Kan lystgass til mor under fødsel påvirke barnet på lengre sikt?

Ulf Wike Ljungblad

Barnelege, PhD

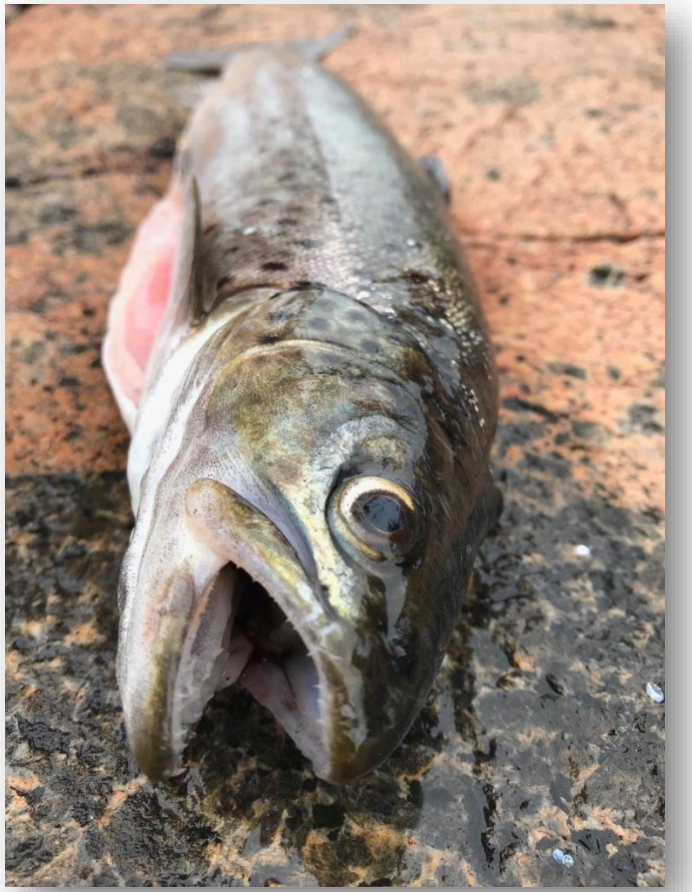
Sykehuset i Vestfold, Tønsberg

SYKEHUSET I VESTFOLD

Økt perinatalt stroke risiko?
Endret metylering av DNA?

30 min

Vitamin B12 og folat hos gravide og hennes barn



Photos by Linda Wike Ljungblad

Hvorfor er vitamin B12 viktig for spedbarn?

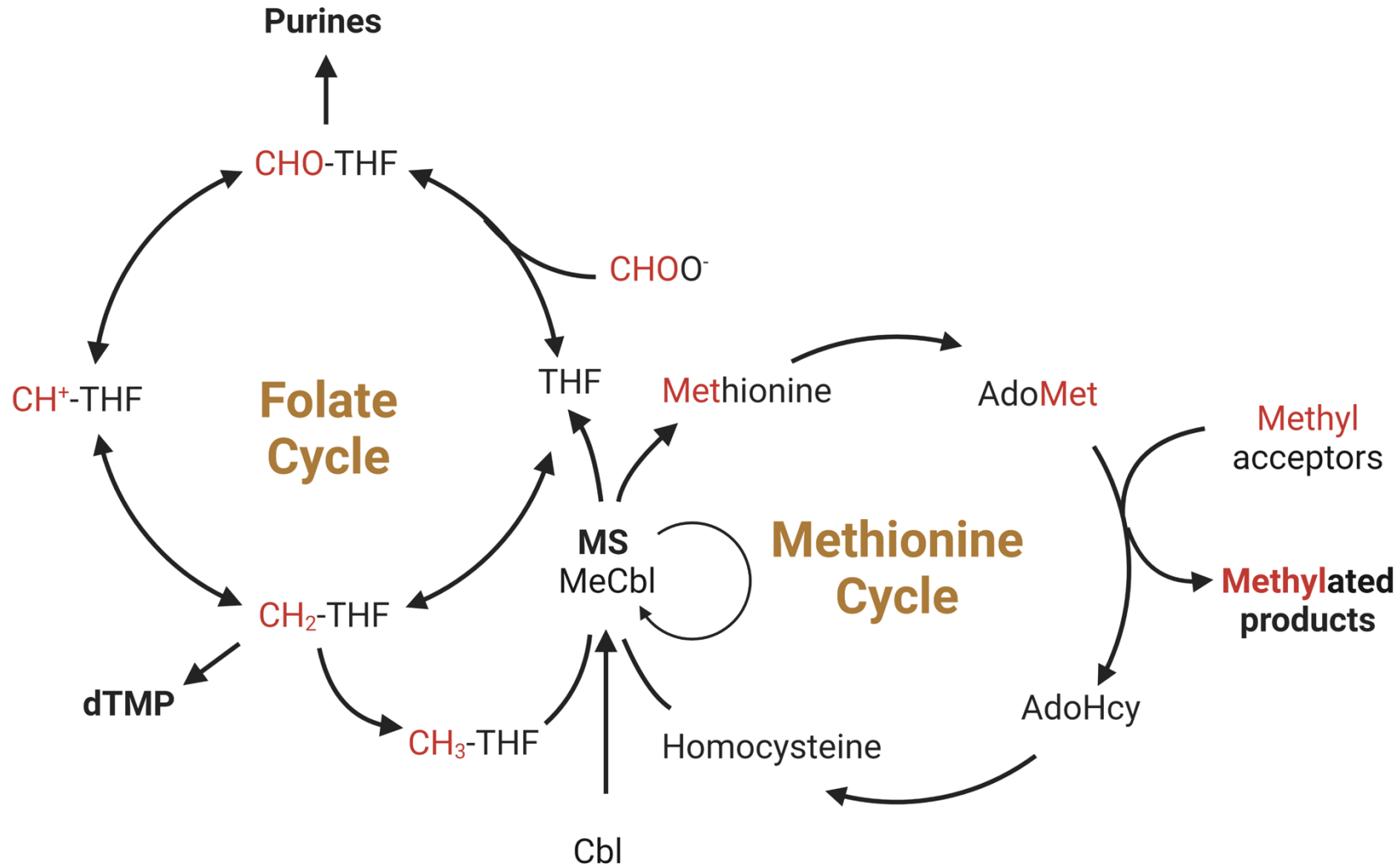
- Hjernens utvikling
- Mangel gir nevrologisk sykdom og dårligere utvikling
- Barnet får B12 fra mor under svangerskapet
- Har mor lav B12 fødes barnet med små B12 reserver
- Måling av B12 hos gravide er ikke del av svangerskapsomsorgen

Green (2017)

- B12 i morsmelk korrelerer til mors nivåer av B12
- Norske anbefalinger: Fullamming til 6 mnd alder
- Vi ser B12 mangel hos spedbarn i klinikken
- B12 mangel kan oppdages hos noen spedbarn via Nyfødtscreeningen

Mütze (2021)
Ganetzky (2021)

SYKEHUSET I VESTFOLD



Adapted from Froese (2019)

methylmalonyl-CoA

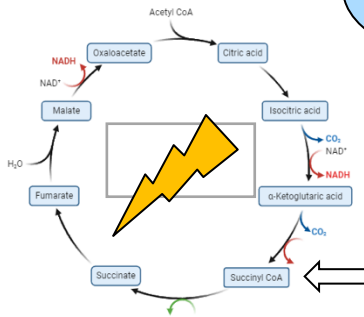
homocysteine

mutase

B12

methionine synthase

B12



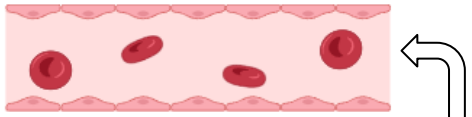
Succinyl-CoA

methionine

Created with BioRender.com

Creative Commons Stock Images
Microsoft PowerPoint

SYKEHUSET I VESTFOLD



homocysteine

homocysteine

homocysteine

methionine synthase

B12

methionine

25/34 fødesteder

Private photo, vessel created with BioRender.com

SYKEHUSET I VESTFOLD

TABLE 1. Mean Maternal Nitrous Oxide Levels (vol. per cent) in Relation to Concentration of N_2O Inflow and Duration of Administration.*

Time (min)	Concentration of N_2O Inflow		
	70%	60%	50%
2–4	19.2 (3)	19.8 (4)	17.7 (2)
5–9	29.3 (3)	25.5 (11)	18.6 (4)
10–14	30.3 (3)	26.4 (6)	—
15–19	30.2 (3)	25.8 (1)	—

* Numbers in parentheses denote number of cases in each group.

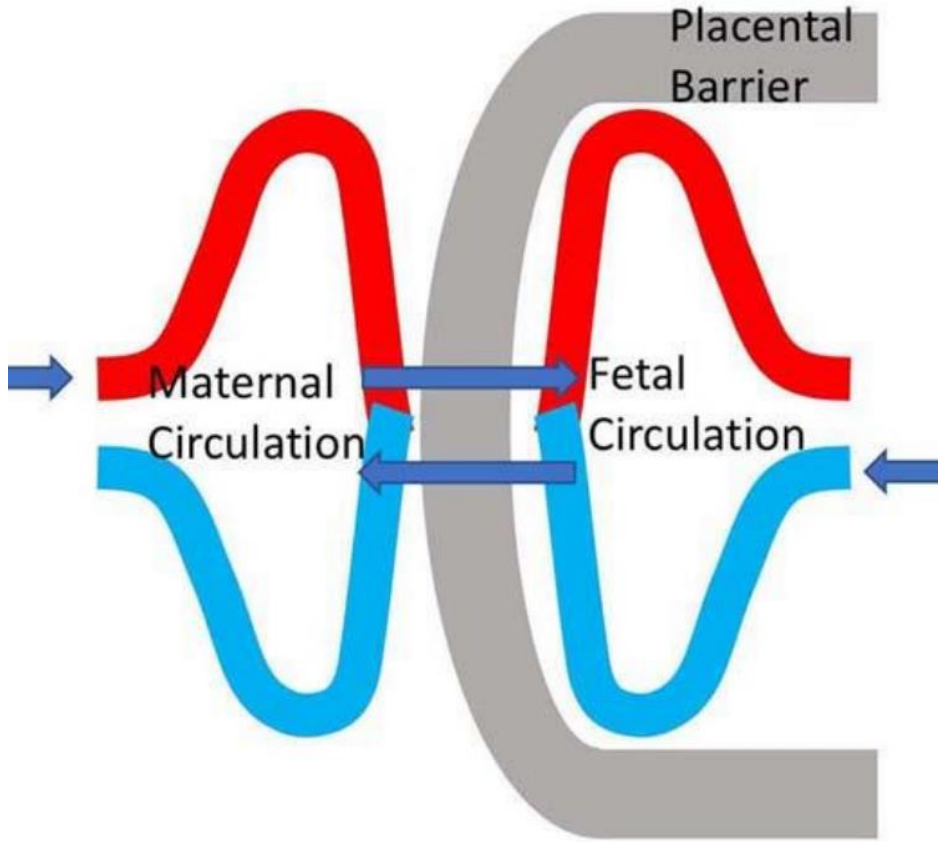


TABLE 2. Umbilical Vein Blood Nitrous Oxide Concentration—Expressed as Ratio of Maternal Level—in Relation to Duration of N_2O Administration.

Time (min)	Number of Cases	Fetal–Maternal N_2O Concentration Ratio	
		Mean ± SE.	Range
2	3	0.64	0.62–0.68
3–4	6	0.83±0.02	0.75–0.89
5–9	18	0.78±0.02	0.55–0.89
10–14	9	0.80±0.02	0.62–0.91
15–19	4	0.81	0.72–0.86

TABLE 3. Umbilical Artery Blood Nitrous Oxide Concentration—Expressed as Ratio of Umbilical Vein Blood N_2O Concentration—in Relation to Duration of N_2O Administration.

Time (min)	Number of Cases	Umbilical Artery–Umbilical Vein N_2O Concentration Ratio	
		Mean ± SE.	Range
2–4	8	0.57±0.05	0.34–0.72
5–9	14	0.72±0.02	0.53–0.84
10–14	7	0.79±0.03	0.67–0.89
15–19	3	0.87	0.84–0.90

Marx (1970)

SYKEHUSET I VESTFOLD

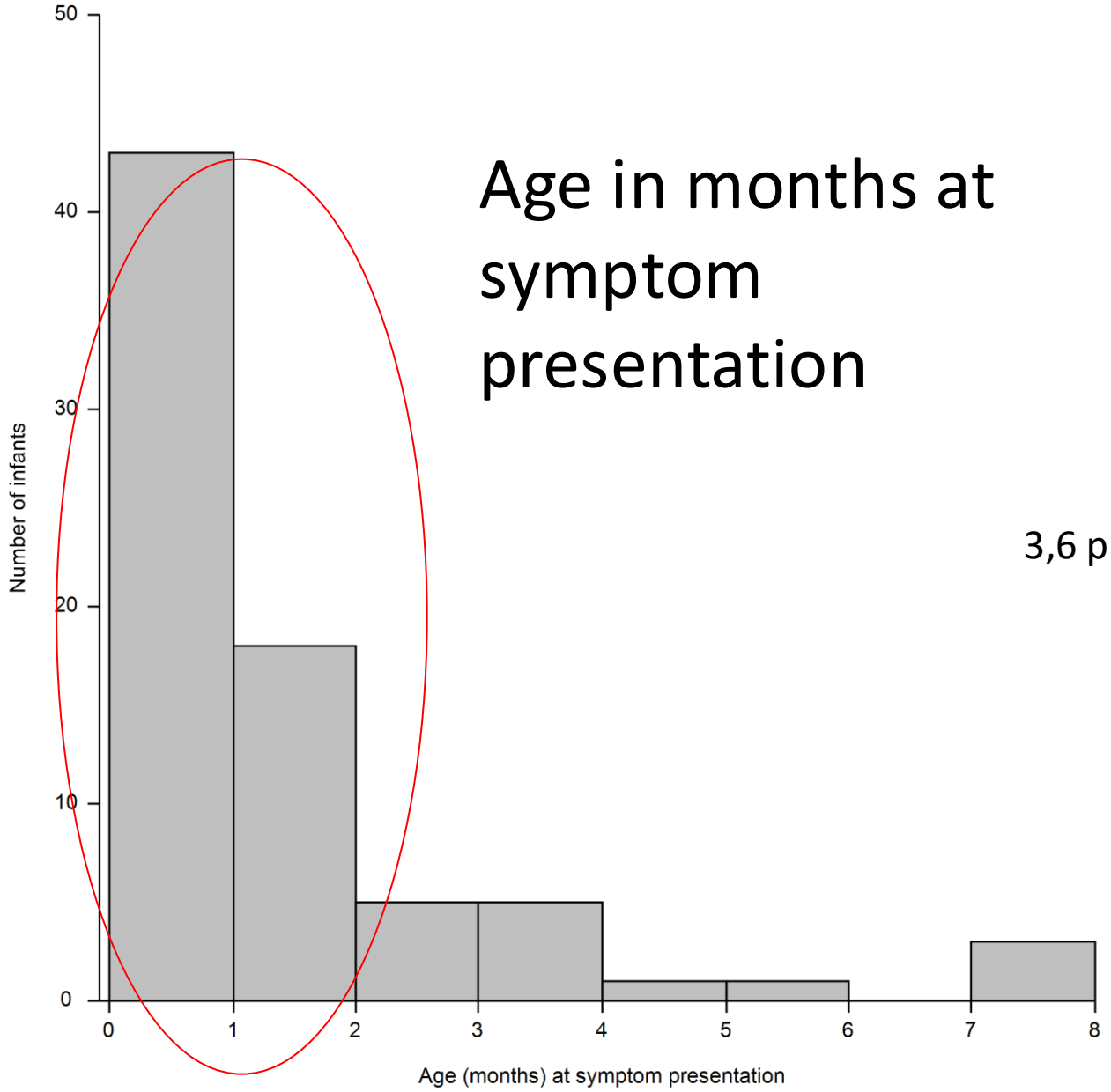
TABLE II. *Methionine synthase activity (methionine nmol h^{-1}/mg protein) following 50% nitrous oxide (mean ± SD). *Significantly less than air control ($P < 0.01$)*

Treatment	n	Immediately after exposure: Maternal	Immediately after exposure: Fetal
Air—60 min	11	1.70 ± 0.35	0.96 ± 0.29
N_2O—15 min	4	0.53 ± 0.22*	0.82 ± 0.03
N_2O—30 min	4	0.23 ± 0.05*	0.25 ± 0.03*
N_2O—60 min	4	0.18 ± 0.03*	0.17 ± 0.06*

Time	n	Recovery after N_2O—60 min: Maternal	Recovery after N_2O—60 min: Fetal
24 h	3	0.50 ± 0.16*	0.21 ± 0.08*
48 h	3	0.72 ± 0.09*	0.55 ± 0.03*
72 h	3	0.83 ± 0.08*	0.82 ± 0.08

Baden (1984)

Age in months at symptom presentation



3,6 per 1000 fødsler

Ljungblad (2022)

SYKEHUSET I VESTFOLD

Symptom or Finding	Cases n=85	Controls n=252	p
Spells (motor seizures, apneas, or absences)	30/76 (39%)	0/250 (0 %)	<0.001
Tremor	21/72 (29%)	13/250 (5.2%)	<0.001
Irritability	12/68 (18%)	19/252 (7.5%)	0.012
Head-lag at pull-to-sit	26/53 (49%)	38/250 (15%)	<0.001
Abnormal eye contact	9/67 (13%)	0/250 (0 %)	<0.001

N=9 infants evaluated after newborn screening test results or due to family history of B12 deficiency are excluded

Ljungblad (2022)

Pediatric Neurology 131 (2022) 4–12

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

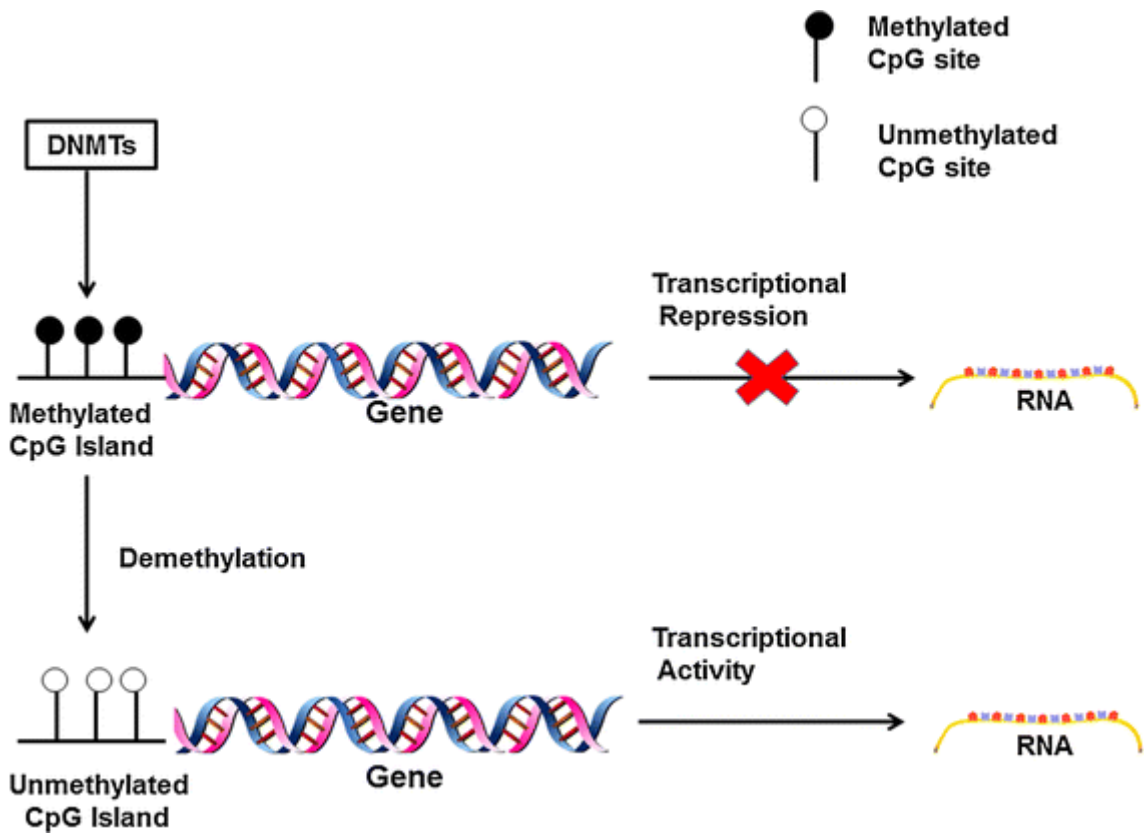
Research Paper

Breastfed Infants With Spells, Tremor, or Irritability: Rule Out Vitamin B12 Deficiency

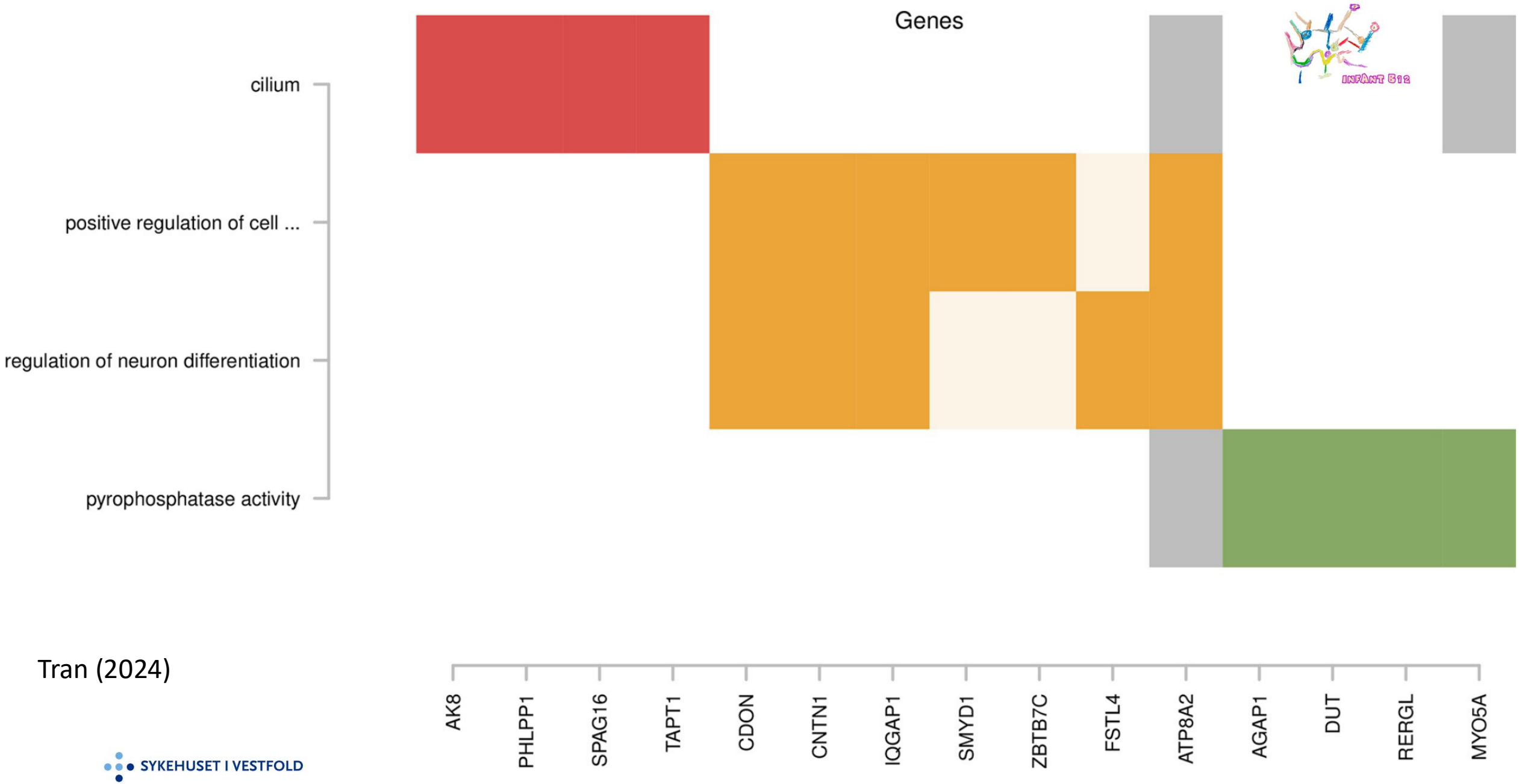
Ulf Wike Ljungblad, MD [a, b, *], Henriette Astrup, MD [c], Lars Mørkrid, MD, PhD [a, d], Helle Borgstrøm Hager, MD [e], Morten Lindberg, MD, PhD [e], Erik A. Eklund, MD, PhD [f], Anne-Lise Bjørke-Monsen, MD, PhD [g, h], Terje Rootwelt, MD, PhD [a, i], Trine Tangeraas, MD, PhD [j]

- Dose lystgass under fødsel var assosiert med både homocystein og metylmalonsyre ved diagnose – jo mer lystgass desto dårligere B12 status
- Ingen mødre var vegetarianere, men 25% hadde kjent B12 mangel og 7% hadde cøliaki
- Fullamming sterkeste risikofaktoren
- Tidligere debut om mor fikk lystgass og barnet ble fullammet

SYKEHUSET I VESTFOLD


Methylated
CpG site
Unmethylated
CpG site
DNMTs
Transcriptional
Repression
Methylated
CpG Island
Gene
RNA
Demethylation
Transcriptional
Activity
Unmethylated
CpG Island
Gene
RNA

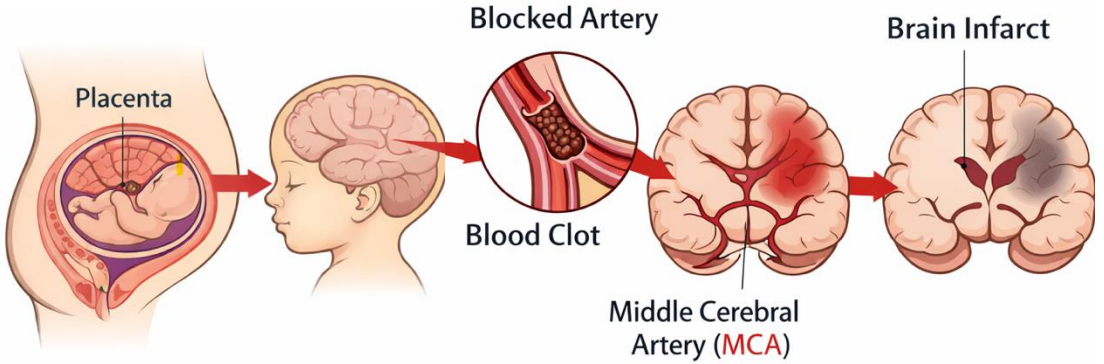
Wang (2017)



Tran (2024)

SYKEHUSET I VESTFOLD

Perinatal hjerneslag



- 1/1600-3000 nyfødte
- Beror på arteriell eller venøs blodpropp
- Viktigste årsak til cerebral parese
- Multifaktoriell etiologi, oftest identifiseres ikke årsak
- Viktige risikofaktorer trolig ikke identifisert
- Både mor og barn i protrombotisk state ved fødsel

Whitaker (2020)

Lystgass er en biologisk plausibel risikofaktor

- Lystgass inaktiverer metioninsyntase irreversibelt (Chanarin 1980)
- Nyfødte sårbare pga lav B12 status (Ljungblad 2021)
- Lystgass brukes mye i Norge ved fødsel (Ljungblad 2022)
- tHcy øker 2-3x hos mor og kan vare i flere dager (Ermens 1991)

Lystgass er en biologisk plausibel risikofaktor

- Lystgass går raskt over placenta og samles i barnet (Marx 1970)
- tHcy er vist å stige hos nyfødte etter lystgass til mor (Ljungblad 2022)
- tHcy er en risikofaktor for slag hos voksne (Fekih-Mrissa 2013)

MTHFR, folat og lystgass

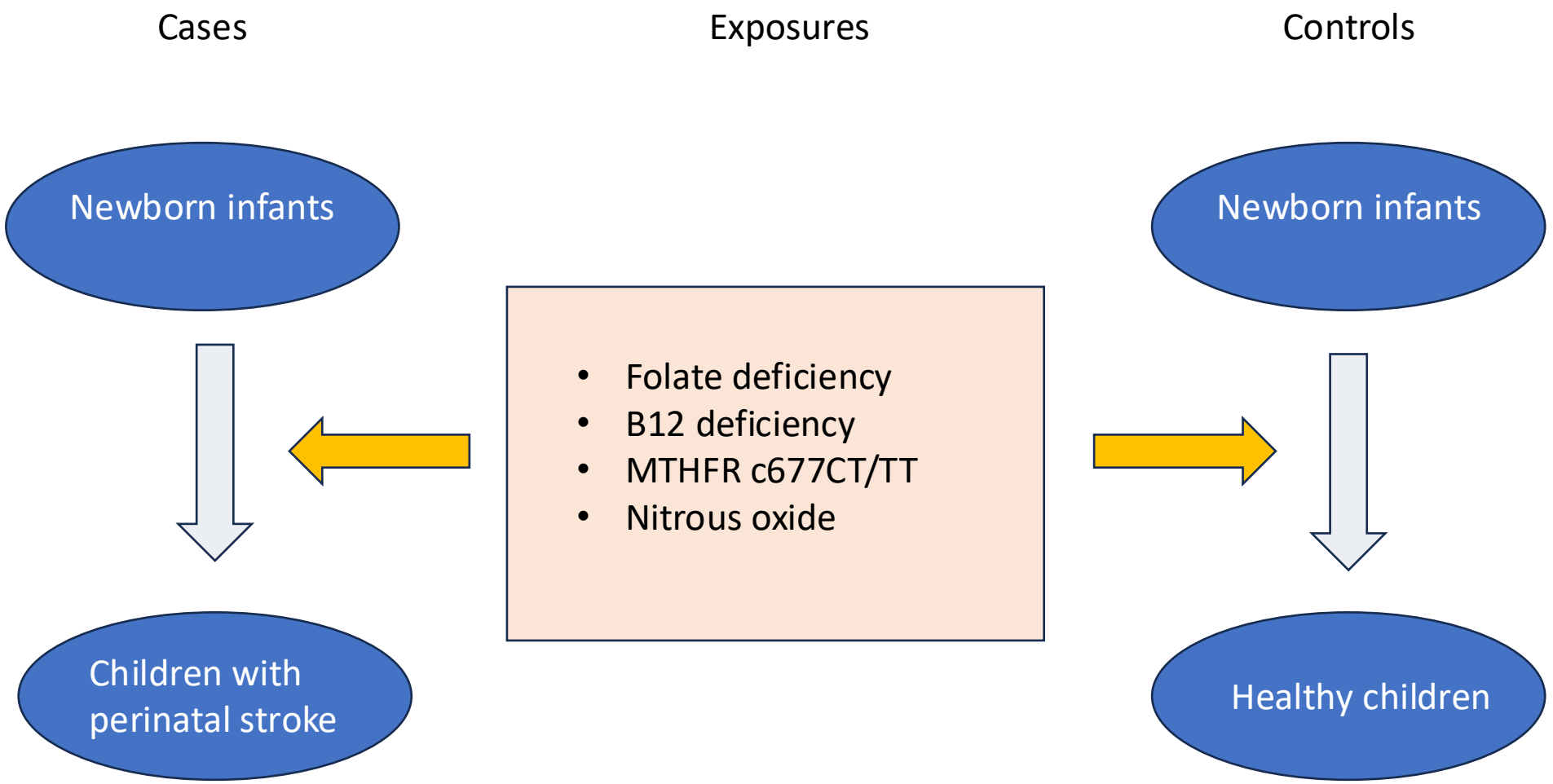
C667T	
CC	45%
CT	43%
TT	12%
A1298C	
AA	54%
AC	38%
CC	8.3%

- Alle som fikk lystgass fikk økt tHcy (Nagele 2008)
- De som var 677TT fikk 3x høyere tHcy enn de med 677CC (Nagele 2008)
- 12% er homocygote for 677T genotypen av MTHFR (Wiik 2023)
- Både økt tHcy og MTHFR genotype er assosiert med slag

  hos voksne (Fekih-Mrissa 2013)

MTHFR, folat og lystgass

- I en ikke folat-substituert populasjon hadde 57% av nyfødte med slag en langsommere MTHFR genotype (Kocaman 2012)
- 30% av gravide hadde folat <10 nmol/L i uke 36 (Bjørkevoll 2023)


Cases
Exposures
Controls
Newborn infants
Newborn infants
Folate deficiency
B12 deficiency
MTHFR c677CT/TT
Nitrous oxide
Children with perinatal stroke
Healthy children

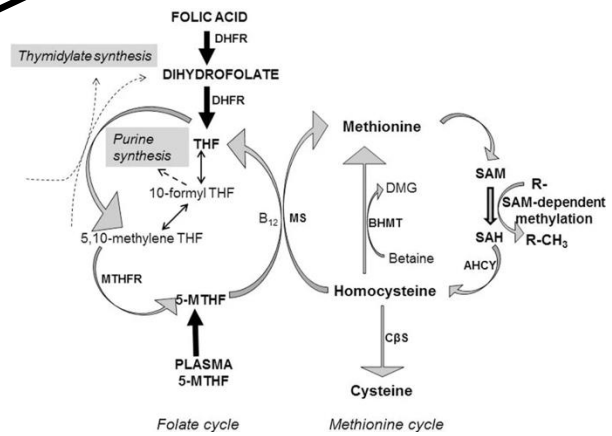
Perinatal Stroke Risk

Low Folate

Low Vitamin B12

c677CT/TT MTHFR genotype

Nitrous Oxide



Mediator: tHcy Level

Lystgass-relaterte kilder

- Baden, J. M., Serra, M., & Mazze, R. I. (1984). Inhibition of fetal methionine synthase by nitrous oxide. *Br. J. Anaesth* (Vol. 56).
- Baden, J. M., Serra, M., Mazze, R. I., & Mazze, I. (1987). Inhibition of rat fetal methionine synthase by nitrous oxide an in vitro study. *Br. J. Anaesth* (Vol. 59).
- Ermens, A. A. M., Refsum, H., Rupreht, J., Spijkers, L. J. M., Guttormsen, A. B., Lindemans, J., Ueland, P. M., & Abels, J. (1991). Monitoring cobalamin inactivation during nitrous amide anesthesia by determination of homocysteine and folate in plasma and urine. Clinical Pharmacology and Therapeutics, 49(4), 385–393.
- Frasca, V., Riazzi, B. S., & Matthews, R. G. (1986). In vitro inactivation of methionine synthase by nitrous oxide. Journal of Biological Chemistry, 261(34), 15823–15826. https://doi.org/10.1016/S0021-9258(18)66636-0
- Froese, D. S., Fowler, B., & Baumgartner, M. R. (2019). Vitamin B12, folate, and the methionine remethylation cycle—biochemistry, pathways, and regulation. *Journal of Inherited Metabolic Disease*, *42*(4), 673–685.
- Landon, M. J., Creagh-Barry, P., McArthur, S., & Charlett, A. (1992). Influence of vitamin B12 status on the inactivation of methionine synthase by nitrous oxide. British Journal of Anaesthesia, 69(1), 81–86.
- Marx, G. F., Joshi, C. W., & Orkin, L. R. (1970). Placental Transmission of Nitrous Oxide. *Anesthesiology*, *32*(5), 429–432.
- Mendoza, J., Purchal, M., Yamada, K., & Koutmos, M. (2023). Structure of full-length cobalamin-dependent methionine synthase and cofactor loading captured in crystallo. *Nature Communications 2023 14:1*, *14*(1), 1–12.
- Nagele, P., Tallchief, D., Blood, J., Sharma, A., & Kharasch, E. D. (2011). Nitrous oxide anesthesia and plasma homocysteine in adolescents. *Anesthesia & Analgesia*, *113*(4), 843–848.
- Tran, C. J., Campbell, T. L., Johnson, R. H., Xie, L. Y., Hultman, C. M., van den Oord, E. J. C. G., & Aberg, K. A. (2024). Cell-type specific methylation changes in the newborn child associated to obstetric pain relief. *PloS One*, *19*(9).