supplementation
Outcome: The homeostatic model assessment for beta-cell function (HOMA-B)
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Placebo, Control	23	-	
Group 1 (1 mg/day)	23	-	
Group 2 (5 mg/day)	23	-	0.05

5.1.D   The homeostatic model assessment for beta-cell function (HOMA-B): Adjusted Model

Population: Overweight Women with Polycystic Ovary Syndrome (PCOS)
Exposure: Folate supplementation
Outcome: The homeostatic model assessment for beta-cell function (HOMA-B): Adjusted Model
Statistical metric: mean change

Group	N	mean change 95% CI (low, high)	*p*-value
Placebo, Control	23	-	
Group 1 (1 mg/day)	23	-	
Group 2 (5 mg/day)	23	-	

Statistical Method(s)

Endpoints: The homeostatic model assessment for beta-cell function (HOMA-B); High-sensitivity C-reactive Protein (Hs-CRP): Adjusted Model; High-sensitivity C-reactive Protein (Hs-CRP)
Adjustment factors:
Statistical metric: mean change
Statistical metric description: The changes across the three groups were compared using one-way analysis of variance with Bonferroni post hoc pair-wise comparisons

Endpoints: The homeostatic model assessment for beta-cell function (HOMA-B): Adjusted Model
Adjustment factors: age, body mass index
Statistical metric: mean change
Statistical metric description: The changes across the three groups were compared using one-way analysis of variance with Bonferroni post hoc pair-wise comparisons

6. BALTACI, 2012

Full citation: Baltaci D, Kutlucan A, Ozturk S, Karabulut I, Ak Yildirim H, Celer A, Celbek G, Kara IH. 2012. Evaluation of vitamin B12 level in middle-aged obese women with metabolic and nonmetabolic syndrome: Case-control study. Turkish Journal of Medical Sciences 42(5): 802-809.

Funding: none reported

TURKISH MIDDLE-AGED WOMEN WITH OBESITY

Age: 36.6 (mean)	Study design: Case-control (n = 219)
Gender: Female Ethnicities: Unknown/Unspecified	Country: Turkey Region: State:
Inclusion criteria: female	Exclusion critieria: being over 50 years of age, current use of corticosteroids or vitamin supplementations, diabetes mellitus, long-term use of proton pump inhibitors (PPIs; 3 months or longer) and metformin, male, strict vegetarianism

6.1. Exposure: Folic acid level

Method	Description	Analysis
serum assay	Table 2 says pg/mL but should be ng/mL. folic acid levels were assayed using competitive immunoassay	n/a

Outcomes

	Outcome	Diagnostic Description
A	Homeostasis model assessment-estimated IR (HOMA-IR) (medical professional or test)	Homeostasis model assessment-estimated IR (HOMA-IR) was also calculated with the following formula: fasting serum glucose (mg/dL) × fasting plasma insulin level (µU/mL) / 405. HOMA-IR was accepted as positive if it was >2.5
B	Metabolic Syndrome vs Obesity only vs Control (medical professional or test)	MetS was defi ned, using criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III, as 3 or more of the following variables and cutoff points: 1) fasting blood sugar of ≥110 mg/dL, 2) triglyceride level of ≥150 mg/dL, 3) high-density lipoprotein cholesterol (HDL-C) of <50 mg/dL in women, 4) waist circumference of >88 cm, and 5) blood pressure of ≥130/85 mmHg . Obesity: Obesity was defined as a BMI value over 29.9 kg/m2, as described by the World Health Organization
C	Obesity (medical professional or test)	MetS was defi ned, using criteria proposed by the National Cholesterol Education Program Adult Treatment Panel III, as 3 or more of the following variables and cutoff points: 1) fasting blood sugar of ≥110 mg/dL, 2) triglyceride level of ≥150 mg/dL, 3) high-density lipoprotein cholesterol (HDL-C) of <50 mg/dL in women, 4)

Outcome	Diagnostic Description
	waist circumference of >88 cm, and 5) blood pressure of ≥130/85 mmHg

Results

6.1.A   Homeostasis model assessment-estimated IR (HOMA-IR)

Population: Turkish middle-aged women with obesity
Exposure: Folic acid level
Outcome: Homeostasis model assessment-estimated IR (HOMA-IR)
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
folic acid level	219	-	0.211

6.1.B   Metabolic Syndrome vs Obesity only vs Control

Population: Turkish middle-aged women with obesity
Exposure: Folic acid level
Outcome: Metabolic Syndrome vs Obesity only vs Control
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
folic acid level	219	-	

6.1.C   Obesity

Population: Turkish middle-aged women with obesity
Exposure: Folic acid level
Outcome: Obesity
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
folic acid level	219	-	0.058

Statistical Method(s)

Endpoints: Homeostasis model assessment-estimated IR (HOMA-IR)
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Data were expressed as means ± standard deviations, medians (interquartile range), or percentages.   Student's t-test was used to compare statistical diff erences of normal variables among the different groups. Correlation between vitamin B12 levels and BMI and HOMA-IR was analyzed using Pearson's correlation analysis

Endpoints: Metabolic Syndrome vs Obesity only vs Control
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Data were expressed as means ± standard deviations, medians (interquartile range), or percentages. One-way ANOVA (Bonferroni test) was used to compare statistical differences for variables of more than 2 groups

Endpoints: Obesity
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Data were expressed as means ± standard deviations, medians (interquartile range), or percentages.   Student's t-test was used to compare statistical diff erences of normal variables among the different groups

7. BALTACI, 2013

Full citation: Baltaci D, Kutlucan A, Turker Y, Yilmaz A, Karacam S, Deler H, Ucgun T, Kara IH. 2013. Association of vitamin B12 with obesity, overweight, insulin resistance and metabolic syndrome, and body fat composition; primary care-based study. Medicinski glasnik : official publication of the Medical Association of Zenica-Doboj Canton, Bosnia and Herzegovina 10(2): 203-210.

VITAMIN B12 AND OBESITY, TURKISH POPULATION

Age: 19.0-53.0 years	Study design: Cross-sectional (n = 976)
Gender: Male and Female Ethnicities: Unknown/Unspecified	Country: Turkey Region: State:
Inclusion criteria:	Exclusion critieria: chronic obstructive pulmonary disease, current use of corticosteroids or vitamin supplementations, diabetes mellitus, end-stage renal disease, long-term use of proton pump inhibitors (PPIs; 3 months or longer) and metformin, pace-makers, pregnancy

7.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	Serum folate assayed with competitive immunoassay	n/a

Outcomes

	Outcome	Diagnostic Description
A	Insulin Resistance (medical professional or test)	Insulin resistance diagnosed according to criteria of the NCEP ATP III recommendations (at least 3 of 5 criteria)
B	Metabolic Syndrome (medical professional or test)	Metabolic Syndrome diagnosed according to criteria of the NCEP ATP III recommendations (at least 3 of 5 criteria)

Results

7.1.A   Insulin Resistance

Population: Overweight and Obese population in Primary Care Centers
Exposure: Serum folate
Outcome: Insulin Resistance
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Serum folate	-	-	

7.1.B Metabolic Syndrome

Population: Overweight and Obese population in Primary Care Centers
Exposure: Serum folate
Outcome: Metabolic Syndrome
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Serum folate	-	-	

Statistical Method(s)

Endpoints: Metabolic Syndrome; Insulin Resistance
Adjustment factors:
Statistical metric: mean
Statistical metric description: Continuous variables as mean +/- SD, comparisons made using Students' t-test

8. BECKER, 2003

Full citation: Becker A, Henry RM, Kostense PJ, Jakobs C, Teerlink T, Zweegman S, Dekker JM, Nijpels G, Heine RJ, Bouter LM, Smulders YM, Stehouwer CD. 2003. Plasma homocysteine and S-adenosylmethionine in erythrocytes as determinants of carotid intima-media thickness: different effects in diabetic and non-diabetic individuals. The Hoorn Study. Atherosclerosis 169(2): 323-330.

DIABETICS IN HOORN STUDY

Age: 68.6 (None)	**Study design:** Cross-sectional (**n =** 231)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Netherlands **Region:** **State:**
Inclusion criteria: had diabetes in 1996-1998, part of HOORN population-based cohort study	**Exclusion critieria:**

8.1. Exposure: Erythrocyte folate

Method	Description	Analysis
assay	We added 0.5 mg of ascorbic acid to 0.5 ml of serum for the determination of total folate. For the determination of total folate in erythrocytes, 1 ml of reagent with ascorbic acid, human serum albumin and sodium azide (ACS:180, Chiron Diagnostics) was added to 50 ml of whole blood. We measured total folate in red blood cell hemolysate and serum...by means of automated chemiluminescence (Chiron Diagnostics).	The intra-assay and interassay CVs for total folate were 4 and 5%, respectively

Outcomes

	Outcome	Diagnostic Description
A	Type 2 Diabetes Mellitus (medical professional or test)	newly diagnosed type 2 diabetes who were diagnosed in a population screening study among the 50-75 years old population held in 2000 (diagnosed from diabetes screening study)

Results

8.1.A Type 2 Diabetes Mellitus

Population: Diabetics in HOORN Study
Exposure: Erythrocyte folate

Outcome: Type 2 Diabetes Mellitus
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Erythrocyte folate	231	-	0.18

Statistical Method(s)

Endpoints: Type 2 Diabetes Mellitus
Adjustment factors: age
Statistical metric: t-test
Statistical metric description: Differences between groups in continuous variables were tested with Student's t-test; in case of a skewed distribution with the Mann/Whitney test; and in case of percentages with the x2 -test, age-adjusted p-values reported.

8.2. Exposure: Serum folate

Method	Description	Analysis
assay	We added 0.5 mg of ascorbic acid to 0.5 ml of serum for the determination of total folate. For the determination of total folate in erythrocytes, 1 ml of reagent with ascorbic acid, human serum albumin and sodium azide (ACS:180, Chiron Diagnostics) was added to 50 ml of whole blood. We measured total folate in red blood cell hemolysate and serum...by means of automated chemiluminescence (Chiron Diagnostics).	The intra-assay and interassay CVs for total folate were 4 and 5%, respectively

Outcomes

	Outcome	Diagnostic Description
A	Type 2 Diabetes Mellitus (medical professional or test)	newly diagnosed type 2 diabetes who were diagnosed in a population screening study among the 50-75 years old population held in 2000 (diagnosed from diabetes screening study)

Results

8.2.A   Type 2 Diabetes Mellitus

Population: Diabetics in HOORN Study
Exposure: Serum folate
Outcome: Type 2 Diabetes Mellitus
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum Folate	231	-	0.24

Statistical Method(s)

Endpoints: Type 2 Diabetes Mellitus
Adjustment factors: age
Statistical metric: t-test
Statistical metric description: Differences between groups in continuous variables were tested with Student's t-test; in case of a skewed distribution with the Mann/Whitney test; and in case of percentages with the $x2$ -test, age-adjusted p-values reported.

9. CAMPBELL, 2012

Full citation: Campbell SK, Lynch J, Esterman A, McDermott R. 2012. Pre-pregnancy predictors of diabetes in pregnancy among Aboriginal and Torres Strait Islander women in North Queensland, Australia. Matern Child Health J 16(6): 1284-1292.

DIABETES IN PREGNANCY, NORTH QUEENSLAND, AUSTRALIA

Age: 23.8 (mean), from 15.0-44.0 years	**Study design:** Cross-sectional (**n** = 220)
Gender: Female **Ethnicities:** Native American of Other Pacific Islander	**Country:** Australia **Region:** North Queensland **State:**
Inclusion criteria: childbearing age (15-44 years)	**Exclusion critieria:** Women who were likely to have been pregnant at the time of their health check based on the date of their health check, the date of their subsequent delivery and the estimated gestation of the pregnancy at the time of birth

9.1. Exposure: Red cell folate

Method	Description	Analysis
assay	Red cell folate was measured with the Bayer Advia Centaur automated immunoassay system (Bayer, Australia) by the Queensland Health Pathology Service in Brisbane	The reference range for this assay was 295–1,800 nmol/l

Outcomes

	Outcome	Diagnostic Description
A	Diabetes during pregnancy (medical professional or test)	Diabetes defined as confirmed by doctors on a medical chart audit or a fasting glucose level >/=7 mmol/l or 2-h glucose tolerance test result of >11.1 mmol (including medical record review)

Results

9.1.A   Diabetes during pregnancy

Population: Diabetes in Pregnancy, North Queensland, Australia 1998-2000
Exposure: Red cell folate
Outcome: Diabetes during pregnancy
Statistical metric: adjusted prevalence ratio

Group	N	adjPR 95% CI (low, high)	p-value
Red cell folate	220	1.0 (0.99, 1.0)	0.23

Statistical Method(s)

Endpoints: Diabetes during pregnancy
Adjustment factors: age, ethnicity
Statistical metric: adjusted prevalence ratio
Statistical metric description: The data were analysed in a generalised linear model (Poisson distribution) with robust variance estimates to calculate prevalence ratios (PRs) and 95% confidence intervals (CIs) with 2 sided P values of 0.05 for baseline characteristics associated with diabetes during the first subsequent pregnancy. The model was adjusted for age and, because it was expected that Aboriginal and Torres Strait Islander women would differ in their anthropometric and metabolic characteristics, ethnicity was included in the adjusted model.

10.   CAPLAN, 1975

HYPOTHYROID AND HYPERTHYROID PATIENTS

Age: 14.0-85.0 years	**Study design:** Case-control (**n = 103**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** United States **Region:** **State:** Wisconsin
Inclusion criteria: abnormal serum thyroxine levels	**Exclusion critieria:** abnormal thyroxine levels not due to thyroid dysfunction, insufficient hematologic data before treatment, severe debilitating disease in addition to thyroid dysfunction, use of drugs known to affect the levels of serum folic acid, vitamin B12 or both

10.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	Lactobacillus casei microbiologie assay	normal values for this laboratory, 5 to 15 ng/ml; indeterminate, 3 to 5 ng/ml; low, <3 ng/ml)

Outcomes

	Outcome	Diagnostic Description
A	Hyperthyroid (medical professional or test)	We confirmed the diagnosis of hypothyroidism or hyperthyroidism by clinical criteria and, when necessary, by measurements of T3-resin uptake, 24-hour thyroidal uptake of sodium iodide I131 (hyperthyroid patients), serum thyrotropin levels (hypothyroid patients)
B	Hypothyroid (medical professional or test)	We confirmed the diagnosis of hypothyroidism or hyperthyroidism by clinical criteria and, when necessary, by measurements of T3-resin uptake, 24-hour thyroidal uptake of sodium iodide I131 (hyperthyroid patients), serum thyrotropin levels (hypothyroid patients)

Results

10.1.A Hyperthyroid

Population: Hypothyroid and Hyperthyroid Patients
Exposure: Serum folate
Outcome: Hyperthyroid
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Serum Folate	-	-	

10.1.B Hypothyroid

Population: Hypothyroid and Hyperthyroid Patients
Exposure: Serum folate
Outcome: Hypothyroid
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum Folate	-	-	

Statistical Method(s)

Endpoints: Hypothyroid
Adjustment factors:
Statistical metric: t-test
Statistical metric description: n/a

Endpoints: Hyperthyroid
Adjustment factors:
Statistical metric: other
Statistical metric description: n/a

11. CHEN, 2010

Full citation: Chen AR, Zhang HG, Wang ZP, Fu SJ, Yang PQ, Ren JG, Ning YY, Hu XJ, Tian LH. 2010. C-reactive protein, vitamin B12 and C677T polymorphism of N-5,10-methylenetetrahydrofolate reductase gene are related to insulin resistance and risk factors for metabolic syndrome in Chinese population. Clin Invest Med 33(5): E290-297.

HAN CHINESE NEWLY DIAGNOSED WITH DIABETES

Age: 57.8 (mean)	**Study design:** Case-control (**n = 213**)
Gender: Male and Female **Ethnicities:** Asian	**Country:** China **Region:** **State:**
Inclusion criteria: enrolled in the Second Hospital at Lanzhou University and newly diagnosed with T2DM according to WHO's criteria, Han Chinese, no history of folate, vitamin or drug use, unrelated to each other	**Exclusion critieria:** anemia, inflammatory diseases, mental or emotional problems, those with untreatable chronic diseases such as cancer, liver disease, kidney disease, coronary heart disease & depression, vitamin or folate deficiency

11.1. Exposure: Serum folate

Method	Description	Analysis
serum	folate and vitamin B12 (Simul TRAC-SNB, folate[125I]/B12[57Co], American ICN Pharmaceuticals, Inc.) were analyzed by radioimmunoassay.	radioimmunoassay

Outcomes

	Outcome	Diagnostic Description
A	Type 2 Diabetes with and without Metabolic Syndrome (medical professional or test)	Patients with Metabolic syndrome must meet at least two of the following criteria besides those for T2DM: 1) fasting serum triglyceride concentration >1.7 mmol/l (150 mg/dl);2) cholesterol concentration of serum high density lipoprotein (HDL) <0.9mmol/l (36 mg/dl) for men or <1.0 mmol/l (40 mg/dl) for women; 3) systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg; and 4) body mass index >25 kg/m2

Results

11.1.A Type 2 Diabetes with and without Metabolic Syndrome

Population: Han Chinese Adults with or without diabetes and Metabolic Syndrome
Exposure: Serum folate
Outcome: Type 2 Diabetes with and without Metabolic Syndrome
Statistical metric: mean

Group	N	mean 95% CI (low, high)	p-value
Serum folate in control	55	-	
Serum folate in T2DM without Metabolic syndrome	40	-	0.05
Serum folate in T2DM with Metabolic syndrome	118	-	0.05

Statistical Method(s)

Endpoints: Type 2 Diabetes with and without Metabolic Syndrome
Adjustment factors:
Statistical metric: mean
Statistical metric description: All data are analyzed by SPSS and presented as mean ± standard deviation (SD). Student's t test, one-way analysis of variance (ANOVA) and Chi Square test were used for comparison of group differences

12. CHILD, 2004

Full citation: Child DF, Hudson PR, Jones H, Davies GK, De P, Mukherjee S, Brain AM, Williams CP, Harvey JN. 2004. The effect of oral folic acid on glutathione, glycaemia and lipids in Type 2 diabetes. Diabetes Nutr Metab 17(2): 95-102.

Funding: None reported

TYPE 2 DIABETICS IN THE UNITED KINGDOM

Age: 59.0 (mean)	**Study design:** Controlled trial (**n** = 27)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** United Kingdom **Region:** **State:**
Inclusion criteria: enrolled in Diabetes Register, Type 2 diabetes mellitis with microalbuminuria	**Exclusion critieria:**

12.1. Exposure: Folate supplementation

Method	Description	Analysis
supplementation	Folic acid supplementation 10 mg daily for 3 months (while keeping usual diet)	intervention

Outcomes

	Outcome	Diagnostic Description
A	Blood HbA1c (medical professional or test)	HbA1c assayed using automated HPLC system (Glycomat 765)
B	Glucose (medical professional or test)	measured in mmol/L; in the present study, fasting glucose... used to derive %B and %S. no logarithmic transformation necessary
C	Glucose/Insulin ratio (medical professional or test)	measured in mmol/mU
D	HOMA beta (medical professional or test)	Homa beta (%)
E	HOMA sensitivity (medical professional or test)	HOMA sensitivity (%)
F	Insulin (medical professional or test)	measured in mU/L; in the present study, fasting glucose... used to derive %B and %S. no logarithmic transformation necessary

Results

12.1.A Blood HbA1c

Population: Type 2 Diabetics in the United Kingdom
Exposure: Folate supplementation
Outcome: Blood HbA1c
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Before treatment with 10 mg folic acid	-	-	0.042
After treatment with 10 mg folic acid	-	-	

12.1.B Glucose

Population: Type 2 Diabetics in the United Kingdom
Exposure: Folate supplementation
Outcome: Glucose
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Before treatment with 10 mg folic acid	-	-	
After treatment with 10 mg folic acid	-	-	0.63

12.1.C Glucose/Insulin ratio

Population: Type 2 Diabetics in the United Kingdom
Exposure: Folate supplementation
Outcome: Glucose/Insulin ratio
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Before treatment with 10 mg folic acid	-	-	
After treatment with 10 mg folic acid	-	-	0.62

12.1.D HOMA beta

Population: Type 2 Diabetics in the United Kingdom
Exposure: Folate supplementation
Outcome: HOMA beta
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Before treatment with 10 mg folic acid	-	-	
After treatment with 10 mg folic acid	-	-	0.83

12.1.E HOMA sensitivity

Population: Type 2 Diabetics in the United Kingdom
Exposure: Folate supplementation
Outcome: HOMA sensitivity
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Before treatment with 10 mg folic acid	-	-	
After treatment with 10 mg folic acid	-	-	0.4

12.1.F   Insulin

Population: Type 2 Diabetics in the United Kingdom
Exposure: Folate supplementation
Outcome: Insulin
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Before treatment with 10 mg folic acid	-	-	
After treatment with 10 mg folic acid	-	-	0.19

Statistical Method(s)

Endpoints: Glucose; Insulin; Glucose/Insulin ratio; HOMA sensitivity; HOMA beta; Blood HbA1c
Adjustment factors:
Statistical metric: mean
Statistical metric description: Linear modelling approach (GLM) was used to test simultaneously the effect of insulin... on each change in HbA1c, etc. Statistical values (p values) are quoted for best-fit models, after elimination of non-significant effects. differences between paired results & p values assessed using Wilcoxon signed rank test and unpaired results with the Wilcoxon Mann Whitney Test; point estimates and 95% confidence intervals for the shift between two distributions claculated by Hodges-Lehmann Estimation

13.   COLLERAN, 2003

Full citation: Colleran KM, Ratliff DM, Burge MR. 2003. Potential association of thyrotoxicosis with vitamin B and folate deficiencies, resulting in risk for hyperhomocysteinemia and subsequent thromboembolic events. Endocr Pract 9(4): 290-295.

PATIENTS WITH THYROTOXICOSIS DUE TO GRAVES' DISEASE

Age:	Study design: Case-control (n = 31)
Gender: Male and Female Ethnicities:	Country: United States Region: State: New Mexico
Inclusion criteria: between ages 18 and 50, newly diagnosed Graves' disease	Exclusion critieria: history of diabetes, renal or liver disease, or anemia or were using oral contraceptive agents, herbal supplements, or multivitamins., vitamin B12 or folate deficiency

13.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	Blood samples were obtained by venipuncture. Analyzed with Immulite Chemiluminescence analyzer [enzyme immunometric assay]	5-20 ng/mL

Outcomes

	Outcome	Diagnostic Description
A	Hyperthyroid (not reported)	newly diagnosed Graves' Disease

Results

13.1.A Hyperthyroid

Population: Patients with thyrotoxicosis due to Graves' Disease
Exposure: Serum folate
Outcome: Hyperthyroid
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Hyperthyroid	21	-	
Posttreatment for hyperthyroid	11	-	
Control	10	-	

Statistical Method(s)

Endpoints: Hyperthyroid
Adjustment factors:
Statistical metric: mean
Statistical metric description: All data were analyzed by using SAS version 6.1 statistical software (SAS Institute, Cary, NC). Descriptive data are reported as the mean ± 1 standard deviation and were compared by using two-tailed Student t tests. In the patients with hyperthyroidism, twotailed tests were used. Significance was inferred if P values were <0.05.

14.   DANGOUR, 2008

Full citation: Dangour AD, Breeze E, Clarke R, Shetty PS, Uauy R, Fletcher AE. 2008. Plasma homocysteine, but not folate or vitamin B-12, predicts mortality in older people in the United Kingdom. J Nutr 138(6): 1121-1128.

MEDICAL RESEARCH COUNCIL TRIAL OF ASSESSMENT AND MANAGEMENT OF OLDER PEOPLE IN THE COMMUNITY

Age: 78.6 (median)	**Study design:** Prospective (**n** = 853)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** United Kingdom **Region:** **State:**
Inclusion criteria: >/= 75 years age old, registered with a general practitioner	**Exclusion critieria:** resident in a long-stay hospital or nursing home, terminally ill

14.1. Exposure: Plasma folate

Method	Description	Analysis
serum assay	Plasma vitamin B-12 and folate concentrations were measured at the Rowett Laboratory using a Becton Dickinson Simultrac kit [immunoradiometric assay] for vitamin B-12 and folate	CV of 9–12% for folate.

Outcomes

	Outcome	Diagnostic Description
A	Diabetes Mellitus (self-reported)	% Diabetes Mellitus (DM) across tertiles of serum folate concentration; In-depth trial assessments included questionnaires seeking information about aspects of health (30), alcohol intake and smoking habits... including past and recent history of heart attack, stroke, cancer, and diabetes.

Results

14.1.A Diabetes Mellitus

Population: Older People in the United Kingdom
Exposure: Plasma folate
Outcome: Diabetes Mellitus
Statistical metric: other

Group	N	other 95% CI (low, high)	p-value
Lowest tertile serum folate concentration	-	-	
Middle tertile serum folate concentration	-	-	
Highest tertile serum folate concentration	-	-	

Statistical Method(s)

Endpoints: Diabetes Mellitus
Adjustment factors: age, sex
Statistical metric: other
Statistical metric description: % by tertiles of folate concentrations; The P-values for test for trend were obtained from a logistic regression model in which the thirds were scored from 1 to 3 and a log-linear model for odds of the outcome assumed. Further models took account of possible confounders from data collected at the in-depth assessment and the nutrition and physical activity interviews.

15.   DEMIRBAS, 2004

Full citation: Demirbas B, Ozkaya M, Cakal E, Culha C, Gulcelik N, Koc G, Serter R, Aral Y. 2004. Plasma homocysteine levels in hyperthyroid patients. Endocr J 51(1): 121-125.

Funding: None reported

HYPERTHYROID PATIENTS

Age: 42.9 (mean)	**Study design:** Case-control (**n** = 24)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Turkey **Region:** **State:**
Inclusion criteria: toxic diffuse goitre	**Exclusion critieria:** major organ or systemic disease

15.1. Exposure: Plasma Folate

Method	Description	Analysis
serum assay	plasma folate measured by radioassay	n/a

Outcomes

	Outcome	Diagnostic Description
A	Hyperthyroidism vs Euthyroidism (normal thyroid) (medical professional or test)	"recently diagnosed hyperthyroid disorder"-- no other information mentioned

Results

15.1.A Hyperthyroidism vs Euthyroidism (normal thyroid)

Population: Hyperthyroid patients
Exposure: Plasma Folate
Outcome: Hyperthyroidism vs Euthyroidism (normal thyroid)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Plasma folate levels	24	-	0.05

Statistical Method(s)

Endpoints: Hyperthyroidism vs Euthyroidism (normal thyroid)
Adjustment factors:
Statistical metric: other
Statistical metric description: statistical analyses via paired sample t test and indep. sample t test using SPSS; obtained data presented as means +/- SD

16.   DIAKOUMOPOULOU, 2005

Full citation: Diakoumopoulou E, Tentolouris N, Kirlaki E, Perrea D, Kitsou E, Psallas M, Doulgerakis D, Katsilambros N. 2005. Plasma homocysteine levels in patients with type 2 diabetes in a Mediterranean population: relation with nutritional and other factors. Nutr Metab Cardiovasc Dis 15(2): 109-117.

DIABETICS IN A MEDITERRANEAN POPULATION

Age: 57.4 (None)	Study design: Case-control (n = 202)
Gender: Male and Female **Ethnicities:**	**Country:** Greece **Region:** **State:** Athens
Inclusion criteria: 40-75 years of age, no history of cancer or leukemia, psoriasis, and alcohol abuse, no history of hypothyroidism, liver disease, active infection, autoimmune diseases, stage III or IV heart failure, uncontrolled hypertension, pregnancy, no history of nephropathy or microalbuminuria, Patient with type 2 diabetes	**Exclusion critieria:** medications known to affect plasma tHcy levels (methotrexate... vitamin supplementation), vitamin or folate deficiency

16.1. Exposure: Serum folate

Method	Description	Analysis
assay	Blood was drawn early in the morning after a 8-10 fast for measurement of biochemical and other study parameters. Plasma levels of vitamin B12 and folate were measured by radioimmunoassay (RIA) methods [SimulTRAC-SNB Radiassay Kit Vitamin B12 [57Co] (Dietary folate also measured by food frequency questionnaire, but no results reported.)	Plasma folate [SimulTRAC-SNB Radiassay Kit Vitamin B12 [57Co]/Folate [125I], ICN Pharmaceuticals, Diagnostic Division, Orangeburg, New York, c.v.=4.8+/-1.3% and 6.3+/-1.9%, respectively]

Outcomes

	Outcome	Diagnostic Description
A	Type 2 diabetes (medical records)	attending the outpatient diabetes clinic of our hospital

Results

16.1.A Type 2 diabetes

Population: Diabetics in a Mediterranean population
Exposure: Serum folate

Outcome: Type 2 diabetes
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	-	-	0.01

Statistical Method(s)

Endpoints: Type 2 diabetes
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Because the plasma values of folate and vitamin B12 were skewed, they were log-transformed to improve normality for statistical testing and back-transformed for presentation in the tables. A two-sample t-test or a Wilcoxon test was used to compare differences between non-diabetic and diabetic subjects.

17. DIEKMAN, 2001

PATIENTS WITH HYPERTHYROIDISM AND HYPOTHYROIDISM

Age: 42.0 (None)	**Study design:** Cross-sectional (**n** = 96)
Gender: Male and Female **Ethnicities:** Asian, Black or African American, White	**Country:** Netherlands **Region:** **State:**
Inclusion criteria: no vitamin supplementation, they did not use any medication known to interfere with thyroid hormone or homocysteine metabolism	**Exclusion critieria:**

17.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	plasma folate measured by radioassay (Dualcount solid phase no boil assay, Diagnostic Products Corporation, Los Angeles, USA)	n/a

Outcomes

	Outcome	Diagnostic Description
A	Hypothyroid and Hyperthryoid (medical professional or test)	patients referred to our out-patient clinic

Results

17.1.A Hypothyroid and Hyperthryoid

Population: Hyperthyroidism and hypothyroidism
Exposure: Serum folate
Outcome: Hypothyroid and Hyperthryoid
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	-	-	0.05

Statistical Method(s)

Endpoints: Hypothyroid and Hyperthryoid
Adjustment factors:
Statistical metric: t-test

Statistical metric description: Data in the transition from the hypo- or hyperthyroid state to the euthyroid state were compared by paired or unpaired Student's t-test when appropriate

18. DINLEYICI, 2006

Full citation: Dinleyici EC, Kirel B, Alatas O, Muslumanoglu H, Kilic Z, Dogruel N. 2006. Plasma total homocysteine levels in children with type 1 diabetes: relationship with vitamin status, methylene tetrahydrofolate reductase genotype, disease parameters and coronary risk factors. J Trop Pediatr 52(4): 260-266.

Funding: None reported

CHILDREN WITH TYPE 1 DIABETES

Age: 10.8 (mean), from 6.0-17.0 years	Study design: Case-control (n = 55)
Gender: Male and Female Ethnicities: Unknown/Unspecified	Country: Turkey Region: State:
Inclusion criteria: case children had type 1 diabetes, nonsmokers	Exclusion critieria:

18.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	folic acid levels were measured with Bayer ACS 180 Plus (immunoassay) Note Table 2 reports in ng/dl, but likely should be ng/ml	n/a

Outcomes

	Outcome	Diagnostic Description
A	Type 1 Diabetes (not reported)	n/a

Results

18.1.A Type 1 Diabetes

Population: Children with Type 1 Diabetes
Exposure: Serum folate
Outcome: Type 1 Diabetes
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	-	-	0.01

Statistical Method(s)

Endpoints: Type 1 Diabetes
Adjustment factors:
Statistical metric: t-test

Statistical metric description: Mann–Whitney U, independent sample t, Chi-squared and Fisher's Exact tests were used for the comparisons. p<0.01

19. DOMÍNGUEZ, 2005

Full citation: Domínguez RO, Marschoff ER, Guareschi EM, Famulari AL, Pagano MA, Serra JA. 2005. Homocysteine, vitamin B 12 and folate in Alzheimer's and vascular dementias: the paradoxical effect of the superimposed type II diabetes mellitus condition. Clin Chim Acta 359(1-2): 163-170.

PATIENTS WITH TYPE II DIABETES MELLITUS

Age: 73.0 (mean)	**Study design:** Case-control (**n = 122**)
Gender: Male and Female **Ethnicities:** White	**Country:** Argentina **Region:** **State:**
Inclusion criteria: recruited from Diabetes Unit of 3 hospitals	**Exclusion critieria:** smoking history, treatments or supplementation with vitamins in the last 5 years

19.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	AxSYM Folate technique (which is a ionic capture assay used for quantitative determination of folate in serum, plasma or human erythrocytes by means of the AxSYM analyzer)	The results are expressed in ng/ml plasma.

Outcomes

	Outcome	Diagnostic Description
A	Type II diabetes (medical professional or test)	Tthe ADA and the WHO criteria were sued for DM patients, and the DSM IV criteria for the non-demented control subjects. (Subjects also recruited with vascular and and Alzheimer's type dementia, some with diabetes as well, but only the diabetics and controls reported here.)

Results

19.1.A Type II diabetes

Population: Patients with Type II diabetes mellitus
Exposure: Serum folate
Outcome: Type II diabetes
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Plasma folate	-	-	0.05

Statistical Method(s)

Endpoints: Type II diabetes
Adjustment factors:
Statistical metric: other
Statistical metric description: A one-way Analysis of Variance (ANOVA) was performed on each variable and the Bonferroni statistic was employed to compare the mean values of groups of patients and controls

20. EBESUNUN, 2012

Full citation: Ebesunun MO, Obajobi EO. 2012. Elevated plasma homocysteine in type 2 diabetes mellitus: a risk factor for cardiovascular diseases. The Pan African medical journal 12: 48.

OBAFEMI AWOLOWO UNIVERSITY TEACHING HOSPITAL, NIGERIA

Age: 52.5 (mean), from 45.0-75.0 years	**Study design:** Case-control (**n = 100**)
Gender: Male and Female **Ethnicities:** Black or African American	**Country:** Nigeria **Region:** Ile-Ife **State:** Osun
Inclusion criteria: Age > 45years, Obese, Patient with type 2 diabetes	**Exclusion critieria:** Patient with liver, renal diseases and any other disease that could affect the outcome of study, Patient with type 1 diabetes

20.1. Exposure: Plasma folate

Method	Description	Analysis
Plasma assay	All blood specimens were drawn in the morning after an overnight fast of 10-14 hours into EDTA and fluoride oxalate bottles and these were immediately placed in ice pack bag. The blood samples were centrifuged using Livingstone centrifuge model LS 90-2 (manufactured by Livingstone Medicals England), the plasma samples were stored at -20°C until analyzed. Plasma folic acid was determined using HPLC.	Accuracy and precision of biochemical tests were monitored by including commercial quality control samples within each batch of test assay.

Outcomes

	Outcome	Diagnostic Description
A	Type 2 diabetes (medical professional or test)	The diagnosis of type 2 DM was assessed by the attending Consultant Physican using clinical history and fasting plasma glucose (FPG) =7.0mmol/L (=126mg/dl) and casual plasma glucose (random plasma glucose) of >11.0mmol/L (=200mg/dl) or the 2-hour plasma glucose of >11.0mmol/L after a 75g oral glucose load.

Results

20.1.A Type 2 diabetes

Population: Medical Outpatient Clinic, Nigeria
Exposure: Plasma folate

Outcome: Type 2 diabetes
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Plasma folate levels	100	-	0.001

Statistical Method(s)

Endpoints: Type 2 diabetes
Adjustment factors:
Statistical metric: other
Statistical metric description: All results were subjected to statistical analyses using SPSS for Windows, version 10.0. The results were expressed mean +/- SD. Differences between means were asses using the student t-test for independent samples. Post Hoc test was also performed. Two-tailed independent t-test of significance at 95% confidence limit p value less than 0.05.

21. ERKOÇOĞLU, 2013

Full citation: Erkoçoğlu M, Ozon ZA, Gocmen R, Alikasifoglu A, Gonc N, Kandemir N. 2013. Carotid intima media thickness in adolescents with increased risk for atherosclerosis. Turk J Pediatr 55(5): 510-518.

Funding: None reported

CAROTID INTIMA MEDIA THICKNESS IN ADOLESCENTS WITH INCREASED RISK FOR ATHEROSCLEROSIS

Age: 14.9 (mean), from 11.9-17.3 years	**Study design:** Case-control (**n =** 80)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Turkey **Region:** **State:**
Inclusion criteria: children 10 years or older, children at risk for atherosclerosis, pubertal children	**Exclusion critieria:** chronic disease, especially celiac disease and/or malabsorption, vitamin supplementation

21.1. Exposure: Serum folate

Method	Description	Analysis
not specified	assay/method not mentioned. Venous blood samples were collected after an overnight fast in all subjects (and before insulin administration in the subjects with diabetes)	n/a

Outcomes

	Outcome	Diagnostic Description
A	Type 1 Diabetes (medical records)	recruited consecutively among the admissions to the outpatient clinic of the Department of Pediatric Endocrinology; Type 1 Diabetes disease onset of at least six months before inclusion into the study

Results

21.1.A Type 1 Diabetes

Population: Adolescents with increased risk for atherosclerosis, Turkey
Exposure: Serum folate
Outcome: Type 1 Diabetes
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Serum folate	-	-	

Statistical Method(s)

Endpoints: Type 1 Diabetes
Adjustment factors:
Statistical metric: mean
Statistical metric description: Differences between groups were assessed using one-way ANOVA for normally distributed data and Kruskal-Wallis for non-normally distributed data.

22. FAULKNER, 2006

Full citation: Faulkner MS, Chao WH, Kamath SK, Quinn L, Fritschi C, Maggiore JA, Williams RH, Reynolds RD. 2006. Total homocysteine, diet, and lipid profiles in type 1 and type 2 diabetic and nondiabetic adolescents. J Cardiovasc Nurs 21(1): 47-55.

DIABETIC ADOLESCENTS

Age: 15.9 (mean), from 13.0-18.9 years	**Study design:** Cross-sectional (**n =** 117)
Gender: Male and Female **Ethnicities:** Asian, Black or African American, Hispanic/Latino, White	**Country:** United States **Region:** Chicago **State:** Illinois
Inclusion criteria: Adolescents had to have been diagnosed with type 1 or 2 diabetes for 1 year, no other chronic illnesses	**Exclusion critieria:**

22.1. Exposure: Folate intake

Method	Description	Analysis
food record	ug/day; 3-day 24-hour food record	Data from the food record were entered into a nutrition analysis software program, Nutritionist VTM (San Bruno, Calif), which can be used to perform a nutrient analysis of food records, diets, recipes, and menus and compare this information to specific nutrient requirements

Outcomes

	Outcome	Diagnostic Description
A	Type 1 and 2 Diabetes (medical records)	Patients recruited from pediatric diabetes clinics, controls recruited from an affluent high school. Information collected included the date of diagnosis, age of their son or daughter, race or ethnicity, history of smoking for the adolescent, and family history of diabetes and heart disease for first-degree and second-degree relatives.

Results

22.1.A Type 1 and 2 Diabetes

Population: Diabetic Adolescents
Exposure: Folate intake
Outcome: Type 1 and 2 Diabetes
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Folate intake in controls	53	-	
Folate intake in Type 1 diabetics	50	-	
Folate intake in Type 2 diabetics	14	-	

Statistical Method(s)

Endpoints: Type 1 and 2 Diabetes
Adjustment factors:
Statistical metric: mean
Statistical metric description: One-way analyses of variance with subsequent post hoc Tukey tests were used to test for significant differences among the mean comparisons of height, weight BMI, dietary energy, macronutrient intake, selected micronutrient intake, and serum concentrations of lipids, lipoproteins, and tHcy for males and for females across the 3 groups: type 1 DM, type 2 DM, and non-DM

23.   GIANNATTASIO, 2010

Full citation: Giannattasio A, Calevo MG, Minniti G, Gianotti D, Cotellessa M, Napoli F, Lorini R, d'Annunzio G. 2010. Folic acid, vitamin B12, and homocysteine levels during fasting and after methionine load in patients with Type 1 diabetes mellitus. J Endocrinol Invest 33(5): 297-299.

PATIENTS WITH TYPE 1 DIABETES MELLITUS, ITALY

Age: 16.7 (mean), from 9.0-31.0 years	**Study design:** Case-control (**n = 164**)
Gender: Male and Female **Ethnicities:** White	**Country:** Italy **Region:** Genoa **State:**
Inclusion criteria: absence of microvascular complications i.e.: persistent microalbuminuria or retinopathy, absence of other risk factors for vascular disease (smoking, hypertension, estroprogestinic therapy, high cholesterol levels), Patient with type 1 diabetes	**Exclusion critieria:** autoimmune disorders like celiac disease and autoimmune thyroid disease

23.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	folic acid levels were measured by means of a competitive chemiluminescent enzyme immunoassay (IMMULITE 2000, Siemens Medical Solution Diagnostics	n/a

Outcomes

	Outcome	Diagnostic Description
A	Type 1 Diabetes (medical professional or test)	Diabetes mellitus was diagnosed according to the 1997 American Diabetes Association Criteria

Results

23.1.A Type 1 Diabetes

Population: Patients with Type 1 diabetes mellitus, Italy
Exposure: Serum folate
Outcome: Type 1 Diabetes
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	164	-	0.0001
Serum folate, men	84	-	0.002
Serum folate, women	80	-	0.0001

Statistical Method(s)

Endpoints: Type 1 Diabetes
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Results are expressed as mean and SD for continuous variables. Two groups were compared using t-Student test for continuous variables

24. GU, 2008

Full citation: Gu W, Lu J, Yang G, Dou J, Mu Y, Meng J, Pan C. 2008. Plasma homocysteine thiolactone associated with risk of macrovasculopathy in Chinese patients with type 2 diabetes mellitus. Adv Ther 25(9): 914-924.

Funding: None reported

CHINESE PATIENTS WITH TYPE 2 DIABETES MELLITUS

Age: 61.9 (mean)	**Study design:** Case-control (**n** = 160)
Gender: Male and Female **Ethnicities:** Asian	**Country:** China **Region:** **State:**
Inclusion criteria:	**Exclusion critieria:** diabetic ketoacidosis, other systemic diseases, severe hepatic or renal diseases (serum creatinine >133 µmol/L), fever, congestive heart failure, as well as acute cardiovascular and cerebrovascular events, glycated hemoglobin (HbA1c) >12%, Patients who received vitamin B complex or folic acid during the past 6 months

24.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	competitive protein binding assay (chemiluminescence assaying kit).	detection limit was 1 pmol/L HcyT

Outcomes

	Outcome	Diagnostic Description
A	Type 2 diabetes (medical professional or test)	One hundred and twenty patients diagnosed with type 2 diabetes who visited the Chinese PLA General Hospital

Results

24.1.A Type 2 diabetes

Population: Chinese Patients with Type 2 Diabetes
Exposure: Serum folate
Outcome: Type 2 diabetes
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	160	-	0.001

Statistical Method(s)

Endpoints: Type 2 diabetes
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Clinical data with normal distribution were expressed as mean±SD, and results with non-normal distribution were shown as the median with 25th and 75th quartiles. Data between the two groups were compared by Student's t test/Mann Whitney U test.

25. GUVEN, 2006

Full citation: Guven MA, Kilinc M, Batukan C, Ekerbicer HC, Aksu T. 2006. Elevated second trimester serum homocysteine levels in women with gestational diabetes mellitus. Arch Gynecol Obstet 274(6): 333-337.

Funding: None reported

WOMEN WITH GESTATIONAL DIABETES MELLITUS (GDM)

Age: 29.0 (None)	**Study design:** Cross-sectional (**n** = 223)
Gender: Female **Ethnicities:** Unknown/Unspecified	**Country:** Turkey **Region:** **State:**
Inclusion criteria: did not take medication (except for iron supplementation) at least 3 months before enrollment, no history of hypertension or cardiovascular disease, no known vitamin deficiency, nonsmokers, no personal or family history of deep venous thrombosis, no previous medical history of diabetes, no significant medical illnesses	**Exclusion critieria:** older than 40 years of age, parity > 5 births, taken/been given oral folate supplementation within 2 weeks before blood sampling

25.1. Exposure: Serum folate

Method	Description	Analysis
Serum assay	Serum folate measured by Automated Chemiluminescence System (Access, Beckman instruments, USA)	(coefficient of variation, 4.7%)

Outcomes

	Outcome	Diagnostic Description
A	Gestational Diabetes Mellitus (GDM) (medical professional or test)	In our institution, we routinely survey our patients between 24 and 28 weeks of gestation with a 50-g oral glucose tolerance test (OGTT). Patients are considered screen-negative when their 1 h blood glucose level is below 140 mg/dl. Those with a 1 h postprandial plasma glucose concentration above this threshold receive a 3-h 100-g OGTT. To ensure consistency, all patients are instructed to add 150 g of carbohydrate to their usual meals for 3 days before taking the 100 g OGTT. Blood samples were collected after a 12 h fast, starting at 8 a.m. and repeated after 60, 120 and 180 min after glucose ingestion. The diagnosis of gestational diabetes was based upon the criteria of Carpenter and Coustan [16] by which after a 100-g oral glucose load two or more of the following plasma values must be met or exceeded: fasting 95 mg/dl, 1 h 180 mg/dl, 2 h 155 mg/dl and 3 h 140 mg/dl; Borderline group had an abnormal 1hr, but a normal 3hr glucose tolerance test.

Results

25.1.A Gestational Diabetes Mellitus (GDM)

Population: Women with gestational diabetes, Turkey
Exposure: Serum folate
Outcome: Gestational Diabetes Mellitus (GDM)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Serum folate	30	-	

Statistical Method(s)

Endpoints: Gestational Diabetes Mellitus (GDM)
Adjustment factors:
Statistical metric: other
Statistical metric description: For all measured parameters, statistical analyses of between-group differences were performed by using ANOVA followed by post-hoc Scheffe test

26.   GYFTAKI, 1979

Full citation: Gyftaki H, Kesse-Elias M, Koutras D, Pandos P, Papazoglou S, Moulopoulos S. 1979. Serum vitamin B12 and folic acid levels in hyperthyroidism. Nuklearmedizin 18(6): 278-282.

Funding: None reported

HYPERTHYROID PATIENTS, GREECE

Age: 38.8 (mean), from 12.0-74.0 years	**Study design:** Case-control (**n** = 118)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Greece **Region:** **State:**
Inclusion criteria: diagnosis of hyperthyroidism	**Exclusion critieria:** elevated hemoglobin A, patients with liver, kidney or gastrointestinal tract diseases with malabsorption

26.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	special radioassay measuring folic acid	pig plasma used as binder

Outcomes

	Outcome	Diagnostic Description
A	Hyperthyroidism (medical professional or test)	diagnosis made on clinical grounds ... and confirmed by laboratory test findings

Results

26.1.A Hyperthyroidism

Population: Hyperthyroid patients, Greece
Exposure: Serum folate
Outcome: Hyperthyroidism
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	-	-	

Statistical Method(s)

Endpoints: Hyperthyroidism
Adjustment factors:
Statistical metric: t-test
Statistical metric description: (in results section) The results were plotted on semilog paper and a logarithmic distribution confirmed. For the statistical analysis of the results the t-test was used after logarithmic transformation of the values.

27. HARDIKAR, 2012

PUNE CHILDREN'S STUDY AT AGE 21

Age: 21.6 (mean), from 21.0-23.0 years	**Study design:** Cross-sectional (**n** = 116)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** India **Region:** **State:**
Inclusion criteria: blood measured on the same day, enrolled in the Pune Children's Study prospective birth cohort	**Exclusion critieria:**

27.1. Exposure: Plasma folate

Method	Description	Analysis
plasma	fasting blood draw	Hemoglobin and hematological parameters were measured on a Beckman Coulter analyzer (AcT Diff, Miami, FL). Plasma folate was measured by microbiologocal assay using a chloramphenicol-resistant strain of Lactobacillus casei. Coefficients of variations for folate measurements were <8%.

Outcomes

	Outcome	Diagnostic Description
A	determinents of HbA1c (medical professional or test)	HbA1c was measured using high-performance liquid chromatography (Bio-Rad D-10; Bio-Rad Laboratories, Hercules, CA) calibrated against the National Glycosylated Standardization Program. Coefficients of variations (CVs) were 1.3% at an HbA1c concentration of 5.8% and 1.2% at a concentration of 10.0%. Bio-Rad External Quality Assurances Services results were within 60.1% of the group mean. The classification of glycemia by HbA1c was performed according to ADA criteria (prediabetes: 5.7–6.4%; diabetes: $6.5%)
B	prediabetes and diabetes (HbA1c >=5.7%) (medical professional or test)	HbA1c was measured using high-performance liquid chromatography (Bio-Rad D-10; Bio-Rad Laboratories, Hercules, CA) calibrated against the National Glycosylated Standardization Program. Coefficients of variations (CVs) were 1.3% at an HbA1c concentration of 5.8% and 1.2% at a concentration of 10.0%. Bio-Rad External Quality Assurances Services results were within 60.1% of the group mean.

Outcome	Diagnostic Description
	The classification of glycemia by HbA1c was performed according to ADA criteria (prediabetes: 5.7–6.4%; diabetes: $6.5%)

Results

27.1.A determinents of HbA1c

Population: Pune Children's Study at 21, 2010-2012
Exposure: Plasma folate
Outcome: determinents of HbA1c
Statistical metric: regression coefficient

Group	N	coefficient 95% CI (low, high)	*p*-value
Plasma folate	-	-	

27.1.B prediabetes and diabetes (HbA1c >=5.7%)

Population: Pune Children's Study at 21, 2010-2012
Exposure: Plasma folate
Outcome: prediabetes and diabetes (HbA1c >=5.7%)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Plasma folate	-	-	

Statistical Method(s)

Endpoints: determinents of HbA1c
Adjustment factors: 2 hr glucose
Statistical metric: regression coefficient
Statistical metric description: Associations between HbA1c and glycemic and nonglycemic factors were assessed using Pearson correlation coefficients, followed by multiple linear regression analysis. The level of significance was set at P < 0.05.

Endpoints: prediabetes and diabetes (HbA1c >=5.7%)
Adjustment factors:
Statistical metric: other
Statistical metric description: Parametric and nonparametric comparisons were performed using ANOVA or Mann-Whitney U test as appropriate.

28.   HELFENSTEIN, 2005

Full citation: Helfenstein T, Fonseca FA, Relvas WG, Santos AO, Dabela ML, Matheus SC, D'Almeida V, Tufik S, Souza FG, Rodrigues PR, Taglieri R, Sousa EF, Izar MC. 2005. Prevalence of myocardial infarction is related to hyperhomocysteinemia but not influenced by C677T methylenetetrahydrofolate reductase and A2756G methionine synthase polymorphisms in diabetic and non-diabetic subjects. Clin Chim Acta 355(1-2): 165-172.

DIABETICS WITHOUT MYOCARDIAL INFARCTION

Age: 58.0 (None)	**Study design:** Case-control (**n = 106**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Brazil **Region:** **State:**
Inclusion criteria: 40-75 years of age	**Exclusion critieria:** congestive heart failure classes III or IV, diabetic retinopathy, diabetics with serum creatinine >2.0 mg/dL, hepatic failure, neoplasms, patients taking vitamins or functional foods, patients with acute coronary, PTCA or coronary artery bypass graft surgery occurring 3 months prior to the study, uncontrolled hypothyroidism

28.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	AxSYM Analyzer (Abbott Laboratories, Abbott Park, IL) using a microparticle enzyme intrinsic factor pathway (immunoassay)-- presented as mg/dL	n/a

Outcomes

	Outcome	Diagnostic Description
A	Diabetes (medical professional or test)	Patients were enrolled according to the presence of either type 2 diabetes mellitus (DM) or prior myocardial infarction (MI), defined by the American Diabetes Association, and the World Health Organization.

Results

28.1.A Diabetes

Population: Diabetics without Myocardial Infarction, Brazil
Exposure: Serum folate
Outcome: Diabetes
Statistical metric: other

Group	N	other 95% CI (low, high)	p-value
serum folate	106	-	0.001

Statistical Method(s)

Endpoints: Diabetes
Adjustment factors:
Statistical metric: other
Statistical metric description: Continuous variables were presented as mean +/-S.E.M. and compared by one-way ANOVA, followed by Tukey's multiple comparison tests

29.   IDZIOR-WALUŚ, 2008

Full citation: Idzior-Walus B, Cyganek K, Sztefko K, Seghieri G, Breschi MC, Walus-Miarka M, Kawalec E, Seretny M, Sieradzki J. 2008. Total plasma homocysteine correlates in women with gestational diabetes. Arch Gynecol Obstet 278(4): 309-313.

PREGNANT WOMEN WITH OR WITHOUT GESTATIONAL DIABETES

Age: 29.3 (None)	**Study design:** Case-control (**n =** 61)
Gender: Female **Ethnicities:** Unknown/Unspecified	**Country:** Poland **Region:** **State:**
Inclusion criteria: pregnant women referred to outpatient diabetic clinic with suspicion of gestational diabetes mellitus (GDM)	**Exclusion critieria:**

29.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	chemiluminescent immunoassay	n/a

Outcomes

	Outcome	Diagnostic Description
A	Gestational Diabetes Mellitus (GDM) (medical professional or test)	based on positive results of test with 50 g glucose load. In all women, the oral glucose tolerance test (OGTT) with 75 g of glucose, according to WHO criteria was performed.

Results

29.1.A Gestational Diabetes Mellitus (GDM)

Population: Pregnant women with or without gestational diabetes mellitus (GDM)
Exposure: Serum folate
Outcome: Gestational Diabetes Mellitus (GDM)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Serum folate	-	-	

Statistical Method(s)

Endpoints: Gestational Diabetes Mellitus (GDM)
Adjustment factors:
Statistical metric: other
Statistical metric description: Non-parametric analyses were used to compare folic acid...because these data were not normally distributed.

30.   IMAMURA, 2010

Full citation: Imamura A, Murakami R, Takahashi R, Cheng XW, Numaguchi Y, Murohara T, Okumura K. 2010. Low folate levels may be an atherogenic factor regardless of homocysteine levels in young healthy nonsmokers. Metabolism 59(5): 728-733.

Funding: None reported

YOUNG HEALTHY MALE NONSMOKERS

Age: 30.3 (mean), from 25.0-39.0 years	**Study design:** Cross-sectional (**n = 71**)
Gender: Male **Ethnicities:** Asian	**Country:** Japan **Region:** **State:**
Inclusion criteria: healthy with normal renal function, were free of any sign or symptoms of heart disease, were taking no medication including antidiabetic, antihypertensive, and lipid-lowering drugs or dietary supplements of vitamins B6 and B12 and folate	**Exclusion critieria:**

30.1. Exposure: Plasma folate

Method	Description	Analysis
assay	Plasma folate determined by a chemiluminescence enzyme immunoassay	n/a

Outcomes

	Outcome	Diagnostic Description
A	Fasting glucose (medical professional or test)	Standard assays were used to measure serum concentrations of glucose; no other information provided
B	Fasting insulin (medical professional or test)	Standard assays were used to measure serum concentrations of insulin levels; no other information provided
C	Hemoglobin A1c (HbA1c) levels (medical professional or test)	Standard assays were used to measure serum concentrations of hemoglobin A1c (HbA1c) levels; no other information provided
D	Homeostatic model of insulin resistance (HOMA-IR) (medical professional or test)	The homeostasis model assessment of insulin resistance (HOMA-IR) was used to estimate insulin sensitivity no other information provided

Results

30.1.A Fasting glucose

Population: Young healthy male nonsmokers, Japan
Exposure: Plasma folate
Outcome: Fasting glucose
Statistical metric: correlation

Group	N	r 95% CI (low, high)	p-value
Plasma folate	71	-0.096	0.42

30.1.B Fasting insulin

Population: Young healthy male nonsmokers, Japan
Exposure: Plasma folate
Outcome: Fasting insulin
Statistical metric: correlation

Group	N	r 95% CI (low, high)	p-value
Plasma folate	71	-0.239	0.046

30.1.C Hemoglobin A1c (HbA1c) levels

Population: Young healthy male nonsmokers, Japan
Exposure: Plasma folate
Outcome: Hemoglobin A1c (HbA1c) levels
Statistical metric: correlation

Group	N	r 95% CI (low, high)	p-value
Plasma folate	71	-0.069	0.57

30.1.D Homeostatic model of insulin resistance (HOMA-IR)

Population: Young healthy male nonsmokers, Japan
Exposure: Plasma folate
Outcome: Homeostatic model of insulin resistance (HOMA-IR)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	p-value
Plasma folate	71	-0.234	0.051

Statistical Method(s)

Endpoints: Fasting glucose; Hemoglobin A1c (HbA1c) levels; Fasting insulin; Homeostatic model of insulin resistance (HOMA-IR)
Adjustment factors:
Statistical metric: correlation
Statistical metric description: Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. Because the levels of triglycerides, fasting insulin, and HOMA-IR were not normally distributed, they were logarithmically transformed before statistical analysis. Pearson correlation coefficients (r) were applied to identify variables associated with variations in plasma folate or homocysteine levels.

31.   KAYA, 2009

Full citation: Kaya C, Cengiz SD, Satiroglu H. 2009. Obesity and insulin resistance associated with lower plasma vitamin B12 in PCOS. Reprod Biomed Online 19(5): 721-726.

Funding: None reported

WOMEN WITH POLYCYSTIC OVARY SYNDROME (PCOS)

Age: 27.0 (None)	**Study design:** Case-control (**n** = 122)
Gender: Female **Ethnicities:** Unknown/Unspecified	**Country:** Turkey **Region:** **State:** Ankara
Inclusion criteria: diagnosed with Polycystic Ovary Syndrome (PCOS) in cases	**Exclusion critieria:** congenital adrenal hyperplasia, Cushing's syndrome, diabetes mellitus, hepatic or renal dysfunction, hyperprolactinaemia, hypertension, smokers, thyroid disorders, treated with hormonal medications, vitamins or drugs that increase Hcy levels within the past 3 months, use of any confounding medications including oral contraceptives, antilipidaemic drugs and insulin-sensitizing drugs within 3 months prior to enrollment, vitamin B12 or folate deficiency, vitamin or folate deficiency

31.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	n electrochemiluminescence immunoassay (ECLIA) (ELECSYS 2010 HITACHI; Roche Diagnostics) with specific chemiluminescence assays	Mean coefficients of variation determined to be intra- and interassay 6.8% and 7.9% for folate

Outcomes

	Outcome	Diagnostic Description
A	All subjects stratified by Insulin resistance (medical professional or test)	All subjects, including cases (n=61) and controls (n=61). Insulin Resistance was measured as follows: Next, all patients underwent a 2-h OGTT with a 75-g glucose load, with determinations of both glucose and insulin at baseline (before glucose load) and after 120 min. Baseline and post-treatment serum levels of insulin were measured using an electrochemiluminescence immunoassay (ECLIA).
B	Polycystic Ovary Syndrome stratified by Insulin resistance (medical professional or test)	All PCOS subjects had irregular menses, and 61% of participants had eight or fewer spontaneous cycles per year. The diagnosis of PCOS was made according to the Rotterdam European Society for Human Reproduction and Embryology... Specifically, all eligible patients presented with at least two of the following three criteria: (i) chronic anovulation, (ii) hyperandrogenism (hirsutism, acne) and/or hyperandrogenaemia and (iii) polycystic tic ovaries. The presence of polycystic ovarian appearance was determined ultrasonographically

Outcome	Diagnostic Description
	(Balen et al., 2003). Oligomenorrhoea (cycle intervals >35 days), amenorrhoea (absence of menstruation for 3 consecutive months), and luteal phase progesterone measurements less than 4 ng/ml in women with regular menstrual cycles were considered indicative of oligo-ovulation. Hirsutism was determined by a modified Ferriman score score above 7. Insulin Resistance was measured as follows: Next, all patients underwent a 2-h OGTT with a 75-g glucose load, with determinations of both glucose and insulin at baseline (before glucose load) and after 120 min. Baseline and post-treatment serum levels of insulin were measured using an electrochemiluminescence immunoassay (ECLIA)

Results

31.1.A All subjects stratified by Insulin resistance

Population: Women with Polycystic Ovary Syndrome (PCOS), Turkey
Exposure: Serum folate
Outcome: All subjects stratified by Insulin resistance
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	122	-	

31.1.B Polycystic Ovary Syndrome stratified by Insulin resistance

Population: Women with Polycystic Ovary Syndrome (PCOS), Turkey
Exposure: Serum folate
Outcome: Polycystic Ovary Syndrome stratified by Insulin resistance
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	61	-	

Statistical Method(s)

Endpoints: Polycystic Ovary Syndrome stratified by Insulin resistance; All subjects stratified by Insulin resistance
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Data are shown as means ± SD. Groups were compared using Student's t test. ShapiroWilk test was used in order to detect whether or not the continuous variables were normally distributed. A P-value <0.05 was considered statistically significant.

32. KIM, 2010

Full citation: Kim DS, Kim YK, Park HK, Cho YI, Jeong SK. 2010. Serum folate and low-density lipoprotein particle size. J Atheroscler Thromb 17(12): 1218-1225.

KOREAN HOSPITAL WORKERS

Age: 43.5 (mean)	**Study design:** Cross-sectional (**n =** 255)
Gender: Male and Female **Ethnicities:** Asian	**Country:** Korea, Democratic People's Republic Of **Region:** **State:**
Inclusion criteria: hospital worker	**Exclusion critieria:** lost to follow up

32.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	electrochemiluminescence immunoassay using Elecsys 2010 (Roche Diagnostics GmbH)	All subsequent analyses were performed according to quartiles of serum folate levels

Outcomes

	Outcome	Diagnostic Description
A	Homeostatis Model Assessment of the Insulin Resistance (HOMA-IR) (medical professional or test)	serum insulin measured by electrochemiluminescence immunoassay and insulin resistance measured by HOMA-IR
B	Metabolic Syndrome (medical professional or test)	Metabolic syndrome identified by the presence of three or more of the following five components, according to the modified criteria of the Third Adults Treatment Panel (modeified ATP-III), with waist cutoffs appropriate for an Asian population: 1) abdominal obesity, 2) high blood pressure, 3) high TG, 4) low HDL, 5) high fasting glucose

Results

32.1.A Homeostatis Model Assessment of the Insulin Resistance (HOMA-IR)

Population: Hospital Workers, South Korea
Exposure: Serum folate
Outcome: Homeostatis Model Assessment of the Insulin Resistance (HOMA-IR)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
1st quartile <6.43 ng/mL	62	-	
2nd quartile 6.43-8.04 ng/mL	66	-	
3rd quartile 8.05-10.3	62	-	

Group	N	other 95% CI (low, high)	*p*-value
4th quartile >10.32 ng/mL	65	-	0.622

32.1.B Metabolic Syndrome

Population: Hospital Workers, South Korea
Exposure: Serum folate
Outcome: Metabolic Syndrome
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
1st quartile <6.43 ng/mL	62	-	
2nd quartile 6.43-8.04 ng/mL	66	-	
3rd quartile 8.05-10.3	62	-	
4th quartile >10.32 ng/mL	65	-	0.827

Statistical Method(s)

Endpoints: Metabolic Syndrome; Homeostatis Model Assessment of the Insulin Resistance (HOMA-IR)
Adjustment factors:
Statistical metric: other
Statistical metric description: Analysis of variance (ANOVA) and student's t-test used to determine statistical differences in continuous variables

33.   KRISHNAVENI, 2009

Full citation: Krishnaveni GV, Hill JC, Veena SR, Bhat DS, Wills AK, Karat CL, Yajnik CS, Fall CH. 2009. Low plasma vitamin B12 in pregnancy is associated with gestational 'diabesity' and later diabetes. Diabetologia 52(11): 2350-2358.

PREGNANT WOMEN IN MYSORE, INDIA

Age: 24.0 (median), from 21.0-26.0 years	**Study design:** Cross-sectional (**n = 772**)
Gender: Female **Ethnicities:** Asian	**Country:** India **Region:** Mysore **State:**
Inclusion criteria: intention to deliver at Holdsworth Memorial Hospital, no history of diabetes, singleton pregnancy	**Exclusion critieria:** death of offspring before follow-up, offspring medically unfit

33.1. Exposure: plasma folate during pregnancy

Method	Description	Analysis
Plasma	plasma folate microbiological assays	Stored fasting plasma samples were used to measure folate. The samples had been stored in freezer with 1 hour of sampling at -80C for 8 years. Samples were transferred on dry ice for laboratory analysis at the Diabetes Research Centre, KEM Hospital, Pune , India, using microbiological assays.

Outcomes

	Outcome	Diagnostic Description
A	Gestational Diabetes Mellitus (GDM) (medical professional or test)	Diabetes was defined as a fasting glucose concentration ≥7.0 and/or 120 min glucose ≥11.1 mmol/l. Women were also classified as having diabetes if they had been diagnosed by a doctor as having diabetes since the index pregnancy. Impaired glucose tolerance (IGT) was a fasting glucose concentration <7.0 mmol/l and 120 min glucose ≥7.8 mmol/l but <11.1 mmol/l. Impaired fasting glucose (IFG) was defined as fasting glucose ≥6.1 mmol/l but <7.0 mmol/l. Metabolic syndrome was defined by the International Diabetes Federation (IDF) criteria recommended for south Asian women. Waist circumference >= 80 cm, and any two of the following: triacyglycerol>=1.7 mmol/l; HDL-cholesterol <1.29 mmol/l; SBP>=130 or DBP>=85 or having treatment for hypertension; fasting glucose >=5.6 mmol/l; or type 2 diabetes
B	Insulin resistance (HOMA-2), during pregnancy	Diabetes was defined as a fasting glucose concentration ≥7.0 and/or 120 min glucose ≥11.1 mmol/l. Women were also classified as having

Outcome	Diagnostic Description
(medical professional or test)	diabetes if they had been diagnosed by a doctor as having diabetes since the index pregnancy. Impaired glucose tolerance (IGT) was a fasting glucose concentration <7.0 mmol/l and 120 min glucose ≥7.8 mmol/l but <11.1 mmol/l. Impaired fasting glucose (IFG) was defined as fasting glucose ≥6.1 mmol/l but <7.0 mmol/l. Metabolic syndrome was defined by the International Diabetes Federation (IDF) criteria recommended for south Asian women. Waist circumference >= 80 cm, and any two of the following: triacyglycerol>=1.7 mmol/l; HDL-cholesterol <1.29 mmol/l; SBP>=130 or DBP>=85 or having treatment for hypertension; fasting glucose >=5.6 mmol/l; or type 2 diabetes.

Results

33.1.A Gestational Diabetes Mellitus (GDM)

Population: Pregnant women in Mysore, India
Exposure: plasma folate during pregnancy
Outcome: Gestational Diabetes Mellitus (GDM)
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
plasma folate	774	1.0 (0.99, 1.0)	0.3

33.1.B Insulin resistance (HOMA-2), during pregnancy

Population: Pregnant women in Mysore, India
Exposure: plasma folate during pregnancy
Outcome: Insulin resistance (HOMA-2), during pregnancy
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
plasma folate	774	-0.001 (-0.003, 0.002)	0.2

Statistical Method(s)

Endpoints: Insulin resistance (HOMA-2), during pregnancy
Adjustment factors: SES, age, family history of diabetes, gestational BMI, parity, religion
Statistical metric: adjusted beta
Statistical metric description: The distributions of HOMA-2 and vitamin B12 concentrations were skewed; these data were log-transformed for analysis where required. ... Other confounding exposures such as maternal age, parity, religion, family history of diabetes and SES were used as covariates in the multiple regression models. The outcomes of interest were anthropometry, insulin resistance and the incidence of GDM during pregnancy, and anthropometry, insulin resistance and the prevalence of diabetes and metabolic syndrome at follow-up. Associations of maternal vitamin B12 and folate concentrations with anthropometry and HOMA-2 during pregnancy and at follow-up were examined using linear regression analysis, and with the incidence of GDM, and the prevalence of diabetes and metabolic syndrome at follow-up, using logistic regression analysis. Interaction terms were used to test for modification by folate status of associations between vitamin B12 status and the several diabetes-related outcomes by using vitamin B12 as two groups (deficiency and normal groups), and tertiles of folate concentrations. p values <0.05 were considered significant. All statistical analyses were performed using SPSS V16.

Endpoints: Gestational Diabetes Mellitus (GDM)
Adjustment factors: SES, age, family history of diabetes, gestational BMI, parity, religion
Statistical metric: adjusted odds ratio
Statistical metric description: The distributions of HOMA-2 and vitamin B12 concentrations were skewed; these data were log-transformed for analysis where required. ... Other confounding exposures such as maternal age, parity, religion, family history of diabetes and SES were used as covariates in the multiple regression models. The outcomes of interest were anthropometry, insulin resistance and the incidence of GDM during pregnancy, and anthropometry, insulin resistance and the prevalence of diabetes and metabolic syndrome at follow-up. Associations of maternal vitamin B12 and folate concentrations with anthropometry and HOMA-2 during pregnancy and at follow-up were examined using linear regression analysis, and with the incidence of GDM, and the prevalence of diabetes and metabolic syndrome at follow-up, using logistic regression analysis. Interaction terms were used to test for modification by folate status of associations between vitamin B12 status and the several diabetes-related outcomes by using vitamin B12 as two groups (deficiency and normal groups), and tertiles of folate concentrations. p values <0.05 were considered significant. All statistical analyses were performed using SPSS V16.

WOMEN IN MYSORE, INDIA, 5 YEARS AFTER PREGNANCY

Age: 24.0 (None), from 21.0-26.0 years	Study design: Prospective (n = 519)
Gender: Female Ethnicities: Asian	Country: India Region: Mysore State:
Inclusion criteria: enrolled in study during pregnancy, intention to deliver at Holdsworth Memorial Hospital, no history of diabetes, singleton pregnancy	Exclusion critieria: death of offspring before follow-up, offspring medically unfit

33.2. Exposure: plasma folate during pregnancy

Method	Description	Analysis
Plasma	plasma folate microbiological assays	Stored fasting plasma samples were used to measure folate. The samples had been stored in freezer with 1 hour of sampling at -80C for 8 years. Samples were transferred on dry ice for laboratory analysis at the Diabetes Research Centre, KEM Hospital, Pune , India, using microbiological assays.

Outcomes

	Outcome	Diagnostic Description
A	Diabetes Mellitus (DM) (medical professional or test)	Diabetes was defined as a fasting glucose concentration ≥7.0 and/or 120 min glucose ≥11.1 mmol/l. Women were also classified as having

	Outcome	Diagnostic Description
		diabetes if they had been diagnosed by a doctor as having diabetes since the index pregnancy. Impaired glucose tolerance (IGT) was a fasting glucose concentration <7.0 mmol/l and 120 min glucose ≥7.8 mmol/l but <11.1 mmol/l. Impaired fasting glucose (IFG) was defined as fasting glucose ≥6.1 mmol/l but <7.0 mmol/l. Metabolic syndrome was defined by the International Diabetes Federation (IDF) criteria recommended for south Asian women. Waist circumference >= 80 cm, and any two of the following: triacyglycerol>=1.7 mmol/l; HDL-cholesterol <1.29 mmol/l; SBP>=130 or DBP>=85 or having treatment for hypertension; fasting glucose >=5.6 mmol/l; or type 2 diabetes
B	Insulin resistance (HOMA-2) (medical professional or test)	Diabetes was defined as a fasting glucose concentration ≥7.0 and/or 120 min glucose ≥11.1 mmol/l. Women were also classified as having diabetes if they had been diagnosed by a doctor as having diabetes since the index pregnancy. Impaired glucose tolerance (IGT) was a fasting glucose concentration <7.0 mmol/l and 120 min glucose ≥7.8 mmol/l but <11.1 mmol/l. Impaired fasting glucose (IFG) was defined as fasting glucose ≥6.1 mmol/l but <7.0 mmol/l. Metabolic syndrome was defined by the International Diabetes Federation (IDF) criteria recommended for south Asian women. Waist circumference >= 80 cm, and any two of the following: triacyglycerol>=1.7 mmol/l; HDL-cholesterol <1.29 mmol/l; SBP>=130 or DBP>=85 or having treatment for hypertension; fasting glucose >=5.6 mmol/l; or type 2 diabetes.
C	Metabolic Syndrome (medical professional or test)	Metabolic syndrome was defined by the International Diabetes Federation (IDF) criteria recommended for south Asian women. Waist circumference >= 80 cm, and any two of the following: triacyglycerol>=1.7 mmol/l; HDL-cholesterol <1.29 mmol/l; SBP>=130 or DBP>=85 or having treatment for hypertension; fasting glucose >=5.6 mmol/l; or type 2 diabetes

Results

33.2.A Diabetes Mellitus (DM)

Population: Pregnant women in Mysore, India
Exposure: plasma folate during pregnancy
Outcome: Diabetes Mellitus (DM)
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Plasma folate levels	519	0.999 (0.98, 1.0)	0.98

33.2.B Insulin resistance (HOMA-2)

Population: Pregnant women in Mysore, India
Exposure: plasma folate during pregnancy
Outcome: Insulin resistance (HOMA-2)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Plasma folate levels	519	-0.0002 (-0.003, 0.003)	0.5

33.2.C Metabolic Syndrome

Population: Pregnant women in Mysore, India
Exposure: plasma folate during pregnancy
Outcome: Metabolic Syndrome
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Plasma folate levels	519	1.01 (0.996, 1.02)	0.2

Statistical Method(s)

Endpoints: Insulin resistance (HOMA-2)
Adjustment factors: SES, age, family history of diabetes, gestational BMI, parity, religion
Statistical metric: adjusted beta
Statistical metric description: The distributions of HOMA-2 and vitamin B12 concentrations were skewed; these data were log-transformed for analysis where required. ... Other confounding exposures such as maternal age, parity, religion, family history of diabetes and SES were used as covariates in the multiple regression models. The outcomes of interest were anthropometry, insulin resistance and the incidence of GDM during pregnancy, and anthropometry, insulin resistance and the prevalence of diabetes and metabolic syndrome at follow-up. Associations of maternal vitamin B12 and folate concentrations with anthropometry and HOMA-2 during pregnancy and at follow-up were examined using linear regression analysis, and with the incidence of GDM, and the prevalence of diabetes and metabolic syndrome at follow-up, using logistic regression analysis. Interaction terms were used to test for modification by folate status of associations between vitamin B12 status and the several diabetes-related outcomes by using vitamin B12 as two groups (deficiency and normal groups), and tertiles of folate concentrations. p values <0.05 were considered significant. All statistical analyses were performed using SPSS V16.

Endpoints: Diabetes Mellitus (DM); Metabolic Syndrome
Adjustment factors: SES, age, family history of diabetes, gestational BMI, parity, religion
Statistical metric: adjusted odds ratio
Statistical metric description: The distributions of HOMA-2 and vitamin B12 concentrations were skewed; these data were log-transformed for analysis where required. ... Other confounding exposures such as maternal age, parity, religion, family history of diabetes and SES were used as covariates in the multiple regression models. The outcomes of interest were anthropometry, insulin resistance and the incidence of GDM during pregnancy, and anthropometry, insulin resistance and the prevalence of diabetes and metabolic syndrome at follow-up. Associations of maternal vitamin B12 and folate concentrations with anthropometry and HOMA-2 during pregnancy and at follow-up were examined using linear regression analysis, and with the incidence of GDM, and the prevalence of diabetes and metabolic syndrome at follow-up, using logistic regression analysis. Interaction terms were used to test for modification by folate status of associations between vitamin B12 status and the several diabetes-related outcomes by using vitamin B12 as two groups (deficiency and normal groups), and tertiles of folate concentrations. p values <0.05 were considered significant. All statistical analyses were performed using SPSS V16.

34.   KRISHNAVENI, 2014

Full citation: Krishnaveni GV, Veena SR, Karat SC, Yajnik CS, Fall CH. 2014. Association between maternal folate concentrations during pregnancy and insulin resistance in Indian children. Diabetologia 57(1): 110-121.

MATERNAL FOLATE AND INSULIN RESISTANCE IN INDIAN CHILDREN

Age: child outcomes assessed throughout life, at 5, 9.5,& 13.5 yrs	**Study design:** Prospective (**n =** 654)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** India **Region:** Mysore **State:**
Inclusion criteria: <32 weeks' gestation at recruitment, intention to deliver at Holdsworth Memorial Hospital (HMH) in Mysore, India, no known history of diabetes, singleton pregnancy	**Exclusion critieria:**

34.1. Exposure: Maternal plasma folate during pregnancy

Method	Description	Analysis
assay	Maternal folate concentrations were analysed using plasma samples stored at −80°C for 8 years; adequate samples were available for 654 mothers who were included in the analysis; microbiological assay for folate	n/a

Outcomes

	Outcome	Diagnostic Description
A	Age 13.5, glucose (0 min) (medical professional or test)	Plasma glucose concentrations were measured by standard enzymatic methods-- a 2 hour oral glucose tolerance test. Results for glucose indicated at times 0 min, 30 min and 120 min-- Glucose (0) indicates glucose at 0 min.
B	Age 13.5, Homeostatic model assessment of Insulin Resistance (HOMA-IR) (medical professional or test)	Insulin resistance was estimated using the HOMA of insulin resistance (HOMA-IR) at all three time points (5, 9.5 and 13.5 years)
C	Age 13.5, insulin (0 min) (medical professional or test)	Plasma insulin concentrations were measured by standard enzymatic methods-- a 2 hour oral glucose tolerance test. Results for insulin

	Outcome	Diagnostic Description
		indicated at times 0 min, 30 min and 120 min-- Insulin (0) indicates insulin at 0 min.
D	Age 5, glucose (0 min) (medical professional or test)	Plasma glucose concentrations were measured by standard enzymatic methods-- a 2 hour oral glucose tolerance test. Results for glucose indicated at times 0 min, 30 min and 120 min-- Glucose (0) indicates glucose at 0 min.
E	Age 5, glucose (120 min) (medical professional or test)	Plasma glucose concentrations were measured by standard enzymatic methods-- a 2 hour oral glucose tolerance test. Results for glucose indicated at times 0 min, 30 min and 120 min-- Glucose (120) indicates glucose at 120 min.
F	Age 5, glucose (30 min) (medical professional or test)	Plasma glucose concentrations were measured by standard enzymatic methods-- a 2 hour oral glucose tolerance test. Results for glucose indicated at times 0 min, 30 min and 120 min-- Glucose (30) indicates glucose at 30 min.
G	Age 5, Homeostatic model assessment of Insulin Resistance (HOMA-IR) (medical professional or test)	Insulin resistance was estimated using the HOMA of insulin resistance (HOMA-IR) at all three time points (5, 9.5 and 13.5 years)
H	Age 5, insulin (0 min) (medical professional or test)	Plasma insulin concentrations were measured by standard enzymatic methods-- a 2 hour oral glucose tolerance test. Results for insulin indicated at times 0 min, 30 min and 120 min-- Insulin (0) indicates insulin at 0 min.
I	Age 5, insulin (120 min) (medical professional or test)	Plasma insulin concentrations were measured by standard enzymatic methods-- a 2 hour oral glucose tolerance test. Results for insulin indicated at times 0 min, 30 min and 120 min-- Insulin (120) indicates insulin at 120 min.
J	Age 5, insulin (30 min) (medical professional or test)	Plasma insulin concentrations were measured by standard enzymatic methods-- a 2 hour oral glucose tolerance test. Results for insulin indicated at times 0 min, 30 min and 120 min-- Insulin (30) indicates insulin at 30 min.
K	Age 9.5, glucose (0 min) (medical professional or test)	Plasma glucose concentrations were measured by standard enzymatic methods-- a 2 hour oral glucose tolerance test. Results for glucose indicated at times 0 min, 30 min and 120 min-- Glucose (0) indicates glucose at 0 min.
L	Age 9.5, glucose (120 min) (medical professional or test)	Plasma glucose concentrations were measured by standard enzymatic methods-- a 2 hour oral glucose tolerance test. Results for glucose indicated at times 0 min, 30 min and 120 min-- Glucose (120) indicates glucose at 120 min.
M	Age 9.5, glucose (30 min) (medical professional or test)	Plasma glucose concentrations were measured by standard enzymatic methods-- a 2 hour oral glucose tolerance test. Results for glucose indicated at times 0 min, 30 min and 120 min-- Glucose (30) indicates glucose at 30 min.
N	Age 9.5, Homeostatic model assessment of Insulin Resistance (HOMA-IR) (medical professional or test)	Insulin resistance was estimated using the HOMA of insulin resistance (HOMA-IR) at all three time points (5, 9.5 and 13.5 years)
O	Age 9.5, insulin (0 min) (medical professional or test)	Plasma insulin concentrations were measured by standard enzymatic methods-- a 2 hour oral glucose tolerance test. Results for insulin indicated at times 0 min, 30 min and 120 min-- Insulin (0) indicates insulin at 0 min.
P	Age 9.5, insulin (120 min)	Plasma insulin concentrations were measured by standard enzymatic

	Outcome	Diagnostic Description
	(medical professional or test)	methods-- a 2 hour oral glucose tolerance test. Results for insulin indicated at times 0 min, 30 min and 120 min-- Insulin (120) indicates insulin at 120 min.
Q	Age 9.5, insulin (30 min) (medical professional or test)	Plasma insulin concentrations were measured by standard enzymatic methods-- a 2 hour oral glucose tolerance test. Results for insulin indicated at times 0 min, 30 min and 120 min-- Insulin (30) indicates insulin at 30 min.

Results

34.1.A Age 13.5, glucose (0 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 13.5, glucose (0 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	0.03 (-0.07, 0.1)	0.6

34.1.B Age 13.5, Homeostatic model assessment of Insulin Resistance (HOMA-IR)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 13.5, Homeostatic model assessment of Insulin Resistance (HOMA-IR)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	0.1 (-0.01, 0.2)	0.03

34.1.C Age 13.5, insulin (0 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 13.5, insulin (0 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	0.1 (0.01, 0.2)	0.02

34.1.D Age 5, glucose (0 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 5, glucose (0 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	0.13 (0.03, 0.2)	0.009

34.1.E Age 5, glucose (120 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy

Outcome: Age 5, glucose (120 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	-0.0003 (-0.005, 0.005)	0.9

34.1.F Age 5, glucose (30 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 5, glucose (30 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	-0.0001 (-0.005, 0.005)	0.96

34.1.G Age 5, Homeostatic model assessment of Insulin Resistance (HOMA-IR)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 5, Homeostatic model assessment of Insulin Resistance (HOMA-IR)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	0.02 (-0.08, 0.1)	0.7

34.1.H Age 5, insulin (0 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 5, insulin (0 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	-0.0001 (-0.005, 0.005)	0.97

34.1.I Age 5, insulin (120 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 5, insulin (120 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	0.001 (-0.004, 0.006)	0.7

34.1.J Age 5, insulin (30 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 5, insulin (30 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	-3e-05 (-0.005, 0.005)	0.99

34.1.K Age 9.5, glucose (0 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 9.5, glucose (0 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	0.08 (-0.02, 0.2)	0.1

34.1.L Age 9.5, glucose (120 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 9.5, glucose (120 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	-0.01 (-0.1, 0.09)	0.9

34.1.M Age 9.5, glucose (30 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 9.5, glucose (30 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	0.03 (-0.07, 0.1)	0.5

34.1.N Age 9.5, Homeostatic model assessment of Insulin Resistance (HOMA-IR)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 9.5, Homeostatic model assessment of Insulin Resistance (HOMA-IR)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	0.1 (0.01, 0.2)	0.03

34.1.O Age 9.5, insulin (0 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 9.5, insulin (0 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	0.09 (0.0003, 0.2)	0.04

34.1.P Age 9.5, insulin (120 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 9.5, insulin (120 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	-0.03 (-0.1, 0.07)	0.6

34.1.Q Age 9.5, insulin (30 min)

Population: Insulin resistance in Indian children
Exposure: Maternal plasma folate during pregnancy
Outcome: Age 9.5, insulin (30 min)
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Maternal plasma folate	-	0.08 (-0.02, 0.2)	0.1

Statistical Method(s)

Endpoints: Age 5, Homeostatic model assessment of Insulin Resistance (HOMA-IR); Age 13.5, glucose (0 min); Age 5, glucose (30 min); Age 5, glucose (120 min); Age 5, glucose (0 min); Age 9.5, glucose (0 min); Age 9.5, glucose (120 min); Age 9.5, Homeostatic model assessment of Insulin Resistance (HOMA-IR); Age 13.5, Homeostatic model assessment of Insulin Resistance (HOMA-IR); Age 9.5, glucose (30 min)
Adjustment factors: child's 9.5-year vitamin B12 and folate concentrations, child's age at follow-up, child's current BMI, child's pubertal stage, child's sex, maternal BMI, maternal gestational diabetes mellitus (GDM) status, maternal parity, maternal religion, maternal socioeconomic status (SES), maternal vitamin B12 concentration
Statistical metric: adjusted beta
Statistical metric description: Associations between maternal ..., folate concentrations and offspring outcomes were examined using multivariate linear regression, adjusting for gestational age (for birth variables) or current age (for childhood variables) and sex. Additional adjustments were made for maternal parity, religion, BMI, GDM and SES, and the children's vitamin B12, folate, current BMI and pubertal stage where relevant; p values of <0.05 were considered significant.

Endpoints: Age 5, insulin (30 min); Age 9.5, insulin (0 min); Age 13.5, insulin (0 min); Age 5, insulin (0 min); Age 9.5, insulin (30 min); Age 9.5, insulin (120 min); Age 5, insulin (120 min)
Adjustment factors: child's 9.5-year vitamin B12 and folate concentrations, child's age at follow-up, child's current BMI, child's pubertal stage, child's sex, maternal BMI, maternal gestational diabetes mellitus (GDM) status, maternal parity, maternal religion, maternal socioeconomic status (SES), maternal vitamin B12 concentration
Statistical metric: adjusted beta
Statistical metric description: log-transformed values. Associations between maternal ..., folate concentrations and offspring outcomes were examined using multivariate linear regression, adjusting for gestational age (for birth variables) or current age (for childhood variables) and sex. Additional adjustments were made for maternal parity, religion, BMI, GDM and SES, and the children's vitamin B12, folate, current BMI and pubertal stage where relevant; p values of <0.05 were considered significant.

35.   LI, 2014A

TYPE 2 DIABETICS, CHINA

Age: 60.7 (mean), from 40.0-70.0 years	**Study design:** Cross-sectional (**n = 291**)
Gender: Male and Female **Ethnicities:** Asian	**Country:** China **Region:** Nanjing **State:**
Inclusion criteria: Patient with type 2 diabetes	**Exclusion critieria:** congestive heart failure classes III or IV, severe liver disease, severe renal dysfunction (creatinine > 147 mmol/L), vitamin supplementation

35.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	Serum folate determined using automated test assays	n/a

Outcomes

	Outcome	Diagnostic Description
A	Type 2 diabetes (medical professional or test)	Diabetes status was biochemically confirmed according to the WHO diagnostic criteria for the classification of diabetes... Patients with macular edema versus without were included in this observation

Results

35.1.A Type 2 diabetes

Population: Chinese type 2 diabetics
Exposure: Serum folate
Outcome: Type 2 diabetes
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Serum folate	-	-	

Statistical Method(s)

Endpoints: Type 2 diabetes
Adjustment factors:

Statistical metric: mean
Statistical metric description: Data expressed as mean (SD) for normally distributed data. The data were cross-sectional observations. p<0.05 was considered statistically significant

36. LI, 2014B

Full citation: Li J, Zhang H, Yan L, Xie M, Chen J. 2014b. Fracture is additionally attributed to hyperhomocysteinemia in men and premenopausal women with type 2 diabetes. J Diabetes Investig 5(2): 236-241.

TYPE 2 DIABETICS AND FRACTURES, CHINA

Age: 54.3 (None)	**Study design:** Cross-sectional (**n** = 292)
Gender: Male and Female **Ethnicities:** Asian	**Country:** China **Region:** Nanjing **State:**
Inclusion criteria: negative history of prior fractures, Type 2 diabetics (men and premenopausal women with regular menstruation)	**Exclusion critieria:** congestive heart failure classes III or IV, injury-associated fractures, other conditions (hypercortisolism, hyperparathyroidism, hypogonadism, hyperthyroidism, etc.), severe liver disease, severe renal dysfunction (creatinine > 147 mmol/L), use of drugs (glucocorticoids, sex steroids, warfarin, bisphosphonates, etc.) related to affecting bone mineral density or fractures

36.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	serum folate determined using automated test assays	n/a

Outcomes

	Outcome	Diagnostic Description
A	Type 2 Diabetes Mellitus (medical professional or test)	Diabetes status was biochemically confirmed in patients according to the World health Organization diagnostic criteria for the classification of diabetes.

Results

36.1.A Type 2 Diabetes Mellitus

Population: Type 2 diabetes, China
Exposure: Serum folate
Outcome: Type 2 Diabetes Mellitus
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Serum folate	-	-	

Statistical Method(s)

Endpoints: Type 2 Diabetes Mellitus
Adjustment factors:
Statistical metric: mean
Statistical metric description: Data expressed as mean (standard deviation) for normally distributed data. The data were cross-sectional observations. P < 0.05 was considered statistically significant.

37.   LIPPI, 2008

Full citation: Lippi G, Montagnana M, Targher G, Salvagno GL, Guidi GC. 2008. Prevalence of folic Acid and vitamin B12 deficiencies in patients with thyroid disorders. Am J Med Sci 336(1): 50-52.

Funding: None reported

PATIENTS WITH THYROID DISORDERS

Age: 55.0 (mean), from 19.0-88.0 years	**Study design:** Retrospective (**n = 946**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Italy **Region:** **State:**
Inclusion criteria: referred by general practitioners for yearly routine blood testing between June 2005 and 2007	**Exclusion critieria:**

37.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	automated chemiluminescence method (Chiron Diagnostics)	Low serum levels of folic acid </= 6.8 nmol/L

Outcomes

	Outcome	Diagnostic Description
A	Thyroid Stimulating Hormone (TSH) level (medical professional or test)	Venous blood from outpatients was routinely collected in the morning by the laboratory personnel on fasting subjects. Serum TSH was quantified by a third generation assay (functional sensitivity of 0.01-0.02 mIU/L with an interassay imprecision 20%) on the Immulite 2000 analyzer (Diagnostic Products Corporation, Los Angeles, CA).4 The reference range (0.2–2.5 mIU/L) was established in accordance with current studies suggesting that TSH values inthe 0.1 to 0.4 mIU/L range may represent thyroid hormone excess, thus citing lower limits between 0.2 and 0.4 mIU/L.

Results

37.1.A Thyroid Stimulating Hormone (TSH) level

Population: Patients with Thyroid Disorders
Exposure: Serum folate
Outcome: Thyroid Stimulating Hormone (TSH) level
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Serum folate	-	-	0.036

Statistical Method(s)

Endpoints: Thyroid Stimulating Hormone (TSH) level
Adjustment factors: Thyroid stimulating hormone, age, sex, vitamin B12
Statistical metric: mean
Statistical metric description: The significance of differences between groups was assessed by the Kruskal-Wallis test (for continuous variables). The skewed variables were logarithmically transformed to improve normality before analysis and then back-transformed to their natural units for presentation. Data are finally shown as mean (2 SD, 95% CI) or percentages. In the fully adjusted multivariable regression model, folic acid and B12 were separately entered as dependent variables, whereas age, gender, TSH, and B12 (or folic acid) were included as covariates.

38. LIU, 2013

Full citation: Liu CP, Lin YL, Lin YH, Pao KY, Wu VC, Su TC, Hung CS, Gau CS, Hwang JJ. 2013. The impact of metabolic syndrome, homocysteine, and b vitamins on carotid artery intima-media thickness in hypertensive patients. Acta Cardiologica Sinica 29(1): 56-63.

Funding: none reported

HYPERTENSTION STUDY, NATIONAL TAIWAN UNIVERSITY HOSPITAL

Age: 70.7 (mean)	**Study design:** Cross-sectional (**n** = 73)
Gender: Male and Female **Ethnicities:** Asian	**Country:** Taiwan, Province Of China **Region:** Taipei **State:**
Inclusion criteria: medically treated hypertensive, received medical treatment/follow-up at National Taiwan Univerisity Hospital, Sept 2003-April 2004	**Exclusion critieria:**

38.1. Exposure: Serum folic acid

Method	Description	Analysis
serum	fasting venous blood sample	Blood collected in serum separation tubes. Following clotting and centrifugation, the serum was stored at -70C until analysis. Serum folic acid levels were measured by immunoassay with IMMULITE 2000 analyzer and the corresponding kits (DPC, Los Angeles, CA). NOTE: paper reports units as ng/L, but assuming it's should be ng/mL.

Outcomes

	Outcome	Diagnostic Description
A	Metabolic Syndrome (medical professional or test)	The diagnosis criteria of metabolic syndrome (MS) were derived from the recent World Health Organization criteria, and NCEP-ATP III with modification for subjects from the Asian-Pacific region. A subject was defined as having MS in the present study when 3 of any of the 5 following criteria were present: 1. systolic blood pressure >= 130 mmHg, or diastolic pressure >= 85 mmHg, or those being treated for hypertension; 2. visceral obesity (for males, a waist circumference >= 90 cm, for females, >= 80 cm); 3. hypertriglyceridemia (>= 150 mg/dL); 4. a low level of HDL cholesterolemia (for males: < 40 mg/dL, for females, < 50 cm); 5. fasting blood glucose >= 110 mg/dL, or those had been treated for diabetes mellitus. All patients in this study were hypertensive, and thereby fulfilled at least one criterion (criteria 1). MS was diagnosed if subjects fulfilled two or more of the other criteria (criteria 2-5).

Results

38.1.A Metabolic Syndrome

Population: National Taiwan University Hospital, 2003-2004
Exposure: Serum folic acid
Outcome: Metabolic Syndrome
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folic acid	-	-	0.815

Statistical Method(s)

Endpoints: Metabolic Syndrome
Adjustment factors:
Statistical metric: t-test
Statistical metric description: The unpaired Student's t-test was used to analyze continuous data.

39. MAHALLE, 2013

Full citation: Mahalle N, Kulkarni MV, Garg MK, Naik SS. 2013. Vitamin B12 deficiency and hyperhomocysteinemia as correlates of cardiovascular risk factors in Indian subjects with coronary artery disease. Journal of cardiology 61(4): 289-294.

INDIAN SUBJECTS WITH CORONARY ARTERY DISEASE

Age: 60.9 (mean), from 25.0-92.0 years	**Study design:** Cross-sectional (**n = 300**)
Gender: Male and Female **Ethnicities:** Asian	**Country:** India **Region:** **State:**
Inclusion criteria: coronary artery disease (CAD) detected on angiography	**Exclusion critieria:** chronic kidney disease, hepatic dysfunction, n, known endocrinal (except diabetes mellitus) or rheumatologic diseases or chronic infections, taking vitamins

39.1. Exposure: Serum folate

Method	Description	Analysis
Serum assay	Microparticle enzyme immunoassay (MEIA)	folate deficiency defined by <3 ng/ml

Outcomes

	Outcome	Diagnostic Description
A	Diabetes Mellitus (medical records)	determined "by history and treatment", type of DM unspecified
B	High-sensitivity C-reactive Protein (Hs-CRP) (medical professional or test)	measured by enzyme linked immunosorbent assay method with kits
C	Homeostatic model of insulin resistance (HOMA-IR) (medical professional or test)	HOMA-insulin resistance = fasting insulin (IU/ml) × fasting glucose (mmol/l)/22.5
D	Insulin (medical professional or test)	Microparticle enzyme immunoassay (MEIA)
E	Interleukin-6 (IL-6) (medical professional or test)	measured by enzyme linked immunosorbent assay method with kits
F	Quantitative insulin sensitivity check index (QUICKI) (medical professional or test)	quantitative insulin sensitivity check index (QUICKI)] [QUICKI = 1/log(fasting insulin U/mL) + log(fasting glucose mg/dL)]
G	TNF-alpha (medical professional or test)	measured by enzyme linked immunosorbent assay method with kits

Results

39.1.A Diabetes Mellitus

Population: Indian subjects with coronary artery disease
Exposure: Serum folate
Outcome: Diabetes Mellitus
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-0.027	0.636

39.1.B High-sensitivity C-reactive Protein (Hs-CRP)

Population: Indian subjects with coronary artery disease
Exposure: Serum folate
Outcome: High-sensitivity C-reactive Protein (Hs-CRP)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	0.023	0.685

39.1.C Homeostatic model of insulin resistance (HOMA-IR)

Population: Indian subjects with coronary artery disease
Exposure: Serum folate
Outcome: Homeostatic model of insulin resistance (HOMA-IR)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-0.017	0.775

39.1.D Insulin

Population: Indian subjects with coronary artery disease
Exposure: Serum folate
Outcome: Insulin
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-0.058	0.315

39.1.E Interleukin-6 (IL-6)

Population: Indian subjects with coronary artery disease
Exposure: Serum folate
Outcome: Interleukin-6 (IL-6)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	0.05	0.387

39.1.F Quantitative insulin sensitivity check index (QUICKI)

Population: Indian subjects with coronary artery disease
Exposure: Serum folate
Outcome: Quantitative insulin sensitivity check index (QUICKI)
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-0.093	0.106

39.1.G TNF-alpha

Population: Indian subjects with coronary artery disease
Exposure: Serum folate
Outcome: TNF-alpha
Statistical metric: correlation

Group	N	r 95% CI (low, high)	*p*-value
Serum folate	-	-0.028	0.627

Statistical Method(s)

Endpoints: Insulin; Homeostatic model of insulin resistance (HOMA-IR); Quantitative insulin sensitivity check index (QUICKI); Interleukin-6 (IL-6); TNF-alpha; High-sensitivity C-reactive Protein (Hs-CRP)
Adjustment factors:
Statistical metric: correlation
Statistical metric description: Pearson correlation was used to evaluate the correlation between inflammatory markers, insulin resistance, and nutritionalfactors.

Endpoints: Diabetes Mellitus
Adjustment factors:
Statistical metric: correlation
Statistical metric description: Data are presented as mean ± SD, median (range) or number (%) unless specified. All parametric data were analyzed by Student's t-test. Pearson correlation was used to evaluate the correlation between inflammatory markers, insulin resistance, and nutritionalfactors.

40. MANIOS, 2014

Full citation: Manios Y, Moschonis G, Papandreou C, Siatitsa PE, Iatridi V, Lidoriki I, Lionis C, Chrousos GP. 2014. Female sex, small size at birth and low family income increase the likelihood of insulin resistance in late childhood: the Healthy Growth Study. Pediatr Diabetes 15(1): 41-50.

HEALTHY GROWTH STUDY

Age: 11.2 (mean), from 9.0-13.0 years	**Study design:** Cross-sectional (**n** = 2195)
Gender: Male and Female **Ethnicities:** White, Other	**Country:** Greece **Region:** **State:**
Inclusion criteria: randomly sampled children in Greece	**Exclusion critieria:**

40.1. Exposure: Maternal Folate supplementation

Method	Description	Analysis
Self-report	mothers were asked to recall and report the following perinatal information: use of nutritional supplements during pregnancy	n/a

Outcomes

	Outcome	Diagnostic Description
A	Insulin Resistance in Children (medical professional or test)	Insulin Resistance measured through homeostasis model assessment (HOMA-IR); this index calculated using fasting glucose (FG) and fasting insulin (IF) in formula: HOMA-IR= (IF (microunits/mL) x FG (mmol/L)/22.5. HOMA-IR >3.16 determined as a cut-off point to define insulin resistance in schoolchildren. Outcome is in children. 28.4% of sample population were determined to be insulin resistant

Results

40.1.A Insulin Resistance in Children

Population: Healthy Growth Study, Greece
Exposure: Maternal Folate supplementation
Outcome: Insulin Resistance in Children
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
No Folic Acid Supplement Use- 2nd Trimester	-	1.0	

Group	N	adjOR 95% CI (low, high)	*p*-value
Yes Folic Acid Supplement Use- 2nd Trimester	-	0.86 (0.52, 1.41)	0.55
No Folic Acid Supplement Use- 3rd Trimester	-	1.0	
Yes Folic Acid Supplement Use- 3rd Trimester	-	0.92 (0.55, 1.53)	0.748

Statistical Method(s)

Endpoints: Insulin Resistance in Children
Adjustment factors: Tanner stage, child BMI
Statistical metric: adjusted odds ratio
Statistical metric description: univariate logistic regression analyses performed to test the effect of the factors under investigation on the occurrence of insulin resistance. Furthermore, multivariable logistic regression analysis was performed including all variables that were significantly associated with IR at a univariate level, also controlling for children's BMI and Tanner stage. Crude and adjusted odds ratios (OR) with 95% CI were derived from the univariate and the multivariable regression models. SPSS was used.

41.   MASHAVI, 2008

Full citation: Mashavi M, Hanah R, Boaz M, Gavish D, Matas Z, Fux A, Shargorodsky M. 2008. Effect of homocysteine-lowering therapy on arterial elasticity and metabolic parameters in metformin-treated diabetic patients. Atherosclerosis 199(2): 362-367.

Funding: None reported

B VITAMIN SUPPLEMENTATION IN METFORMIN-TREATED DIABETIC PATIENTS

Age: 60.9 (mean)	**Study design:** Controlled trial (**n =** 57)
Gender: Male and Female **Ethnicities:**	**Country:** Israel **Region:** Tel Aviv **State:**
Inclusion criteria: with type 2 diabetes treated with at least 1500 mg/d of metformin	**Exclusion critieria:** electrolyte abnormalities, elevation of liver enzymes to more than twice the upper normal lmit, history of cerebrovascular accident (CVA) within 6 months prior to study, history of major surgery within 6 months prior to study, history of myocardial infarction within 6 months prior to study, if they had active unstable angina in the 6 months before or at the time of enrollment, plasma creatinine > 2 mg/dL, unbalanced endocrine disease or any disease that might affect absorption of medications

41.1. Exposure: B-vitamin treatment to lower Hcy

Method	Description	Analysis
intervention	Treatment group received Hcy-lowering therapy as 1000 mcg folate, 400 mcg vitamin B12, and 10 mg of B6 Control Group received matching placebo capsules	intervention

Outcomes

	Outcome	Diagnostic Description
A	Fasted glucose, 4 months (medical professional or test)	Blood sampling for full chemistry and metabolic parameters, including fasting glucose,HbA1C, folic acid.
B	Fasted HbA1c, 4 months (medical professional or test)	Blood sampling for full chemistry and metabolic parameters, including fasting glucose,HbA1C, folic acid.
C	Folic acid (medical professional or test)	Blood sampling for full chemistry and metabolic parameters, including fasting glucose,HbA1C, folic acid.
D	Homeostatic model of insulin resistance (HOMA-IR), 4 months (medical professional or test)	Blood sampling for full chemistry and metabolic parameters, including fasting glucose,HbA1C, folic acid. Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated by the following formula: fasting plasma insulin (mU/ml) × fasting plasma glucose (mg/dl)/405

Results

41.1.A Fasted glucose, 4 months

Population: B vitamin supplementation in metformin-treated diabetics
Exposure: B-vitamin treatment to lower Hcy
Outcome: Fasted glucose, 4 months
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Placebo group	-	-	
Treatment group	-	-	0.94

41.1.B Fasted HbA1c, 4 months

Population: B vitamin supplementation in metformin-treated diabetics
Exposure: B-vitamin treatment to lower Hcy
Outcome: Fasted HbA1c, 4 months
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Placebo group	-	-	
Treatment group	-	-	0.86

41.1.C Folic acid

Population: B vitamin supplementation in metformin-treated diabetics
Exposure: B-vitamin treatment to lower Hcy
Outcome: Folic acid
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Placebo group	29	-	
Treatment group	28	-	0.0001

41.1.D Homeostatic model of insulin resistance (HOMA-IR), 4 months

Population: B vitamin supplementation in metformin-treated diabetics
Exposure: B-vitamin treatment to lower Hcy
Outcome: Homeostatic model of insulin resistance (HOMA-IR), 4 months
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Placebo group	-	-	
Treatment group	-	-	0.29

Statistical Method(s)

Endpoints: Homeostatic model of insulin resistance (HOMA-IR), 4 months; Fasted glucose, 4 months; Fasted HbA1c, 4 months; Folic acid
Adjustment factors: baseline homocysteine
Statistical metric: t-test
Statistical metric description: descriptive statistics were calculated and reported as mean ± standard

deviation. Continuous variables were compared by treatment group using the t-test for independent samples. Additionally, univariate general linear modeling (GLM) was used to compare outcomes by treatment assignment controlling for baseline values of covariates. Within a given treatment group, the t-test for paired samples was used to compare before versus post-treatment values of outcomes.

42.   MEHMET, 2012

Full citation: Mehmet E, Aybike K, Ganidagli S, Mustafa K. 2012. Characteristics of anemia in subclinical and overt hypothyroid patients. Endocr J 59(3): 213-220.

Funding: None reported

HYPOTHYROIDISM, TURKEY

Age: 45.0 (mean)	**Study design:** Case-control (**n = 400**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Turkey **Region:** **State:**
Inclusion criteria: admission for possible thyroid disorder	**Exclusion critieria:** multifactorial anemia or anemia due to other reasons including hemolytic anemias, gastrointestinal or genitourinary losses due to malignancy and/or acute/subacute blood losses from the respiratory, gastrointestinal, or genitourinary system, patients who were under the treatment that might affect blood parameters such as steroids or who had received anemia treatment previously, presence of any comorbid disease like renal insufficiency/failure, coronary heart disease, uncontrolled hypertension, diabetes mellitus, or any endocrine system disease other than hypothyroidism (subclinical, overt hypothyroidism), prior thyroid disorder and/or treatment history

42.1. Exposure: Serum folate

Method	Description	Analysis
assay	folic acid (3-34 ng/mL)a... were carried out from blood samples which were taken from patients after a fasting of at least 10 hours. assay not mentioned	not specified

Outcomes

	Outcome	Diagnostic Description
A	Hypothyroidism (medical professional or test)	Measurements of TSH, FT3, and FT4 were done with Architec i2000 SR device. The measurement of anti TPO and anti Tg values was carried out by Elecsys 2010 device. Overt hypothyroidism diagnosis was made when elevated TSH and low levels of free T4 and/or free T3 were observed. Subclinical hypothyroidism was defined as an elevated serum TSH with normal free T4 and free T3 levels.

Results

42.1.A Hypothyroidism

Population: Hypothyroidism, Turkey
Exposure: Serum folate
Outcome: Hypothyroidism
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Serum folate	-	-	0.025

Statistical Method(s)

Endpoints: Hypothyroidism
Adjustment factors:
Statistical metric: mean
Statistical metric description: Descriptive analyses were used for variables in their groups. Chi square test, student-t tests, and Anova tests were applied for the examination of the relations between the variables.

43. MELONI, 2005

Full citation: Meloni GF, Tonolo GC, Zuppi C, Zappacosta B, Musumeci S. 2005. Hyper-homocysteinemia is not a main feature of juvenile uncomplicated type 1 diabetes. J Atheroscler Thromb 12(1): 14-19.

Funding: Noe reported

TYPE 1 DIABETES, ITALY

Age: 12.7 (mean), from 2.0-29.0 years	**Study design:** Case-control (**n** = 282)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Italy **Region:** **State:**
Inclusion criteria: Patient with type 1 diabetes	**Exclusion critieria:** clinical signs of chronic microvascular or macrovascular complications

43.1. Exposure: Serum folate

Method	Description	Analysis
assay	not specified (blood samples were collected in the morning after 12 hours of fasting)	not mentioned

Outcomes

	Outcome	Diagnostic Description
A	Type 1 Diabetes (medical professional or test)	all diagnosed-- either newly or known diagnosis

Results

43.1.A Type 1 Diabetes

Population: Type 1 Diabetes in Italy
Exposure: Serum folate
Outcome: Type 1 Diabetes
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Serum folate	-	-	

Statistical Method(s)

Endpoints: Type 1 Diabetes
Adjustment factors:
Statistical metric: mean
Statistical metric description: mean and st. deviation calculated for each studied parameter and the differences evaluated with student T test

44.   MIETUS-SNYDER, 2012

SUPPLEMENT BAR INTERVENTION TRIAL

Age: 44.9 (mean), from 19.0-81.0 years	**Study design:** Controlled trial (**n** = 25)
Gender: Male and Female **Ethnicities:** Asian, Hispanic/Latino, White	**Country:** United States **Region:** **State:**
Inclusion criteria: healthy adults	**Exclusion critieria:**

44.1. Exposure: Supplement bar

Method	Description	Analysis
supplement bar	supplement bar fortified with 203 ug of folate each (with other nutrients) eaten twice daily for 2 weeks (so 406 ug/day of folate from bars)	n/a

Outcomes

	Outcome	Diagnostic Description
A	Fasting glucose (medical professional or test)	Plasma fasting glucose measured using standard procedures by a commercial provider (ARUP Laboratories)
B	Fasting insulin (medical professional or test)	Insulin measured using standard procedures by a commercial provider (ARUP Laboratories)
C	Homeostatic model of insulin resistance (HOMA-IR) (medical professional or test)	Insulin resistance was estimated using the homeostatic model of insulin resistance (HOMA-IR), calculated as fasting glucose [mM] x fasting insulin [uIU/L] / 22.5

Results

44.1.A Fasting glucose

Population: Supplement bar intervention, 2 week trial
Exposure: Supplement bar
Outcome: Fasting glucose
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Supplement bar, 2 weeks	25	-	0.33

44.1.B Fasting insulin

Population: Supplement bar intervention, 2 week trial
Exposure: Supplement bar
Outcome: Fasting insulin
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Supplement bar, 2 weeks	25	-	0.31

44.1.C Homeostatic model of insulin resistance (HOMA-IR)

Population: Supplement bar intervention, 2 week trial
Exposure: Supplement bar
Outcome: Homeostatic model of insulin resistance (HOMA-IR)
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Supplement bar, 2 weeks	25	-	0.28

Statistical Method(s)

Endpoints: Fasting insulin; Homeostatic model of insulin resistance (HOMA-IR); Fasting glucose
Adjustment factors:
Statistical metric: t-test
Statistical metric description: paired t tests were used to test for significant change between baseline and after 2 wk consumption of the bar

45.   MÜLLNER, 2013

BASELINE OF CASE-CONTROL INTERVENTION, DIABETES OUTPATIENT CLINIC, AUSTRIA

Age: 64.6 (None)	**Study design:** Cross-sectional (**n = 97**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Austria **Region:** Vienna **State:**
Inclusion criteria: Patient with type 2 diabetes, stable body weight, dietary habits, and physical activity levels for at least 4 weeks, stable metabolic control	**Exclusion critieria:** intake of fish oil capsules and other fatty acids, intent to change dietary habits, frequency of physical activity or body weight, smoking

45.1. Exposure: Plasma folate

Method	Description	Analysis
serum	Plasma concentration of folic acid was measured according to routine diagnostic tests on Siemens Immulite 2000 analyzer (Siemens Healthcare Diagnostics, Tarrytown, USA) at the laboratory of the Health Centre South, Vienna using chemiluminescent enzyme immunoassay. Folic acid in erythrocytes was measured with radioimmunoassay.	Standard curves were drawn and sample values calculated according to the protocol published by the kit producer (MP Biomedicals, Germany).

Outcomes

	Outcome	Diagnostic Description
A	Type 2 diabetes (medical professional or test)	Patients with T2DM (36 treated with insulin, 40 treated with oral antidiabetic medication) were recruited from a local diabetes clinic. Individuals with T2DM had to have stable metabolic control (constant medication regarding glucose, lipid and uric acid metabolism), HbA1c concentration <9.5%, serum total cholesterol (TC) <300 mg/dl (<7.76 mmol/l), serum triglycerides <500 mg/dl (<5.7 mmol/l) and serum creatinine <2.5 mg/dl (<221 µmol/l).

Results

45.1.A Type 2 diabetes

Population: Baseline of case-control intervention, Diabetes Outpatient Clinic
Exposure: Plasma folate
Outcome: Type 2 diabetes
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Plasma folate	97	-	

Statistical Method(s)

Endpoints: Type 2 diabetes
Adjustment factors:
Statistical metric: other
Statistical metric description:

45.2. Exposure: RBC folate

Method	Description	Analysis
red blood cell	Plasma concentration of folic acid was measured according to routine diagnostic tests on Siemens Immulite 2000 analyzer (Siemens Healthcare Diagnostics, Tarrytown, USA) at the laboratory of the Health Centre South, Vienna using chemiluminescent enzyme immunoassay. Folic acid in erythrocytes was measured with radioimmunoassay.	Standard curves were drawn and sample values calculated according to the protocol published by the kit producer (MP Biomedicals, Germany).

Outcomes

	Outcome	Diagnostic Description
A	Type 2 diabetes (medical professional or test)	Patients with T2DM (36 treated with insulin, 40 treated with oral antidiabetic medication) were recruited from a local diabetes clinic. Individuals with T2DM had to have stable metabolic control (constant medication regarding glucose, lipid and uric acid metabolism), HbA1c concentration <9.5%, serum total cholesterol (TC) <300 mg/dl (<7.76 mmol/l), serum triglycerides <500 mg/dl (<5.7 mmol/l) and serum creatinine <2.5 mg/dl (<221 µmol/l).

Results

45.2.A Type 2 diabetes

Population: Baseline of case-control intervention, Diabetes Outpatient Clinic
Exposure: RBC folate

Outcome: Type 2 diabetes
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
RBC folate level	97	-	

Statistical Method(s)

Endpoints: Type 2 diabetes
Adjustment factors:
Statistical metric: other
Statistical metric description:

46.   NDREPEPA, 2008

Full citation: Ndrepepa G, Kastrati A, Braun S, Koch W, Kolling K, Mehilli J, Schomig A. 2008. Circulating homocysteine levels in patients with type 2 diabetes mellitus. Nutr Metab Cardiovasc Dis 18(1): 66-73.

Funding: None reported

TYPE 2 DIABETES MELLITUS, GERMANY

Age: median [25th,75th]: With diabetes: 69.6 [62.0; 76.1] Without diabetes: 66.5 [58.5; 74.6]	**Study design:** Cross-sectional (**n = 2121**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Germany **Region:** **State:**
Inclusion criteria: Patient with type 2 diabetes	**Exclusion critieria:** acute inflammatory states or malignancies, advanced renal disease

46.1. Exposure: Plasma folate

Method	Description	Analysis
assay	folate measured using AxSYM System (Abbott Laboratories, Abbott Park, IL, USA). Folate concentration was measured with an ion capture assay, which utilizes a soluble affinity reagent composed of folate binding protein coupled to monoclonal antibodies which are, in turn, coupled to a polyanion	The analytical sensitivity of the AxSYM folate assay is 0.9 ng/mL

Outcomes

	Outcome	Diagnostic Description
A	Type 2 diabetes (medical professional or test)	Diabetes mellitus was defined on the basis of ongoing active treatment with hypoglycemic drugs or insulin. Patients on dietary treatment alone had to have documentation of abnormal fasting blood glucose or a glucose tolerance test according to the World Health Organization criteria for the diagnosis of diabetes

Results

46.1.A Type 2 diabetes

Population: Patients with type 2 diabetes mellitus, Germany
Exposure: Plasma folate
Outcome: Type 2 diabetes
Statistical metric: Wilcoxon Test

Group	N	Wilcoxon Test 95% CI (low, high)	*p*-value
Plasma folate	-	-	0.21

Statistical Method(s)

Endpoints: Type 2 diabetes
Adjustment factors:
Statistical metric: Wilcoxon Test
Statistical metric description: Data are presented as median [25th, 75th percentiles]...Normality of distribution for continuous variables was tested by the KolmogoroveSmirnov test. Continuous data were compared with Wilcoxon rank-sum test or KruskaleWallis rank-sum test

47.   ORTEGA-AZORÍN, 2012

Full citation: Ortega-Azorín C, Sorli JV, Asensio EM, Coltell O, Martinez-Gonzalez MA, Salas-Salvado J, Covas MI, Aros F, Lapetra J, Serra-Majem L, Gomez-Gracia E, Fiol M, Saez-Tormo G, Pinto X, Munoz MA, Ros E, Ordovas JM, Estruch R, Corella D. 2012. Associations of the FTO rs9939609 and the MC4R rs17782313 polymorphisms with type 2 diabetes are modulated by diet, being higher when adherence to the Mediterranean diet pattern is low. Cardiovasc Diabetol 11: 137.

BASELINE PREDIMED (PREVENCION CON DIETA MEDITERRANEA) STUDY, 2003-2009

Age: 66.9 (mean), from 55.0-80.0 years	**Study design:** Cross-sectional (**n = 7052**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Spain **Region:** **State:**
Inclusion criteria: without prior CVD	**Exclusion critieria:**

47.1. Exposure: folic acid intake

Method	Description	Analysis
questionnaire	A validated 137-item food frequency questionnaire was administered to all participants. Energy and nutrient intake were calculated from Spanish food composition tables.	Dichotomous variables for nutrient intake were created using as cut-off points the sample mean.

Outcomes

	Outcome	Diagnostic Description
A	Type 2 diabetes (medical professional or test)	Participants were recruited between 2003 and 2009 in Primary Care Centers affiliated to 11 recruiting centers (teaching Hospitals) in Spain. Cases were diagnosed with type 2 diabetes or at least three of the following cardiovascular risk factors in subjects without type 2 diabetes (controls): current smoking, hypertension, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, overweight/obesity, or family history of premature coronary heart disease.

Results

47.1.A Type 2 diabetes

Population: Baseline, PREDIMED Study
Exposure: folic acid intake
Outcome: Type 2 diabetes
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Folic acid intake	7052	-	0.77

Statistical Method(s)

Endpoints: Type 2 diabetes
Adjustment factors:
Statistical metric: t-test
Statistical metric description: We used t-test and ANOVA to compare crude means of continuous variables. Statistical analyses were performed with the SPSS package, version 15.0 (SPSS, Chicago, IL). All tests were two-tailed and P values <0.05 were considered statistically significant. P-value was the comparison between subjects with type 2 diabetes and non-diabetes.

48.   ORZECHOWSKA-PAWILOJC, 2007

Full citation: Orzechowska-Pawilojc A, Sworczak K, Lewczuk A, Babinska A. 2007. Homocysteine, folate and cobalamin levels in hypothyroid women before and after treatment. Endocrine Journal 54(3): 471-476.

Funding: none reported

HYPOTHYROID WOMEN WITH L-THYROXINE THERAPY

Age: 34.7 (mean), from 20.0-52.0 years	**Study design:** Case-control (**n = 61**)
Gender: Female **Ethnicities:** Unknown/Unspecified	**Country:** Poland **Region:** **State:**
Inclusion criteria: newly, non-treated hypothyroidism, regular menses	**Exclusion critieria:** clinical or history of arteriosclerotic disease, diseases that change plasma homocysteine levels, drugs that change plasma homocysteine levels (i.e. vitamin B12 and B6 antagonists, anticonvulsants, thiazides, fibrates), excess of coffee or alcohol consumption, lactation, oral contraceptives, pregnancy, special restriction diet

48.1. Exposure: Serum folate

Method	Description	Analysis
assay	MEIA assay by IMx analyzer	reference range: 2.9-18.7 ng/mL

Outcomes

	Outcome	Diagnostic Description
A	Hypothyroidism (medical professional or test)	Diagnosis of hypothyroidism was based on clinical and basal serum TSH values >5 mU/L. All hypothyroid women had Hashimoto disease (positive thyroid peroxidase antibodies and characteristical in ultrasonography)

Results

48.1.A Hypothyroidism

Population: Hypothyroid Women treated with L-thyroxine therapy, Poland
Exposure: Serum folate
Outcome: Hypothyroidism
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	-	-	0.001

Statistical Method(s)

Endpoints: Hypothyroidism
Adjustment factors:
Statistical metric: t-test
Statistical metric description: hypothyroid and control data compared with Student's paired t-test.

49. ORZECHOWSKA-PAWILOJC, 2009

Full citation: Orzechowska-Pawilojc A, Siekierska-Hellmann M, Syrenicz A, Sworczak K. 2009. Homocysteine, folate, and cobalamin levels in hyperthyroid women before and after treatment. Endokrynol. Pol. 60(6): 443-448.

Funding: None reported

HYPERTHYROID WOMEN BEFORE AND AFTER TREATMENT

Age: 34.3 (mean), from 19.0-52.0 years	**Study design:** Case-control (**n = 60**)
Gender: Female **Ethnicities:** Unknown/Unspecified	**Country:** Poland **Region:** **State:**
Inclusion criteria: newly, non-treated hypothyroidism, regular menses	**Exclusion critieria:** clinical or history of arteriosclerotic disease, diseases that change plasma homocysteine levels, drugs that change plasma homocysteine levels (i.e. vitamin B12 and B6 antagonists, anticonvulsants, thiazides, fibrates), excess of coffee or alcohol consumption, lactation, oral contraceptives, pregnancy, special restriction diet

49.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	Serum folic acid was determined by MEIA assay (Abbott Laboratories) by IMx analyzer	The reference range was: 2.9-18.7 ng/ml

Outcomes

	Outcome	Diagnostic Description
A	Hyperthyroidism (medical professional or test)	Diagnosis of hyperthyroidism was based on clinical examination and basal serum TSH values < 0.3 mU/L and fT4 > 24 pmol/L or fT3 > 5.3 pmol/L

Results

49.1.A Hyperthyroidism

Population: Hyperthyroid Women, Poland
Exposure: Serum folate
Outcome: Hyperthyroidism
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	-	-	0.001

Statistical Method(s)

Endpoints: Hyperthyroidism
Adjustment factors:
Statistical metric: t-test
Statistical metric description: The data of the hyperthyroid group (before and after treatment) and the control group were determined using Student´s paired t-test.

50.   PEÑA, 2013

Full citation: Peña AS, Maftei O, Dowling K, Gent R, Wiltshire E, MacKenzie K, Couper J. 2013. Folate fortification and supplementation do not provide vascular health benefits in type 1 diabetes. J Pediatr 163(1): 255-260.

DOSE-RESPONSE CROSSOVER TRIAL IN TYPE 1 DIABETICS, 2010-2011

Age: 15.1 (mean), from 10.0-18.0 years	**Study design:** Controlled trial (**n = 20**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Australia **Region:** South Australia **State:** Adelaide, South Australia
Inclusion criteria: Adolescents had to have been diagnosed with type 1diabetes for >1 year, treated at the diabetes clinics at the Women's and Children's Hospital	**Exclusion critieria:** celiac or thyroid disease, retinopathy or microalbuminuria, smoking history, treatment with statins or ACE inhibitors, vitamin B12 deficiency, vitamin supplementation

50.1. Exposure: folic acid solution challenge, once per month

Method	Description	Analysis
0, 0.5, 2, 5	Each participant received in a random order 4 interventions (1 per month): a single treatment of 1 of 3 folic acid doses (0.5, 2, and 5 mg) or placebo, as a 10-mL solution, on the study morning immediately after baseline fasting investigations.	intervention

Outcomes

	Outcome	Diagnostic Description
A	Fasted glucose (medical professional or test)	Glucose was measured by the hexokinase spectophotometry method (Synchron cx5ce; Beckman Coultur)

Results

50.1.A Fasted glucose

Population: Dose-response crossover trial, Adelaide, Australia, 2010-2011
Exposure: folic acid solution challenge, once per month
Outcome: Fasted glucose
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Placebo	20	3.45 (-5.3, 10.2)	
0.5mg	20	0.95 (-9.8, 10.6)	
2mg	20	1.9 (-8.9, 19.6)	

Group	N	other 95% CI (low, high)	*p*-value
5mg	20	1.65 (-9.3, 12.8)	

Statistical Method(s)

Endpoints: Fasted glucose
Adjustment factors:
Statistical metric: other
Statistical metric description: Reported as Median change and range. Skilling-Mack tests were used to evaluate changes in glucose between the 4 visits, according to the intervention. Statistical significance was inferred with a value of P < .05.

TYPE 1 DIABETICS IN TRIALS, PRE (2002-2003)/POST (2010-2011) FORTIFICATION

Age: 15.1 (mean)	**Study design:** Cross-sectional (**n =** 55)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Australia **Region:** South Australia **State:** Adelaide, South Australia
Inclusion criteria: Adolescents had to have been diagnosed with type 1diabetes for >1 year, treated at the diabetes clinics at the Women's and Children's Hospital	**Exclusion critieria:** celiac or thyroid disease, retinopathy or microalbuminuria, smoking history, treatment with statins or ACE inhibitors, vitamin B12 deficiency, vitamin supplementation

50.2. Exposure: mandatory food fortification, Australia

Method	Description	Analysis
120 mg of folic acid/100 g of bread	6 months after the introduction of mandatory folate fortification of wheat flour (120 mg of folic acid/100 g of bread) in Australia (September 2009),a comparison was made between children with type 1 diabetes from the present trial evaluated during 2010-2011 and children with type 1 diabetes from our previous acute folic acid interventional trial evaluated during 2002-2003	population-level exposure, no consideration of actual intake but folate levels measured and were significantly higher in the post-fortification group

Outcomes

	Outcome	Diagnostic Description
A	Fasted glucose (medical professional or test)	Glucose was measured by the hexokinase spectophotometry method (Synchron cx5ce; Beckman Coultur)

	Outcome	Diagnostic Description
B	Fasted HbA1c (medical professional or test)	Unknown. (HbA1c was measurement method references Pena, 2007 for method as it did for glucose, but this paper did not measure HbA1c.)
C	Insulin dosage (medical records)	insulin dosage reports in units/kg/d

Results

50.2.A Fasted glucose

Population: Trial in type 1 diabetics, Adelaide, Australia, 2003-2003 and 2010-2011
Exposure: mandatory food fortification, Australia
Outcome: Fasted glucose
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
2002-2003, pre-fortification	35	-	
2010-2011, post-fortification	20	-	

50.2.B Fasted HbA1c

Population: Trial in type 1 diabetics, Adelaide, Australia, 2003-2003 and 2010-2011
Exposure: mandatory food fortification, Australia
Outcome: Fasted HbA1c
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
2002-2003, pre-fortification	35	-	
2010-2011, post-fortification	20	-	

50.2.C Insulin dosage

Population: Trial in type 1 diabetics, Adelaide, Australia, 2003-2003 and 2010-2011
Exposure: mandatory food fortification, Australia
Outcome: Insulin dosage
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
2002-2003, pre-fortification	35	-	
2010-2011, post-fortification	20	-	

Statistical Method(s)

Endpoints: Insulin dosage; Fasted HbA1c; Fasted glucose
Adjustment factors:
Statistical metric: mean
Statistical metric description: ANOVA

51.   RUDY, 2005

Full citation: Rudy A, Kowalska I, Straczkowski M, Kinalska I. 2005. Homocysteine concentrations and vascular complications in patients with type 2 diabetes. Diabetes Metab 31(2): 112-117.

Funding: None reported

VASCULAR COMPLICATIONS, TYPE 2 DIABETES

Age: 62.2 (mean)	**Study design:** Case-control (**n =** 82)
Gender: Not reported **Ethnicities:** Unknown/Unspecified	**Country:** Poland **Region:** Bialystok **State:**
Inclusion criteria: Patient with type 2 diabetes	**Exclusion critieria:** diabetes plus overt renal insufficiency an/or other serious medical problems

51.1. Exposure: Folic acid level

Method	Description	Analysis
assay	studied and control group blood samples were taken in order to measure the levels of folic acid (RIA-radioimmunoassay)	n/a

Outcomes

	Outcome	Diagnostic Description
A	Type 2 diabetes (not reported)	patients type 2 diabetes hospitalized in the Department of Endocrinology, Diabetology and Internal Medicine-likely diagnosed professionally

Results

51.1.A Type 2 diabetes

Population: Vascular complications, Type 2 diabetics
Exposure: Folic acid level
Outcome: Type 2 diabetes
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Folic acid level	-	-	0.05

Statistical Method(s)

Endpoints: Type 2 diabetes
Adjustment factors:
Statistical metric: mean

Statistical metric description: Results are shown as mean values ± SD. Differences between groups were determined using non-parametric Mann-Whiney U test

52.   RUSSO, 2006

Full citation: Russo GT, Di Benedetto A, Alessi E, Ientile R, Antico A, Nicocia G, La Scala R, Di Cesare E, Raimondo G, Cucinotta D. 2006. Mild hyperhomocysteinemia and the common C677T polymorphism of methylene tetrahydrofolate reductase gene are not associated with the metabolic syndrome in Type 2 diabetes. J Endocrinol Invest 29(3): 201-207.

Funding: none reported

METABOLIC SYNDROME IN TYPE 2 DIABETES

Age: 51.4 (mean)	**Study design:** Case-control (**n = 100**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Italy **Region:** **State:**
Inclusion criteria: Patient with type 2 diabetes	**Exclusion critieria:** any major medical condition or use of medications potentially influencing tHcy plasma concentration in the last 6 months preceding the study, current insulin treatment, documented cardiovascular disease, fasting serum creatinine >1.5 mg/dL (>132.7 umol/L), long-term diagnosis of diabetes (>10 yr), macroalbuminuria (Albustix positive)

52.1. Exposure: Plasma folate

Method	Description	Analysis
assay	plasma folate measured by radioassay	CV 3.8%

Outcomes

	Outcome	Diagnostic Description
A	Metabolic syndrome (MS) in diabetics (medical professional or test)	T2D diagnosed according to the Amerian Diabetes Association (ADA) 1997 criteria MS (metabolic syndrome) defined according to the WHO criteria

Results

52.1.A Metabolic syndrome (MS) in diabetics

Population: Type 2 Diabetes with or without Metabolic syndrome, Italy, 40-60 year olds
Exposure: Plasma folate
Outcome: Metabolic syndrome (MS) in diabetics
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Plasma folate	-	-	

Statistical Method(s)

Endpoints: Metabolic syndrome (MS) in diabetics
Adjustment factors: age, creatinine, plasma folate, sex, vitamin B12
Statistical metric: other
Statistical metric description: data given as mean +/- SD; ANOVA performed for continuous variables

53. SAINANI, 2009

INSULIN RESISTANCE IN CONTROL SUBJECTS

Age: 42.8 (mean), from 30.0-60.0 years	**Study design:** Case-control (**n** = 65)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** India **Region:** Mumbai **State:**
Inclusion criteria: negative stress test, no established deficiency of folate of vitamin B12, no history of coronary artery disease, normal chest X-ray, normal ECG, no vitamin supplementation	**Exclusion critieria:**

53.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	folic acid levels were determined by radioimmunoassay [Diasorin ® SimullTRACSNB Radioimmunoassay kit vitamin B12 (57Co)/ folate (125I)].	reduced folic acid (defined as <10 nmol/l) level determined

Outcomes

	Outcome	Diagnostic Description
A	Insulin Resistance (medical professional or test)	Serum insulin was determined by radioimmunoassay (DSL-1600 Insulin Radioimmunoassay, DSL Inc Texas, USA). The degree of insulin resistance was estimated using homeostasis model assessment (HOMA-IR). According to the decision rule by Stern et al. insulin resistance is diagnosed when HOMA-IR>4.65 or BMI>27.5kg/m2 and HOMAI-IR>3.6

Results

53.1.A Insulin Resistance

Population: Insulin resistant in controls, Mumbai
Exposure: Serum folate
Outcome: Insulin Resistance
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	-	-	

Statistical Method(s)

Endpoints: Insulin Resistance
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Results were expressed as mean ± standard deviation; differences assessed using Student's t-test.

54. SAKUTA, 2005

Full citation: Sakuta H, Suzuki T, Yasuda H, Ito T. 2005. Plasma folate levels in men with type 2 diabetes. Int J Vitam Nutr Res 75(5): 307-311.

Funding: None reported

JAPANESE MALE SELF DEFENSE WORKERS

Age: 52.9 (mean)	**Study design:** Cross-sectional (**n =** 974)
Gender: Male **Ethnicities:** Asian	**Country:** Japan **Region:** Setagaya, Tokyo **State:**
Inclusion criteria: pesonnel of Self-Defense Forces, undergone a retirement health-check	**Exclusion critieria:**

54.1. Exposure: Plasma folate

Method	Description	Analysis
assay	fasting plasma folate measured by chemiluminescence immunoassay.	reference range: 2.4-9.8 ng/L

Outcomes

	Outcome	Diagnostic Description
A	Fasting plasma glucose (medical professional or test)	Oral 75 g glucose tolerance test
B	Type 2 Diabetes Mellitus (medical professional or test)	Oral 75 g glucose tolerance test; diagnosis of T2 Diabetes made based on World Health Organization criteria

Results

54.1.A Fasting plasma glucose

Population: Japanese Male Self Defense Workers
Exposure: Plasma folate
Outcome: Fasting plasma glucose
Statistical metric: adjusted beta

Group	N	adjβ 95% CI (low, high)	*p*-value
Plasma folate	-	0.173	0.001

54.1.B Type 2 Diabetes Mellitus

Population: Japanese Male Self Defense Workers
Exposure: Plasma folate
Outcome: Type 2 Diabetes Mellitus
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Plasma folate	-	-	0.05

Statistical Method(s)

Endpoints: Fasting plasma glucose
Adjustment factors: body mass index, daily ethanol consumption, daily number of cigarettes smoked, frequency of exercise enough to make a sweat, vegetable intake, vitamin constant use
Statistical metric: adjusted beta
Statistical metric description: Regression analyses done with plasma folate as dependent variables and metabolic parameters as independent variables. Continuous variables presented as mean +/- SD
Presented below as beta: standard regression coefficient

Endpoints: Type 2 Diabetes Mellitus
Adjustment factors:
Statistical metric: other
Statistical metric description: Comparison of means between multiple pairs of groups after one-way ANOVA, post hoc analysis by Fisher's protected least-significant difference

55. SALARDI, 2000

Full citation: Salardi S, Cacciari E, Sassi S, Grossi G, Mainetti B, Dalla Casa C, Pirazzoli P, Cicognani A, Gualandi S. 2000. Homocysteinemia, serum folate and vitamin B12 in very young patients with diabetes mellitus type 1. J Pediatr Endocrinol Metab 13(9): 1621-1627.

Funding: None reported

VERY YOUNG PATIENTS WITH TYPE 1 DIABETES

Age: 20.7 (mean), from 13.6-32.2 years	**Study design:** Case-control (**n = 146**)
Gender: Male and Female **Ethnicities:**	**Country:** Italy **Region:** **State:**
Inclusion criteria: early onset of complications, late onset of complications or complete absence of complications after many years of disease	**Exclusion critieria:** hypertension, oral contraceptives, renal failure, smoking

55.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	measured by RIA [radioimmunoassay] method ACS:180	mean normal value was 7.2 ng/mL (range: 1.1-20 ng/mL) for folate

Outcomes

	Outcome	Diagnostic Description
A	Type 1 Diabetes (not reported)	no mention of how Type 1 diabetes was diagnosed; patients with complications subdivided by onset of complications, duration of disease

Results

55.1.A Type 1 Diabetes

Population: Very Young Patients with Type 1 Diabetes, Italy
Exposure: Serum folate
Outcome: Type 1 Diabetes
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate, all	-	-	
Serum folate, excl. hyperhomocysteinemia	-	-	
Serum folate, males	-	-	
Serum folate, females	-	-	0.06

Statistical Method(s)

Endpoints: Type 1 Diabetes
Adjustment factors:
Statistical metric: t-test
Statistical metric description: presented as median and interquartile range (IQR); statistical significance was assessed using Student's t-test

56. SANCHEZ-MARGALET, 2002

HYPERINSULINEMIC OBESE MEN

Age: 45.6 (mean), from 33.0-55.0 years	**Study design:** Cross-sectional (**n = 20**)
Gender: Male **Ethnicities:** White	**Country:** Spain **Region:** **State:**
Inclusion criteria: non-diabetic, non-hypertensive, obese	**Exclusion critieria:**

56.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	folate and B12 levels were measured by an IMX-System autoanalyser (immunoassay)	n/a

Outcomes

	Outcome	Diagnostic Description
A	Hyperinsulinemia (medical professional or test)	They were divided into two groups, according to the basal insulin levels: Group 1, normoinsulinemic (<9 U/ml), and Group 2, hyperinsulinemic (> 9 U/ml). To further assess the insulin resistance state in these subjects, they undertook an oral glucose tolerance test, receiving 75 g glucose. Plasma glucose, insulin and homocysteine were measured at 0, 60 and 120 min.

Results

56.1.A Hyperinsulinemia

Population: Hyperinsulinemic obese subjects, male, Spain
Exposure: Serum folate
Outcome: Hyperinsulinemia
Statistical metric: mean

Group	N	mean 95% CI (low, high)	*p*-value
Serum folate	-	-	

Statistical Method(s)

Endpoints: Hyperinsulinemia
Adjustment factors:
Statistical metric: mean
Statistical metric description: Values are expressed as means +/- S.E.M. Data were analyzed by analysis of variance for multiple comparison, and post test (Bonferroni) was used to test the degree of significance of the differences between groups.

57. SATYANARAYANA, 2011

TYPE 2 DIABETES IN PERUVIAN HOSPITALS

Age: 54.4 (mean)	**Study design:** Case-control (**n = 300**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Peru **Region:** **State:**
Inclusion criteria: Patient with type 2 diabetes	**Exclusion critieria:** control and diabetic subjects on nutritional supplements for the last 6 months, history of nephropathy and complications other than diabetic retinopathy

57.1. Exposure: Plasma folate

Method	Description	Analysis
assay	folic acid measured by a solid phase radioimmunoassay method using a commercially available kit designed for simultaneous measurement of these vitamins (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA)	n/a

Outcomes

	Outcome	Diagnostic Description
A	Type 2 Diabetes mellitus, without retinopathy (medical records)	T2D patients recruited from hospital; no more specific details on how diabetes was diagnosed, just retinopathy

Results

57.1.A Type 2 Diabetes mellitus, without retinopathy

Population: Peruvian Type 2 diabetics
Exposure: Plasma folate
Outcome: Type 2 Diabetes mellitus, without retinopathy
Statistical metric: mean

Group	N	mean 95% CI (low, high)	p-value
Plasma folate	150	-	0.05

Statistical Method(s)

Endpoints: Type 2 Diabetes mellitus, without retinopathy
Adjustment factors:
Statistical metric: mean
Statistical metric description: Mean and SD of vitamins were calculated. Comparison of mean values of these variables across groups was done by one-way ANOVA F test with post hoc Tukey test.

58.   SEGHIERI, 2003

Full citation: Seghieri G, Breschi MC, Anichini R, De Bellis A, Alviggi L, Maida I, Franconi F. 2003. Serum homocysteine levels are increased in women with gestational diabetes mellitus. Metabolism 52(6): 720-723.

WOMEN WITH GESTATIONAL DIABETES MELLITUS (GDM)

Age: 32.7 (mean)	**Study design:** Cross-sectional (**n** = 93)
Gender: Female **Ethnicities:** Unknown/Unspecified	**Country:** Italy **Region:** **State:**
Inclusion criteria: gestational diabetes mellitus (GDM)	**Exclusion critieria:** Women who had taken oral folate supplements 2 weeks before the oral glucose tolerance test (OGTT)

58.1. Exposure: Serum folate

Method	Description	Analysis
serum assay	serum folic acid assayed by standardized automated methods using common commercial kits.	CV intra-assay 3.1%

Outcomes

	Outcome	Diagnostic Description
A	Gestational Diabetes Mellitus (GDM) (medical professional or test)	all participants underwent ...a 100-g, 3-hour oral glucose tolerance test (OGTT) between the 24th and the 28th gestational week at the Outpatient Clinic of the Diabetes Unit of the Hospital of Pistoia ...According to this protocol a full 100-g, 3-hour OGTT should be performed in all women who are glucose intolerant to a previous 1-hour 50-g oral glucose challenge or have other risk factors for GDM (history of glucose intolerance or of macrosomia during the previous pregnancies or history of diabetes in first-degree relatives). Both plasma glucose and insulin measurements were performed in all women at baseline and after 100 g glucose oral load at 60, 120, and 180 minutes. GDM was diagnosed in 15 women using the criteria suggested by the American Diabetes Association.

Results

58.1.A Gestational Diabetes Mellitus (GDM)

Population: Italian Women with Gestational Diabetes Mellitus
Exposure: Serum folate
Outcome: Gestational Diabetes Mellitus (GDM)
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	p-value
Serum folate	-	-	

Statistical Method(s)

Endpoints: Gestational Diabetes Mellitus (GDM)
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Two-tailed unpaired Student's t test was used to calculate differences in mean values between diabetic and nondiabetic women. Univariate and multiple logistic regression analyses were performed to determine associative relationships between variables. Values are expressed as means+/- SD, and P <.05 was considered significant.

59. SEMPÉRTEGUI, 2011

METABOLIC SYNDROME IN THE ELDERLY

Age: 74.4 (mean)	**Study design:** Cross-sectional (**n = 352**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Ecuador **Region:** Quito **State:**
Inclusion criteria: mental competence, older than 65 years of age, willingness to provide written informed consent	**Exclusion critieria:**

59.1. Exposure: Plasma folate

Method	Description	Analysis
assay	Blood samples were obtained at the field stations. A 10 ml venous blood sample was drawn after an overnight fast, into an EDTA-treated tube and a tube without anticoagulant... no more mention of lab methods besides "cut-off point for plasma vitamin inadequacies were defined as folate </=5 ng/ml"	n/a

Outcomes

	Outcome	Diagnostic Description
A	Metabolic Syndrome (medical professional or test)	We used the MetS definition of the International Diabetes Federation and also report the prevalence of MetS using the Adult Treatment Panel III (ATP III) definition(29). The IDF definition(21) requires participants to have central obesity defined by ethnic and sex-specific waist circumference cut-points (men .90 cm, women .80 cm), plus two of the four other components

Results

59.1.A Metabolic Syndrome

Population: Metabolic syndrome in the elderly
Exposure: Plasma folate

Outcome: Metabolic Syndrome
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
Plasma folate	-	1.04 (0.94, 1.16)	

Statistical Method(s)

Endpoints: Metabolic Syndrome
Adjustment factors: age, sex
Statistical metric: adjusted odds ratio
Statistical metric description: Multiple logistic regression models, also controlling for age and sex, were fitted to determine whether selected blood micronutrient status, high Hcy or high CRP (as binary variables) were associated with the presence of MetS

60. SETOLA, 2004

Full citation: Setola E, Monti LD, Galluccio E, Palloshi A, Fragasso G, Paroni R, Magni F, Sandoli EP, Lucotti P, Costa S, Fermo I, Galli-Kienle M, Origgi A, Margonato A, Piatti P. 2004. Insulin resistance and endothelial function are improved after folate and vitamin B12 therapy in patients with metabolic syndrome: relationship between homocysteine levels and hyperinsulinemia. European Journal of Endocrinology 151(4): 483-489.

FOLATE AND VITAMIN B12 THERAPY IN PATIENTS WITH METABOLIC SYNDROME

Age: 67.3 (mean)	**Study design:** Controlled trial (**n =** 50)
Gender: Male and Female **Ethnicities:**	**Country:** Italy **Region:** **State:**
Inclusion criteria: patients with metabolic syndrome	**Exclusion critieria:**

60.1. Exposure: Folic acid and B12 supplementation

Method	Description	Analysis
intervention	In group 1, patients were treated with diet plus placebo for 2 months. In group 2, patients were treated for 1 month with diet plus placebo and then for 1 month with diet plus oral folic acid (folic acid, 5 mg/day plus vitamin B12)	n/a

Outcomes

	Outcome	Diagnostic Description
A	Fasting glucose (medical professional or test)	Plasma glucose was measured with a glucose oxidasebased analyzer (Beckman Glucose Analyzer; Beckman, Fullerton, CA, USA)
B	Fasting insulin (medical professional or test)	Serum insulin levels (intra-assay C.V. 3.0%, interassay C.V. 5.0%) were assayed with a microparticle enzyme immunoassay
C	Homeostasis model assessment (HOMA) (medical professional or test)	homeostasis model assessment (HOMA) index was used. The following formula was applied (glucose (mmol/l) x insulin (uU/ml)/22.5)

Results

60.1.A Fasting glucose

Population: Patients with metabolic syndrome, Italy
Exposure: Folic acid and B12 supplementation
Outcome: Fasting glucose
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Group 1: diet + placebo	25	-	
Group 2: diet + folic acid & B12	25	-	

60.1.B Fasting insulin

Population: Patients with metabolic syndrome, Italy
Exposure: Folic acid and B12 supplementation
Outcome: Fasting insulin
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Group 1: diet + placebo	25	-	
Group 2: diet + folic acid & B12	25	-	0.01

60.1.C Homeostasis model assessment (HOMA)

Population: Patients with metabolic syndrome, Italy
Exposure: Folic acid and B12 supplementation
Outcome: Homeostasis model assessment (HOMA)
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Group 1: diet + placebo	25	-	
Group 2: diet + folic acid & B12	25	-	0.01

Statistical Method(s)

Endpoints: Homeostasis model assessment (HOMA); Fasting glucose; Fasting insulin
Adjustment factors:
Statistical metric: t-test
Statistical metric description: All data are given as means+/-S.E.M. Comparisons within groups were performed by Student's t-test for paired data

61. SOLINI, 2006

Full citation: Solini A, Santini E, Ferrannini E. 2006. Effect of short-term folic acid supplementation on insulin sensitivity and inflammatory markers in overweight subjects. Int J Obes (Lond) 30(8): 1197-1202.

Funding: None reported

SHORT-TERM FOLIC ACID SUPPLEMENTATION IN OVERWEIGHT SUBJECTS

Age: ages 29-61; placbo group: 49+/-8; folate group: 50 +/-7	**Study design:** Controlled trial (**n =** 60)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Italy **Region:** **State:**
Inclusion criteria: body mass index (BMI) between 25–29 kg/m2, normal glucose tolerance	**Exclusion critieria:** chronic drug treatment

61.1. Exposure: Supplemental folic acid, 3 months

Method	Description	Analysis
intervention	and were randomly assigned to receive either placebo or folic acid treatment (2.5 mg /daily) for 3 months	n/a

Outcomes

	Outcome	Diagnostic Description
A	Fasting glucose (medical professional or test)	Fasting glucose (mg/dl) assayed by standard enzymatic methods.
B	Fasting insulin (medical professional or test)	Plasma insulin was measured using radioimmunoassay
C	Homeostatic model of insulin resistance (HOMA) (medical professional or test)	The HOMA index (=fasting plasma glucose (mmol/l) fasting plasma insulin (mU/l)/22.5) was used as a proxy for insulin resistance.

Results

61.1.A Fasting glucose

Population: Short-term folate supplementation in overweight yet nondiabetic Italian subjects
Exposure: Supplemental folic acid, 3 months
Outcome: Fasting glucose
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Placebo	30	-	
Folic acid (2.5mg)	30	-	

61.1.B Fasting insulin

Population: Short-term folate supplementation in overweight yet nondiabetic Italian subjects
Exposure: Supplemental folic acid, 3 months
Outcome: Fasting insulin
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Placebo	30	-	
Folic acid (2.5mg)	30	-	0.004

61.1.C Homeostatic model of insulin resistance (HOMA)

Population: Short-term folate supplementation in overweight yet nondiabetic Italian subjects
Exposure: Supplemental folic acid, 3 months
Outcome: Homeostatic model of insulin resistance (HOMA)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Placebo	30	-	
Folic acid (2.5mg)	30	-	0.03

Statistical Method(s)

Endpoints: Fasting glucose; Fasting insulin; Homeostatic model of insulin resistance (HOMA)
Adjustment factors:
Statistical metric: other
Statistical metric description: Treatment-induced changes were analyzed by multivariate analysis. In these models, the dependent variable (final value – baseline value) was regressed against the baseline value and the treatment group (placebo or folic acid); an interaction term was always calculated. Placebo-adjusted differences (and their s.e.m.) were then obtained by contrast analysis.

62. SONG, 2009

Full citation: Song Y, Cook NR, Albert CM, Van Denburgh M, Manson JE. 2009. Effect of homocysteine-lowering treatment with folic acid and B vitamins on risk of type 2 diabetes in women: a randomized, controlled trial. Diabetes 58(8): 1921-1928.

WOMEN'S ANTIOXIDANT AND FOLIC ACID CARDIOVASCULAR STUDY (WAFACS)

Age: 63.0 (mean)	**Study design:** Controlled trial (**n** = 4252)
Gender: Female **Ethnicities:** Unknown/Unspecified	**Country:** United States **Region:** **State:** Massachusetts
Inclusion criteria: history of cardiovascular disease (CVD) or three or more CVD risk factors, older than 40 years of age	**Exclusion critieria:** any serious non-CVD illness, currently using warfarin or other anticoagulants, diabetes at baseline, history of cancer (excluding nonmelanoma skin cancer) within the past 10 years,

62.1. Exposure: B-vitamin supplementation

Method	Description	Analysis
folic acid supplement	combination pill of folic acid (2.5 mg/day), vitamin B6 (50 mg/day), and vitamin B12 (1 mg/day) vs placebo	n/a

Outcomes

	Outcome	Diagnostic Description
A	Incident Type 2 Diabetes (self-reported)	Diabetes status was evaluated at baseline, and all the participants were also asked annually whether and when they had been diagnosed with diabetes after randomization. Women who reported a diagnosis of diabetes during the follow-up were mailed supplementary questionnaires to confirm their self-reported diagnoses. The supplementary diabetes questionnaire was specifically designed to collect further detailed information on diabetes symptoms, screening test, and hypoglycemic medication. Based on the American Diabetes Association diagnostic criteria (28), actual glucose levels at fasting or oral glucose tolerance testing, diabetic symptoms, and/or hypoglycemic medication were combined together to confirm the self-reported incident cases of diabetes in a blinded fashion. The screening rate of having blood glucose testing among our study population was relatively high (85–90%). The observed high agreement between annual follow-up questionnaire

Outcome	Diagnostic Description
	and supplementary questionnaire (positive predictive value = 96%) suggests that self-reported diabetes possesses excellent predictive ability for true diabetes status in this cohort of U.S. female health professionals, who are likely to report accurate diagnostic information

Results

62.1.A Incident Type 2 Diabetes

Population: Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS) substudy incident Type 2 Diabetes and Vitamin B supplementation
Exposure: B-vitamin supplementation
Outcome: Incident Type 2 Diabetes
Statistical metric: adjusted relative risk

Group	N	adjRR 95% CI (low, high)	*p*-value
1–2 years follow-up	-	0.79 (0.55, 1.12)	
3–5 years follow-up	-	0.97 (0.73, 1.28)	
0–5 years follow-up	-	0.89 (0.72, 1.11)	
>/= 5 years follow-up	-	0.95 (0.7, 1.3)	
Total	-	0.91 (0.76, 1.09)	
Compliance (>2/3rds of pills)	-	0.87 (0.72, 1.05)	

Statistical Method(s)

Endpoints: Incident Type 2 Diabetes
Adjustment factors: alcohol intake, body mass index, coffee intake, family history of diabetes, multivitamin use, physical activity, postmenopausal hormone use, smoking status
Statistical metric: adjusted relative risk
Statistical metric description: multivariate-adjusted model; . Primary analyses were performed on an intention-to-treat basis, including all randomized women after excluding those with self-reported diabetes at baseline. We used Cox proportional hazards models to calculate the estimates of hazard ratio expressed as relative risks (RRs) and 95% CI for randomized treatment versus placebo, after adjustment for age and other randomized treatments (vitamin E, vitamin C, and -carotene)... To examine the effect of actual as opposed to assigned folic acid/B vitamin treatment, we carried out a sensitivity analysis according to compliance. Women were censored if and when they stopped taking at least two-thirds of their study pills or were missing compliance information

63. SPADA, 2007

Full citation: Spada RS, Stella G, Calabrese S, Bosco P, Anello G, Gueant-Rodriguez RM, Romano A, Benamghar L, Fontaine T, Gueant JL. 2007. Association of vitamin B12, folate and homocysteine with functional and pathological characteristics of the elderly in a mountainous village in Sicily. Clin Chem Lab Med 45(2): 136-142.

FUNCTIONAL AND CLINICAL CHARACTERISTICS OF ELDERLY IN SICILY

Age: 70.6 (mean), from 60.0-85.0 years	**Study design:** Cross-sectional (**n = 280**)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Italy **Region:** Central Sicily **State:**
Inclusion criteria: elderly between 60 and 85 years of age	**Exclusion critieria:**

63.1. Exposure: Plasma folate

Method	Description	Analysis
assay	folate concentrations were assayed using a Folates immunoassay kit on an ACS 180 automated chemiluminescent system	n/a

Outcomes

	Outcome	Diagnostic Description
A	Diabetes Mellitus (self-reported)	personal interview on self-reported signs and symptoms of diseases and their risk factors

Results

63.1.A Diabetes Mellitus

Population: Elderly in Sicily
Exposure: Plasma folate
Outcome: Diabetes Mellitus
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Plasma folate	-	-	0.028

Statistical Method(s)

Endpoints: Diabetes Mellitus
Adjustment factors:
Statistical metric: t-test

Statistical metric description: Continuous variables are reported as mean and SD. A Student's t-test for unpaired data and Bonferroni adjustment were used for comparing continuous variables

64. STELLA, 2007

Full citation: Stella G, Spada RS, Calabrese S, Bosco P, Anello G, Gueant-Rodriguez RM, Romano A, Benamghar L, Proto C, Castellano A, Fajardo A, Lipari L, Sirna S, Gueant JL. 2007. Association of thyroid dysfunction with vitamin B12, folate and plasma homocysteine levels in the elderly: a population-based study in Sicily. Clin Chem Lab Med 45(2): 143-147.

Funding: None reported

THYROID FUNCTION IN ELDERLY IN SICILY

Age: 60.0-85.0 years	**Study design:** Cross-sectional (**n =** 279)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Italy **Region:** Sicily **State:**
Inclusion criteria: elderly between 60 and 85 years of age	**Exclusion critieria:** neurological or cardiovascular diseases related to Hcy, vitamin B12 and/or folate, Renal failure or creatinine blood levels higher than 1.10 mg/dL (100 umol/L)

64.1. Exposure: Plasma folate

Method	Description	Analysis
assay	folate determined by microparticle enzyme immunoassay (MEIA) using an Abbott IMX automated benchtop analyzer system (Abbott Diagnostic, Rome, Italy	n/a

Outcomes

	Outcome	Diagnostic Description
A	Free Tri-iodothyronine (FT3) (medical professional or test)	FT3 values between 1.80 and 4.60 pg/mL were considered normal. The FT3 quartiles below are: Q1 (<2.93 pmol/L), Q2 (2.93-3.14 pmol/L), Q3 (3.15-3.41 pmol/L), Q4 (>3.41 pmol/L)
B	Thyroid stimulating hormone (TSH) (medical professional or test)	TSH values higher than 4.0 mIU/L and lower than 0.25 mIU/L were considered indicative of hypothyroidism and hyperthyroidism, respectively. The TSH quartiles below are: Q1 (<0.67 mIU/L), Q2 (0.67-1.24 mIU/L), Q3 (1.24-1.87 mIU/L), Q4 (>1.87 mIU/L)

Results

64.1.A Free Tri-iodothyronine (FT3)

Population: Thyroid Function in Elderly, Sicily
Exposure: Plasma folate
Outcome: Free Tri-iodothyronine (FT3)
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Plasma folate	-	-	0.022

64.1.B Thyroid stimulating hormone (TSH)

Population: Thyroid Function in Elderly, Sicily
Exposure: Plasma folate
Outcome: Thyroid stimulating hormone (TSH)
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Plasma folate	-	-	

Statistical Method(s)

Endpoints: Thyroid stimulating hormone (TSH); Free Tri-iodothyronine (FT3)
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Statistical analyses were performed using Student's t-test for continuous variables and a x2 test to compare prevalence. A p-value <0.05 indicated statistical significance

65.   STEWART, 2009

Full citation: Stewart CP, Christian P, Schulze KJ, Leclerq SC, West KP, Jr., Khatry SK. 2009. Antenatal micronutrient supplementation reduces metabolic syndrome in 6- to 8-year-old children in rural Nepal. J Nutr 139(8): 1575-1581.

CHILDREN OF MOTHERS ENROLLED IN ANTENATAL TRIAL IN NEPAL

Age: 7.5 (mean), from 6.2-8.5 years	**Study design:** Controlled trial (**n = 3524**)
Gender: Not reported **Ethnicities:** Asian	**Country:** Nepal **Region:** rural Nepal (Terai region) **State:**
Inclusion criteria: mother enrolled in trial during pregnancy	**Exclusion critieria:** lost to follow up

65.1. Exposure: Maternal antenatal micronutrient supplementation

Method	Description	Analysis
supplementation	A total of 4926 women were enrolled in early pregnancy and were provided daily supplements from the time of enrollment through 3 mo postpartum with: 1) vitamin A alone as the control; 2) folic acid (400 ug); 3) folic acid with iron (60 mg); 4) folic acid with iron and zinc (30 mg); or 5) a multiple micronutrient supplement containing folic acid, iron, zinc, and an additional 11 vitamins and minerals (10 mg vitamin D as cholecalciferol, 10 mg vitamin E as d-a tocopherol, 1.6 mg thiamine, 1.8 mg riboflavin, 20 mg niacin, 2.2 mg vitamin B-6, 2.6 mg vitamin B-12, 100 mg vitamin C, 65 mg vitamin K as phylloquinone, 2.0 mg Cu, 100 mg Mg)	intervention

Outcomes

	Outcome	Diagnostic Description
A	At Risk for Metabolic Syndrome (medical professional or test)	The criteria employed here to define metabolic syndrome were chosen to be similar to the recommendations of the National Cholesterol Education Program (NCEP) ATP III guidelines for adults (20), with modifications made to use child-specific values where possible. A child was classified as "at risk" if they met $3 of the following criteria: 1) plasma glucose $85th percentile of the study population, because few of the children had a glucose concentration above the traditionally recommended cutpoint of 5.6 mmol/L (16); 2) plasma HDL cholesterol , 0.9 mmol/L, as recommended by the NCEP report on cholesterol in children and adolescents (21); 3) plasma triglycerides $ 1.7 mmol/L, as recommended by the NCEP guidelines for adults, because there is no separate recommendation for children (20); 4) SBP or DBP $ 90th percentile of the U.S. reference population (18); and 5) waist circumference >/-85th percentile of the study population. For comparison, the definition was also tested by including HbA1C rather than glucose as the indicator of hyperglycemia.
B	Fasted Glucose (medical professional or test)	plasma glucose of fasted children analyzed using a Cholestech LDX analyzer
C	Fasted HOMA (homeostasis model assessment) (medical professional or test)	homeostasis model assessment (HOMA) = (FPI x FPG)/22.5, where FPI is fasting plasma insulin concentration (mU/L) and FPG is fasting plasma glucose (mmol/L) (19).
D	Fasted Insulin (medical professional or test)	Plasma insulin was measured using an ultrasensitive sandwich immunoassay (Alpco Diagnostics).
E	Hemoglobin A1C (medical professional or test)	Whole blood was analyzed on the day of collection to measure glycated hemoglobin (HbA1c) using a DCA 2000 analyzer with

	Outcome	Diagnostic Description
		standard test kits
F	Plasma Glucose (medical professional or test)	plasma glucose (in mmol/L) was measured using a Cholestech LDX analyzer

Results

65.1.A At Risk for Metabolic Syndrome

Population: Children of mothers enrolled in antenatal trial
Exposure: Maternal antenatal micronutrient supplementation
Outcome: At Risk for Metabolic Syndrome
Statistical metric: adjusted odds ratio

Group	N	adjOR 95% CI (low, high)	*p*-value
control (vit A)	75	1.0 (1.0, 1.0)	
folic acid + vit A	47	0.63 (0.41, 0.97)	0.05
folic acid +iron + vit A	74	1.02 (0.7, 1.49)	
folic acid + iron + zinc + vit A	70	0.95 (0.65, 1.4)	
multiple micronutrient supplement	80	1.0 (0.69, 1.45)	

65.1.B Fasted Glucose

Population: Children of mothers enrolled in antenatal trial
Exposure: Maternal antenatal micronutrient supplementation
Outcome: Fasted Glucose
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
control (vit A)	396	-	
folic acid + vit A	383	-	
folic acid +iron + vit A	370	-	
folic acid + iron + zinc + vit A	399	-	
multiple micronutrient supplement	463	-	

65.1.C Fasted HOMA (homeostasis model assessment)

Population: Children of mothers enrolled in antenatal trial
Exposure: Maternal antenatal micronutrient supplementation
Outcome: Fasted HOMA (homeostasis model assessment)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
control (vit A)	396	-	
folic acid + vit A	383	-	
folic acid +iron + vit A	370	-	
folic acid + iron + zinc + vit A	399	-	
multiple micronutrient supplement	463	-	

65.1.D Fasted Insulin

Population: Children of mothers enrolled in antenatal trial
Exposure: Maternal antenatal micronutrient supplementation

Outcome: Fasted Insulin
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
control (vit A)	396	-	
folic acid + vit A	383	-	
folic acid +iron + vit A	370	-	
folic acid + iron + zinc + vit A	399	-	
multiple micronutrient supplement	463	-	

65.1.E   Hemoglobin A1C

Population: Children of mothers enrolled in antenatal trial
Exposure: Maternal antenatal micronutrient supplementation
Outcome: Hemoglobin A1C
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
control (vit A)	735	-	
folic acid + vit A	658	-	
folic acid +iron + vit A	674	-	
folic acid + iron + zinc + vit A	708	-	
multiple micronutrient supplement	749	-	

65.1.F   Plasma Glucose

Population: Children of mothers enrolled in antenatal trial
Exposure: Maternal antenatal micronutrient supplementation
Outcome: Plasma Glucose
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
control (vit A)	735	-	
folic acid + vit A	658	-	
folic acid +iron + vit A	674	-	
folic acid + iron + zinc + vit A	708	-	
multiple micronutrient supplement	749	-	

Statistical Method(s)

Endpoints: Fasted Glucose; Plasma Glucose
Adjustment factors: child's age at follow-up
Statistical metric: other
Statistical metric description: glucose... followed a log-normal distribution and are thus expressed as medians and interquartile ranges. The relative mean ferences were estimated on the log scale and coefficients were exponentiated to calculate the percent difference between treatment groups.

Endpoints: Hemoglobin A1C
Adjustment factors: child's age at follow-up
Statistical metric: other
Statistical metric description: HbA1c data followed a normal distribution and, therefore, the difference

in means was compared across treatment groups using generalized estimation equations (GEE) with exchangeable correlation to account for the fact that communities, not individuals, had been randomized

Endpoints: At Risk for Metabolic Syndrome
Adjustment factors: child's age at follow-up, design effect, fasting status
Statistical metric: adjusted odds ratio
Statistical metric description: Dichotomous variables were analyzed using GEE logistic regression models with exchangeable correlation (22), metabolic syndrome models were also adjusted for fasting state.

Endpoints: Fasted HOMA (homeostasis model assessment)
Adjustment factors: child's age at follow-up
Statistical metric: other
Statistical metric description: HOMA ratio followed a log-normal distribution andthus expressed as medians and interquartile ranges. The relative mean ferences were estimated on the log scale and coefficients were exponentiated to calculate the percent difference between treatment groups.

Endpoints: Fasted Insulin
Adjustment factors: child's age at follow-up
Statistical metric: other
Statistical metric description: insulin... followed a log-normal distribution and thus expressed as medians and interquartile ranges. The relative mean ferences were estimated on the log scale and coefficients were exponentiated to calculate the percent difference between treatment groups.

66.   STEWART, 2011

MATERNAL SUPPLEMENTATION AND OFFSPRING INSULIN RESISTANCE

Age: 6-8 years of age	**Study design:** Controlled trial (**n =** 545)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Nepal **Region:** District of Sarlahi **State:**
Inclusion criteria: mother-child pairs	**Exclusion critieria:**

66.1. Exposure: Maternal folate supplementation, by baseline folate and B12 status

Method	Description	Analysis
supplement	Reporting results from Folic acid group by maternal vitamin status. Treatment groups: a control; 2) folic acid (400 ug); 3) folic acid+iron (60 mg ferrous fumarate); 4) folic acid+iron+zinc (30 mg zinc sulfate); or 5) multiple micronutrients containing folic acid, iron, zinc, and an additional 11 vitamins and minerals (10 mg vitamin D as cholecalciferol, 10 mg vitamin E as d-a tocopherol, 1.6 mg thiamine, 1.8 mg riboflavin, 20 mg niacin, 2.2 mg vitamin B-6, 2.6 mg vitamin B-12, 100 mg vitamin C, 65 mg vitamin K as phylloquinone, 2.0 mg Cu, 100 mg Mg). All supplements were given with 1000 mg RE of preformed vitamin A (retinyl palmitate) and compared to vitamin A alone as control	n/a (see other exposure for maternal serum folate)

Outcomes

	Outcome	Diagnostic Description
A	Child homeostasis model assessment (HOMA-IR) (medical professional or test)	The HOMA-IR was calculated using the standard ratio formula: HOMA-IR = (FPI 3 FPG)/22.5, where FPI is fasting plasma insulin (pmol/L) and FPG is fasting plasma glucose (mmol/L)

Results

66.1.A Child homeostasis model assessment (HOMA-IR)

Population: Maternal supplementation and Offspring insulin resistance, Nepal
Exposure: Maternal folate supplementation, by baseline folate and B12 status
Outcome: Child homeostasis model assessment (HOMA-IR)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
High vitamin B-12 (>/= 148 pmol/L)	57	-	0.18
Low vitamin B-12 (<148 pmol/L)	20	-	0.64
High Folate (>/= 14.2 nmol/L)	40	-	0.23
Low Folate (<14.2 nmol/L)	37	-	0.69

Statistical Method(s)

Endpoints: Child homeostasis model assessment (HOMA-IR)
Adjustment factors:
Statistical metric: other

Statistical metric description: The percent difference in HOMA-IR was also calculated stratified on maternal baseline folate or vitamin B-12 status categorized as deficient and nondeficient. To examine the interaction between baseline folate and vitamin B-12 status and micronutrient supplementation on child HOMA-IR, generalized estimation equations were used to account for the cluster- randomized study design. The interaction between treatment group and baseline folate or vitamin B-12 status was tested by including an interaction term into the model and testing its significance. P , 0.1 was considered significant for interactions. Analyses were performed using Stata SE v. 11.

66.2. Exposure: Maternal plasma folate during pregnancy

Method	Description	Analysis
plasma assay	a blood draw at baseline and in late pregnancy for the assessment of micronutrient status. In the maternal samples, plasma folate was measured with a microbiological assay using a chloramphenicol-resistant strain of Lactobacillus rhamnosus (NCIMB 10463)	n/a

Outcomes

	Outcome	Diagnostic Description
A	Offspring homeostatic model of assessment for insulin resistance (HOMA-IR)- Adjusted Model (medical professional or test)	The HOMA-IR was calculated using the standard ratio formula: HOMA-IR = (FPI 3 FPG)/22.5, where FPI is fasting plasma insulin (pmol/L) and FPG is fasting plasma glucose (mmol/L)
B	Offspring homeostatic model of assessment for insulin resistance (HOMA-IR)- Crude Model (medical professional or test)	The HOMA-IR was calculated using the standard ratio formula: HOMA-IR = (FPI 3 FPG)/22.5, where FPI is fasting plasma insulin (pmol/L) and FPG is fasting plasma glucose (mmol/L)

Results

66.2.A Offspring homeostatic model of assessment for insulin resistance (HOMA-IR)- Adjusted Model

Population: Maternal supplementation and Offspring insulin resistance, Nepal
Exposure: Maternal plasma folate during pregnancy
Outcome: Offspring homeostatic model of assessment for insulin resistance (HOMA-IR)- Adjusted Model
Statistical metric: regression coefficient

Group	N	coefficient 95% CI (low, high)	*p*-value
Log plasma folate-- Baseline (early pregnancy)	-	1.01 (-0.25, 2.26)	0.12
Folate x b12 interaction-- baseline	-	-0.18 (-0.41, 0.05)	0.13
Log plasma folate-- Late pregnancy	-	-0.31 (-1.1, 0.49)	0.45
Folate x b12 interaction-- late pregnancy	-	0.06 (-0.1, 0.23)	0.46

66.2.B Offspring homeostatic model of assessment for insulin resistance (HOMA-IR)- Crude Model

Population: Maternal supplementation and Offspring insulin resistance, Nepal
Exposure: Maternal plasma folate during pregnancy
Outcome: Offspring homeostatic model of assessment for insulin resistance (HOMA-IR)- Crude Model
Statistical metric: regression coefficient

Group	N	coefficient 95% CI (low, high)	*p*-value
Log plasma folate-- Baseline (early pregnancy)	-	0.09 (-0.05, 0.23)	0.23
Folate x b12 interaction-- baseline	-	-	
Log plasma folate-- Late pregnancy	-	0.01 (-0.1, 0.13)	0.81
Folate x b12 interaction-- late pregnancy	-	-	

Statistical Method(s)

Endpoints: Offspring homeostatic model of assessment for insulin resistance (HOMA-IR)- Crude Model
Adjustment factors:
Statistical metric: regression coefficient
Statistical metric description: The association between maternal folate and vitamin B-12 status during early and late pregnancy and child HOMA-IR was assessed using linear regression models. Household SES factors, ethnicity, paternal occupation, maternal literacy, maternal age at enrollment in the trial, BMI at baseline, parity, height, smoking and alcohol consumption during pregnancy, birth weight, and child age and gender were considered as potential confounding variables. Covariates were chosen for inclusion in the final model if they were significant in bivariate associations (P < 0.05) with either baseline folate or vitamin B-12 status or offspring HOMA and remained significant in multivariate models.

Endpoints: Offspring homeostatic model of assessment for insulin resistance (HOMA-IR)- Adjusted Model
Adjustment factors: both folate and vitamin b12, child age, child ethnicity, child gender, maternal height, maternal literacy, radio ownership, vitamin B12
Statistical metric: regression coefficient
Statistical metric description: The association between maternal folate and vitamin B-12 status during early and late pregnancy and child HOMA-IR was assessed using linear regression models. Household SES factors, ethnicity, paternal occupation, maternal literacy, maternal age at enrollment in the trial, BMI at baseline, parity, height, smoking and alcohol consumption during pregnancy, birth weight, and child age and gender were considered as potential confounding variables. Covariates were chosen for inclusion in the final model if they were significant in bivariate associations (P < 0.05) with either baseline folate or vitamin B-12 status or offspring HOMA and remained significant in multivariate models.

67. TARIM, 2004

Full citation: Tarim E, Bagis T, Kilicdag E, Erkanli S, Aslan E, Sezgin N, Kuscu E. 2004. Elevated plasma homocysteine levels in gestational diabetes mellitus. Acta Obstet Gynecol Scand 83(6): 543-547.

Funding: None reported

PREGNANT WOMEN IN TURKEY, 24-28WKS

Age: 27.75 (mean)	**Study design:** Cross-sectional (**n = 304**)
Gender: Female **Ethnicities:** Other	**Country:** Turkey **Region:** **State:**
Inclusion criteria: uncomplicated pregnancies who were at 24–28weeks gestation	**Exclusion critieria:** diseases of thyroid, folic acid and vitaminB12 deficiency, history of significant medical illness, hypertension

67.1. Exposure: Plasma folate

Method	Description	Analysis
assay	plasma folic acid measured with electrochemiluminescence technique in a Roche Modular Analytics E170 immunoassay analyzer	n/a

Outcomes

	Outcome	Diagnostic Description
A	Gestational Diabetes Mellitus (medical professional or test)	Screening is performed with a 50-g oral glucose load, and a patient is considered negative when their blood glucose is <=135mg/ dL. Women with blood glucose levels > 135 mg/dL undergo a 3-h 100-g oral glucose tolerance test (OGTT). To ensure consistency, all patients are instructed to add 150 g of carbohydrate to their usual meals for 3 days before the OGTT. Blood samples are collected at 0800 h (after 12 h of fasting) and at 60, 120 and 180 min after glucose ingestion. Plasma glucose levels are measured using the glucose oxidase method, and plasma insulin concentrations are measured by microparticle enzyme immunoassay (AxSYM insulin assay; Abbott, Tokyo, Japan). The OGTT results are interpreted according to the criteria of Carpenter and Coustan (9). The cutoff levels for the fasting and the 1-, 2- and 3-h plasma glucose levels are 95, 180, 155 and 140mg/dL, respectively. A patient is diagnosed with GDM if her glucose levels at two or more of the time points exceed these cutoffs.

67.1.A Gestational Diabetes Mellitus

Population: Gestational diabetes mellitus and folate in mothers, Turkey
Exposure: Plasma folate
Outcome: Gestational Diabetes Mellitus
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Plasma folate	-	-	

Statistical Method(s)

Endpoints: Gestational Diabetes Mellitus
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Data are expressed as mean +/- SD. An analysis of variance (ANOVA) test was used to analyze differences among the three groups. Differences between the two groups were analyzed using the independent Student's t-test and the Mann– Whitney U-test.

68. VAYÁ, 2011

Full citation: Vayá A, Carmona P, Badia N, Perez R, Mijares AH, Corella D. 2011. Homocysteine levels and the metabolic syndrome in a Mediterranean population: a case-control study. Clin Hemorheol Microcirc 47(1): 59-66.

METABOLIC SYNDROME IN A MEDITERRANEAN POPULATION

Age: 50.0 (mean)	Study design: Case-control (n = 159)
Gender: Male and Female Ethnicities: White	Country: Spain Region: Eastern Spain State:
Inclusion criteria: both cases and controls were Caucasians and from Eastern Spain	Exclusion critieria: hepatic, renal, thyroid infectious or autoimmune diseases, malignancy, pregnancy, previous atherothrombotic or thromboembolic disease

68.1. Exposure: Serum folate

Method	Description	Analysis
assay	serum folic acid determined with Immulite Assay	n/a

Outcomes

	Outcome	Diagnostic Description
A	Metabolic Syndrome (medical professional or test)	Metabolic Syndrome was defined according to the NCEP ATPIII criteria modified by Grundy et al. [17] as having three or more risk factors, including the following: Waist circumference ≥102 cm for men and >88 cm for women; triglycerides ≥150 mg/dL or drug treatment for elevated triglycerides; HDL-cholesterol <40 mg/dL for men and <50 mg/dL for women or drug treatment to increase HDL-cholesterol; glucose ≥100 mg/dL or drug treatment for elevated glucose or a diagnosis of diabetes; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or on hypertensive treatment.

Results

68.1.A Metabolic Syndrome

Population: Metabolic syndrome in cases vs control; Spain
Exposure: Serum folate
Outcome: Metabolic Syndrome
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	159	-	0.977

Statistical Method(s)

Endpoints: Metabolic Syndrome
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Data are expressed as means and standard deviation. To compare the differences in continuous variables between the two groups a t-test was used and an ANOVA test for more than two groups

69.   VAYÁ, 2012

Full citation: Vayá A, Rivera L, Hernandez-Mijares A, de la Fuente M, Sola E, Romagnoli M, Alis R, Laiz B. 2012. Homocysteine levels in morbidly obese patients: its association with waist circumference and insulin resistance. Clin Hemorheol Microcirc 52(1): 49-56.

Funding: None reported

MORBIDLY OBESE WITH OR WITHOUT METABOLIC SYNDROME

Age: 43.0 (None)	**Study design:** Case-control (**n = 132**)
Gender: Male and Female **Ethnicities:** White	**Country:** Spain **Region:** Eastern Spain **State:**
Inclusion criteria: both cases and controls were Caucasians and from Eastern Spain	**Exclusion critieria:** organic, malignant, haematological, infectious or inflammatory disease, previous history of ischaemic heart disease or stroke, previous thromboembolism, secondary obesity (hypothyroidism, Cushing syndrome), supplementation with folic acid or vitamin B12

69.1. Exposure: Serum folate

Method	Description	Analysis
assay	serum folic acid determined in an Immulite Assay	n/a

Outcomes

	Outcome	Diagnostic Description
A	Metabolic Syndrome (medical professional or test)	Metabolic syndrome was defined according to the NCEP ATPIII criteria modified by Grundy et al. [9] as having three or more risk factors, including the following: abdominal obesity (waist circumference >102 cm for men, >88 cm for women); triglycerides >150 mg/dL or drug treatment for elevated triglycerides); HDL-cholesterol <40 mg/dL for men, <50 mg/dL for women, or drug treatment to increase HDL-cholesterol; glucose >100 mg/dL or drug treatment for elevated glucose or diagnosed diabetes; systolic blood pressure >130 mmHg, diastolic blood pressure >85 mmHg or on hypertensive treatment.

Results

69.1.A Metabolic Syndrome

Population: Morbidly obese with or without Metabolic syndrome, Spain
Exposure: Serum folate
Outcome: Metabolic Syndrome
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	66	-	0.833

Statistical Method(s)

Endpoints: Metabolic Syndrome
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Data are expressed as means and standard deviation. To compare the differences in continuous variables between the two groups a t-test was used and an ANOVA test for more than two groups

70.   WASILEWSKA, 2003

Full citation: Wasilewska A, Narkiewicz M, Rutkowski B, Lysiak-Szydlowska W. 2003. Is there any relationship between lipids and vitamin B levels in persons with elevated risk of atherosclerosis? Med Sci Monit 9(3): CR147-151.

Funding: None reported

VITAMIN B LEVELS IN PERSONS WITH ELEVATED RISK OF ATHEROSCLEROSIS

Age: 55.4 (mean), from 24.0-80.0 years	**Study design:** Case-control (**n = 155**)
Gender: Male and Female **Ethnicities:**	**Country:** Poland **Region:** **State:**
Inclusion criteria:	**Exclusion critieria:** history of organ transplantation, thyroid, systemic, or neoplastic diseases

70.1. Exposure: Plasma folate

Method	Description	Analysis
assay	folate measured by Ion Capture Assay on IMx Analyzer	n/a

Outcomes

	Outcome	Diagnostic Description
A	Non Insulin Dependent Diabetes Mellitus (NIDDM) (not reported)	not specified, but patients were getting treatment for Non Insulin Dependent Diabetes Mellitus (NIDDM) and were hospitalized, so likely diagnosed by medical professional

Results

70.1.A Non Insulin Dependent Diabetes Mellitus (NIDDM)

Population: Patients with Non Insulin Dependent Diabetes Mellitus (NIDDM), Poland
Exposure: Plasma folate
Outcome: Non Insulin Dependent Diabetes Mellitus (NIDDM)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Plasma folate	-	-	

Statistical Method(s)

Endpoints: Non Insulin Dependent Diabetes Mellitus (NIDDM)
Adjustment factors:
Statistical metric: other
Statistical metric description: results reported as mean +/- SD, calculated for continous variables.

Group comparisons were made with one-way analysis of variance (ANOVA) and level of statistical significance set at $p<0.05$

71.   WILTSHIRE, 2001

Full citation: Wiltshire E, Thomas DW, Baghurst P, Couper J. 2001. Reduced total plasma homocyst(e)ine in children and adolescents with type 1 diabetes. J Pediatr 138(6): 888-893.

Funding: None reported

TYPE 1 DIABETES IN CHILDREN AND ADOLESCENTS

Age: 13.6 (mean)	**Study design:** Case-control (**n** = 137)
Gender: Male and Female **Ethnicities:** Unknown/Unspecified	**Country:** Australia **Region:** Adelaide **State:**
Inclusion criteria: children and adolescents with type 1 diabetes, Subjects had had diabetes for at least 6 months, subjects with diabetes without ketosis or hypoglycemia	**Exclusion critieria:**

71.1. Exposure: Red cell folate

Method	Description	Analysis
assay	Red cell folate were measured with an Ion Capture reaction (IMx folate, Abbott Laboratories, Sydney, Australia). At the same time, Food frequency questionnaires assessing intake of B vitamins taken	n/a

Outcomes

	Outcome	Diagnostic Description
A	Type I Diabetes Mellitus (not reported)	recruited consecutively from the diabetes clinic at the Women's and Children's Hospital in Adelaide, Australia. likely diagnosed by medical professional

Results

71.1.A Type I Diabetes Mellitus

Population: Type 1 diabetes, Australia
Exposure: Red cell folate
Outcome: Type I Diabetes Mellitus
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Red cell folate	-	-	0.001

71.2. Exposure: Serum folate

Method	Description	Analysis
assay	Serum folate was measured with an Ion Capture reaction (IMx folate, Abbott Laboratories, Sydney, Australia). At the same time, Food frequency questionnaires assessing intake of B vitamins taken	n/a

Outcomes

	Outcome	Diagnostic Description
A	Type I Diabetes Mellitus (not reported)	recruited consecutively from the diabetes clinic at the Women's and Children's Hospital in Adelaide, Australia. likely diagnosed by medical professional

Results

71.2.A Type I Diabetes Mellitus

Population: Type 1 diabetes, Australia
Exposure: Serum folate
Outcome: Type I Diabetes Mellitus
Statistical metric: t-test

Group	N	t-test 95% CI (low, high)	*p*-value
Serum folate	-	-	0.002

Statistical Method(s)

Endpoints: Type I Diabetes Mellitus
Adjustment factors:
Statistical metric: t-test
Statistical metric description: Data that were not normally distributed were log-transformed for analysis and expressed as geometric means. Group comparisons were determined with Student's t or χ2 tests.

72.   XUN, 2012

HYPERTENSION AMONG AMERICAN YOUNG ADULTS IN CARDIA STUDY

Age: 24.9 (mean), from 18.0-30.0 years	**Study design:** Cross-sectional (**n** = 4440)
Gender: Male and Female **Ethnicities:** Black or African American, White	**Country:** United States **Region:** **State:**
Inclusion criteria:	**Exclusion critieria:** diagnosed hypertension at baseline, implausible total energy intake (<800 or >8000 kcal/d for men and <600 or >6000 kcal/d for women, missing data on folate intake

72.1. Exposure: Folate intake

Method	Description	Analysis
dietary questionnaire	CARDIA dietary-history questionnaire, an intervieweradministered quantitative food-frequency questionnaire, was designed to assess habitual eating patterns. The validity and reproducibility of the CARDIA dietary history have been evaluated and discussed elsewhere (10, 11). Dietary assessment was conducted 3 times at baseline and examination year 7 and year 20. Participants were asked to recall their usual dietary intakes over the past month. They were asked general questions about their diet, which elicited specific foods consumed in an open-ended fashion. They were then asked to report the frequency, amount of food consumption, and method of preparation for each item named. Information on folate-containing supplements was also collected. Values for total folate and other B vitamin intake included dietary and supplemental sources.	Folate intake was measured 3 times at baseline and follow-ups in 1992 (year 7) and 2005 (year 20) Median intake (all in Afr Americans)of folate per Q1: 84.4 ug/1000 kcal/day; Q3: 142.7 ug/1000 kcal/day; Q5: 296.6 ug/1000 kcal/day. Median intake (all in whites) of folate per Q1: 109.1 ug/1000 kcal/day; Q3: 200.8 ug/1000 kcal/day; Q5: 394.8 ug/1000 kcal/day

Outcomes

	Outcome	Diagnostic Description
A	Homeostatic model of insulin resistance (HOMA-IR) (not reported)	no details of plasma glucose and insulin measurements and how they factor into HOMA-IR

Results

72.1.A Homeostatic model of insulin resistance (HOMA-IR)

Population: Hypertension among American young adults
Exposure: Folate intake
Outcome: Homeostatic model of insulin resistance (HOMA-IR)
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
Q1- African American (AA)	445	-	
Q3- AA	446	-	
Q5 - AA	445	-	0.02
Q1- Caucasian American (wh)	442	-	
Q3- wh	443	-	

Group	N	other 95% CI (low, high)	*p*-value
Q5- wh	443	-	0.01

Statistical Method(s)

Endpoints: Homeostatic model of insulin resistance (HOMA-IR)
Adjustment factors:
Statistical metric: other
Statistical metric description: Two-sided tests were used and P 0.05 was considered statistically significant. Chi-square test, ANOVA, and KruskalWallis test were used to compare the baseline characteristics of participants according to quintiles of folate intake within each race subgroup as appropriate.

73.   YAJNIK, 2008

PUNE MATERNAL NUTRITION STUDY (PMNS): INSULIN RESISTANCE IN OFFSPRING

Age: 6.1 (median)	**Study design:** Cross-sectional (**n =** 653)
Gender: Male and Female **Ethnicities:** Asian	**Country:** India **Region:** **State:**
Inclusion criteria: pregnant women	**Exclusion critieria:**

73.1. Exposure: Maternal Erythrocyte folate at 28 weeks

Method	Description	Analysis
assay	As previously described, maternal erythrocyte folate concentrations were measured at the time of the original study (1993–1996), taking all necessary precautions in the collection, transport and storage of samples (Rao S, Intake of micronutrient-rich foods in rural Indian mothers is associated with the size of their babies at birth: Pune maternal nutrition study, J Nutr 2001; 131: 1217-24): maternal red cell folate measured at 18 and 24 weeks using radioimmunoassay	Low erythrocyte folate concentrations defined as <283 nmol/l, respectively

Outcomes

	Outcome	Diagnostic Description
A	Homeostatic model of insulin resistance (HOMA-IR), age 6 (medical professional or test)	Insulin resistance was calculated using the fasting insulin and glucose concentrations (homeostatic model assessment of insulin resistance [HOMA-R]); Plasma glucose was measured using an Hitachi 911 automated analyser (Hitachi, Tokyo, Japan) by the glucose oxidase peroxidase method. Plasma insulin was measured using a Delfia technique

Results

73.1.A Homeostatic model of insulin resistance (HOMA-IR), age 6

Population: Pune Maternal Nutrition Study (PMNS), India
Exposure: Maternal Erythrocyte folate at 28 weeks
Outcome: Homeostatic model of insulin resistance (HOMA-IR), age 6
Statistical metric: other

Group	N	other 95% CI (low, high)	*p*-value
<734 nmol/L	129	-	
734–691 nmol/L	136	-	
962–1,268 nmol/L	131	-	
≥1,269 nmol/L	127	-	0.001

Statistical Method(s)

Endpoints: Homeostatic model of insulin resistance (HOMA-IR), age 6
Adjustment factors: child's age, child's sex, child's birthweight, gestation at delivery, mother's pre-pregnant height and fat mass, mother's protein intake at the time of measurement, skinfold thicknesses, socioeconomic status (SES)
Statistical metric: other
Statistical metric description: Skewed variables were transformed to normality using the following transformations: log to the base e (ln) (plasma vitamin B12 [18 weeks], erythrocyte folate concentrations). Relationships between maternal nutritional variables andoutcomes in the children were analysed using multiple linear regression. As a final stage of the analysis, we summarised the interrelationships between maternal factors and outcomes in the children using principal components analysis (PCA) and conditional independence analysis.