



# Infant Vitamin B12 Deficiency



Thanks to

The Infants and Families

The Committee

The Medical Faculty

Vestfold Hospital

Main Supervisor Trine Tangeraas

Co-supervisors

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Ellen Ruud

Erik A Eklund

Terje Rootwelt



By Erik Wike Ljungblad

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Images Microsoft PowerPoint



- Background
- Aims
- Overview of methods and results
- Results from four papers
- Summary



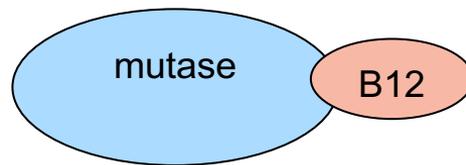
Photos by Linda Wike Ljungblad



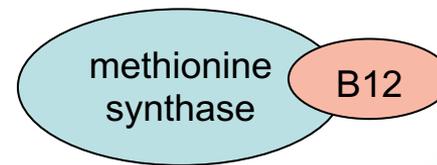
Photo by Linda Wike Ljungblad



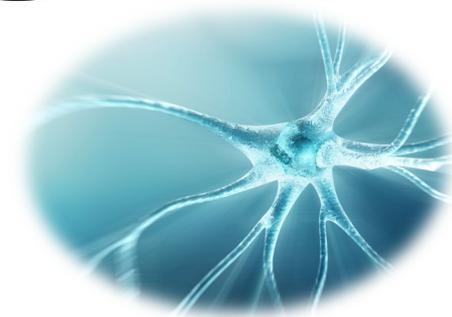
methylmalonyl-CoA



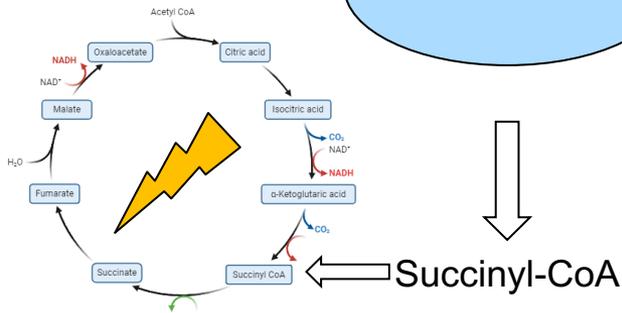
homocysteine



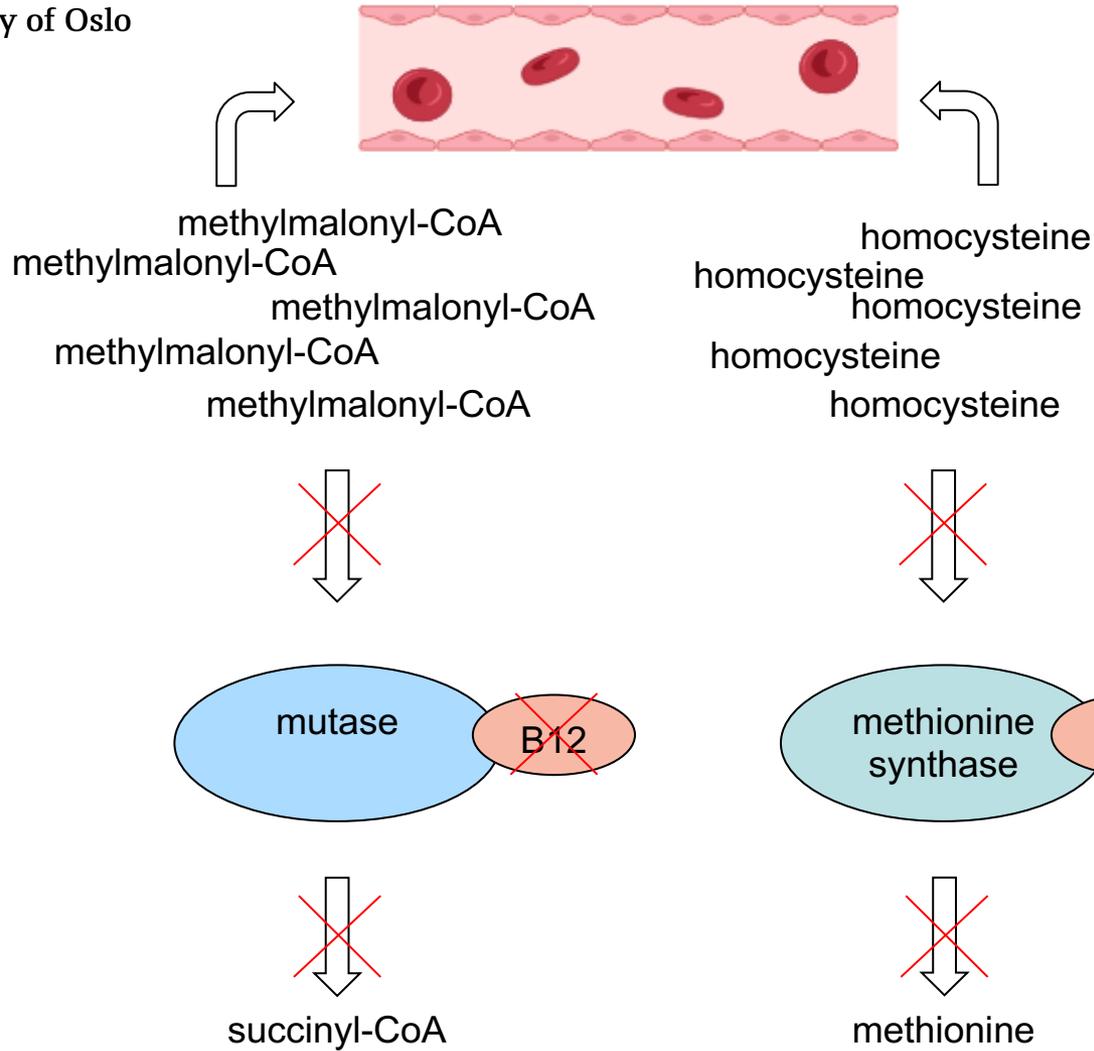
methionine

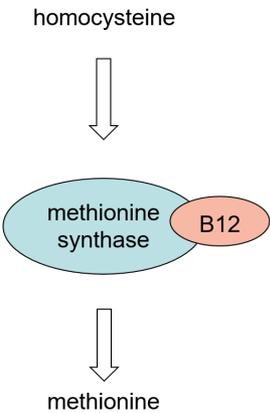
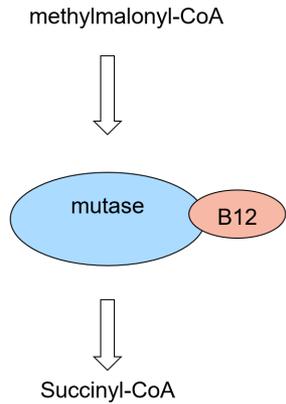


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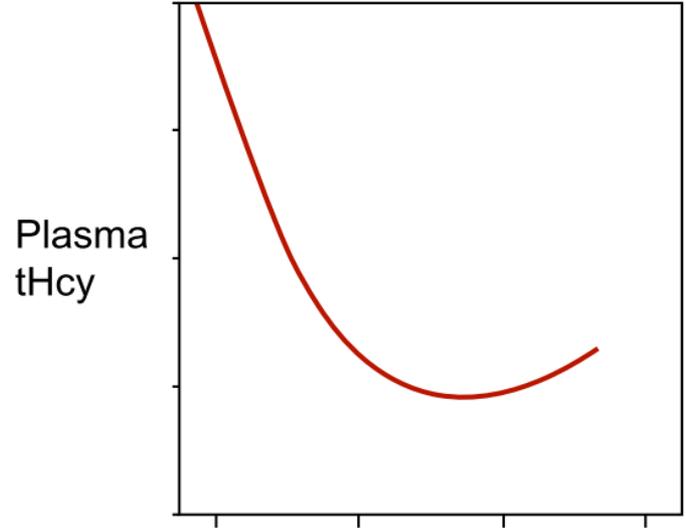
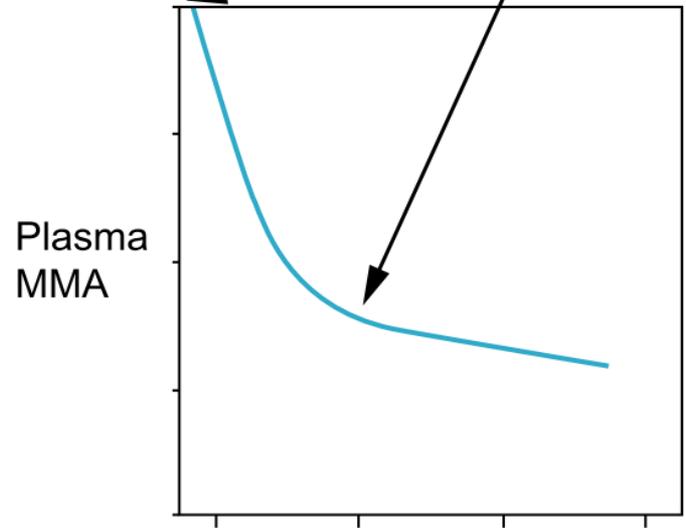
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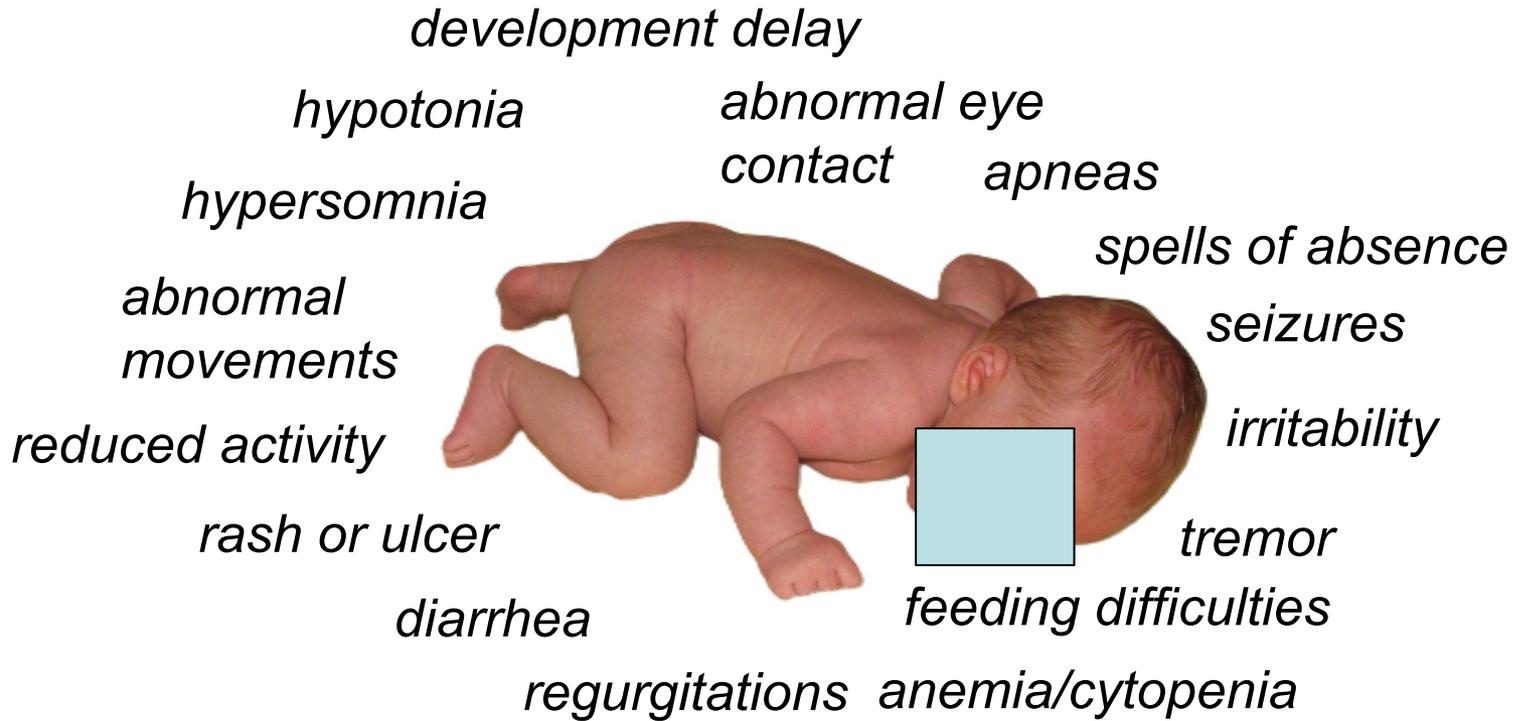
**Classical  
deficiency**

**Metabolic  
insufficiency**



200 400 600 800  
Plasma vitamin B<sub>12</sub> (pmol/L)

Smith, Warren et al. (2018), see Figure 4 in the Thesis.



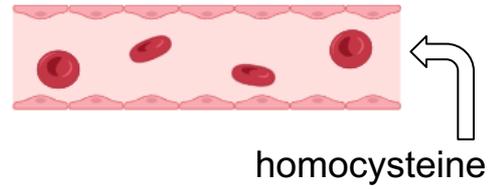
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Private photo

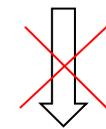
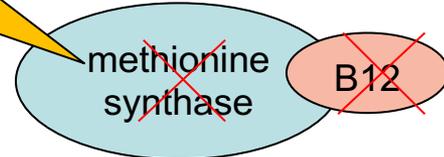
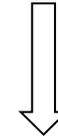


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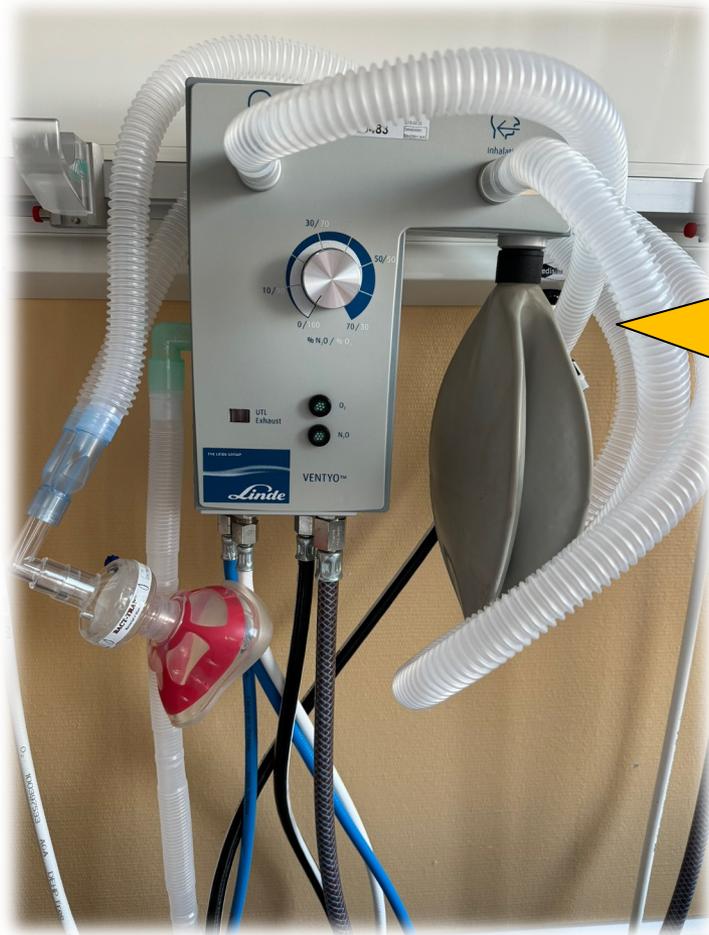


homocysteine

homocysteine



methionine



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REGULAR ARTICLE

## B12 deficiency is common in infants and is accompanied by serious neurological symptoms

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2.Department of Clinical Science, Paediatrics, Umeå University, Umeå, Sweden

**Keywords**

Apparent life-threatening event, Infant nutrition, Neurological symptoms, Seizures, Vitamin B12 deficiency

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**ABSTRACT**

**Aim:** Adverse neurological symptoms have been linked to vitamin B12 deficiency in infants. This explorative study described the clinical presentation associated with vitamin B12 deficiency in this age group.

**Methods:** The study comprised infants who were born between 2004 and 2012 and were tested for vitamin B12 levels after they were admitted to a hospital with neurological symptoms at less than one year of age. Vitamin B12 deficiency was defined as low cobalamin in serum and/or increased homocysteine and/or increased methylmalonate. It was diagnosed according to the applicable International Classification of Diseases, 10th revision, and recorded as vitamin B12 deficiency in the medical records. All information was retrieved from medical records and compared to symptomatic infants with normal levels.

**Results:** Of the 121 infants tested, 35 had vitamin B12 deficiency and 86 had normal levels.

NOVEMBER 3, 1962

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## VITAMIN-B<sub>12</sub> DEFICIENCY IN INDIAN INFANTS Clinical Syndrome

JADHAV

et al

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J. K. G. WEBB  
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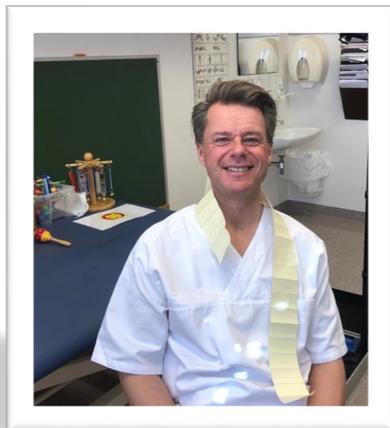
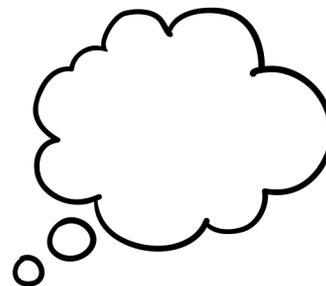
## Common Metabolic Profile in Infants Indicating Impaired Cobalamin Status Responds to Cobalamin Supplementation

Anne-Lise Bjørke-Monsen, Ingrid Torsvik, Hege Sætran, Trond Markestad and Per Magne Ueland

*Pediatrics* 2008;122:83-91  
DOI: 10.1542/peds.2007-2716

vitamin-B<sub>12</sub> content of breast-milk (Baker et al. 1962). This may lead to frank vitamin-B<sub>12</sub> deficiency in breast-fed infants.





- How common is symptomatic vitamin B12 deficiency in infants?
- What are the symptoms?
- What are the risk factors?
- Can we predict it with newborn screening?



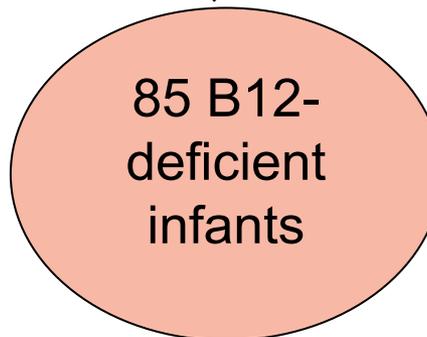
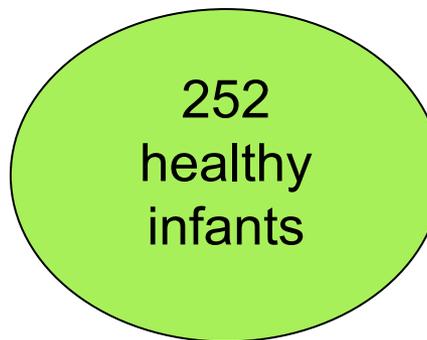
Birth



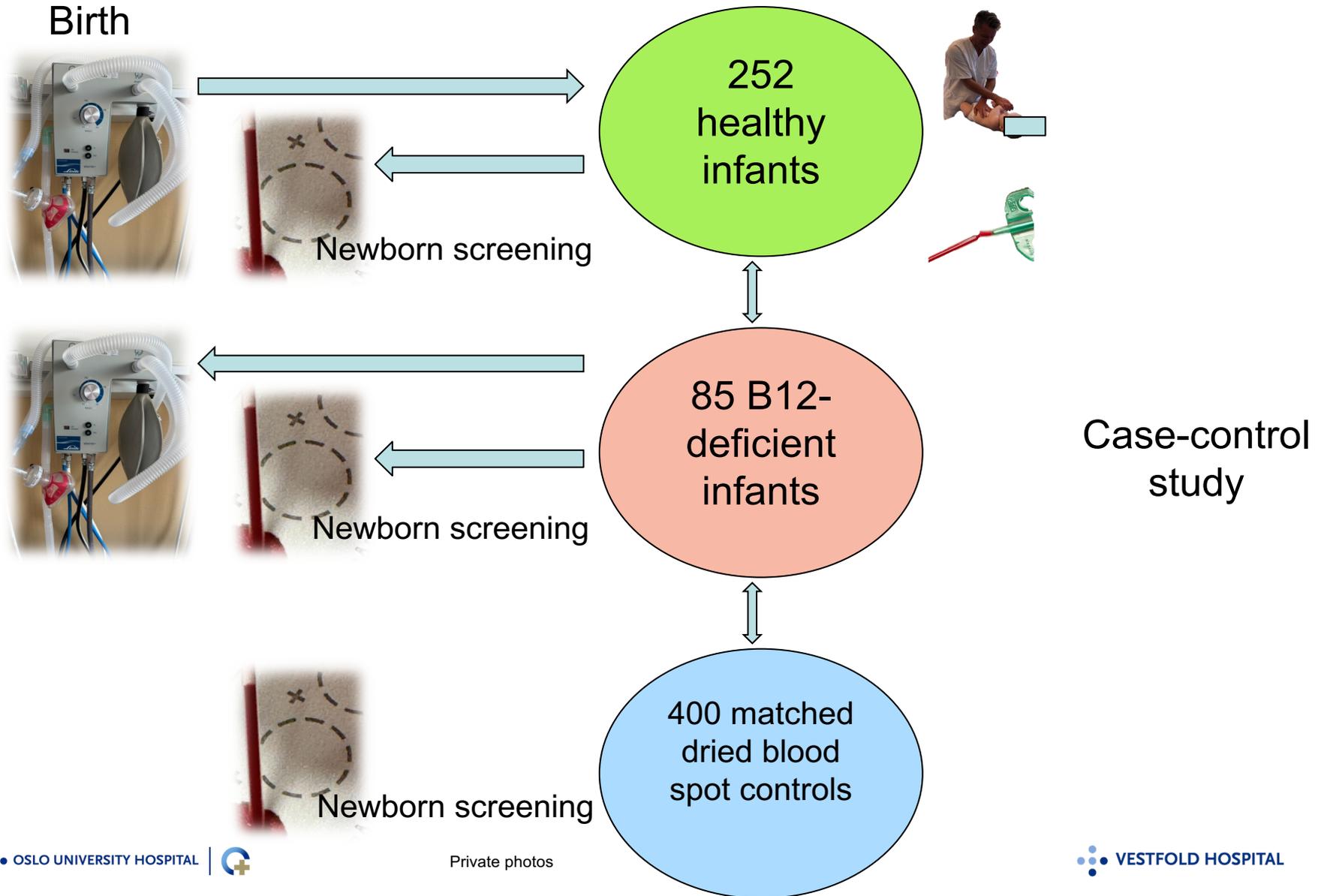
Prospective  
observational  
study

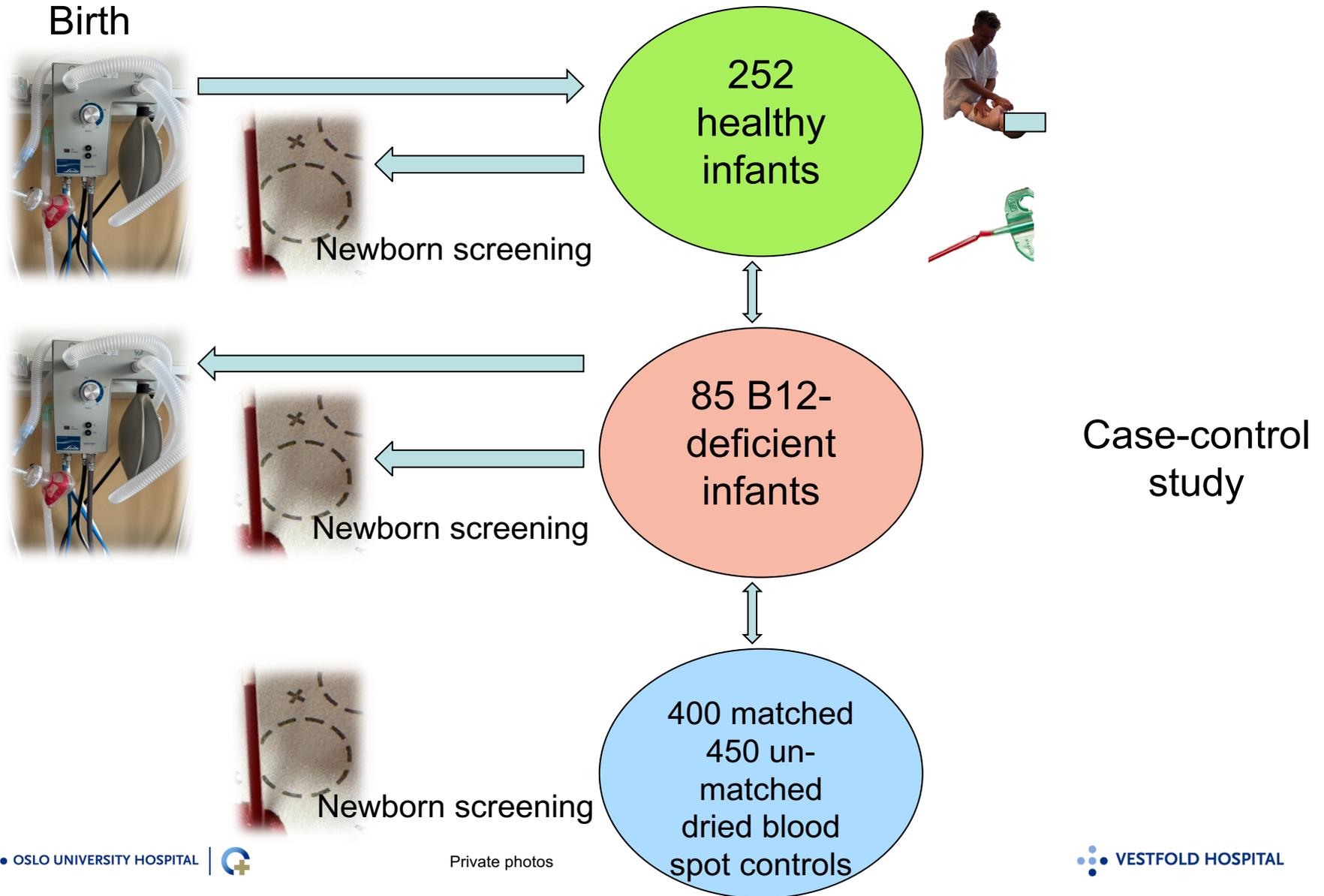


Birth



Case-control  
study

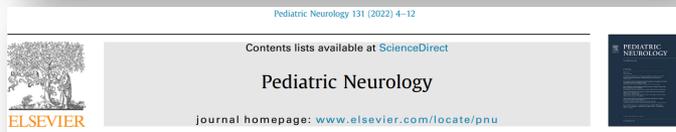






### The prevalence and clinical relevance of hyperhomocysteinemia suggesting vitamin B12 deficiency in presumed healthy infants

Ulf Wike Ljungblad <sup>a,b,\*</sup>, Henriette Paulsen <sup>c</sup>, Lars Mørkrid <sup>a,d</sup>, Rolf D. Pettersen <sup>e</sup>, Helle Borgstrøm Hager <sup>f</sup>, Morten Lindberg <sup>f</sup>, Henriette Astrup <sup>g</sup>, Erik A. Eklund <sup>h</sup>, Anne-Lise Bjørke-Monsen <sup>i,j</sup>, Terje Rootwelt <sup>a,k</sup>, Trine Tangeraa <sup>c,k</sup>



Research Paper

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

Ulf Wike Ljungblad, MD <sup>a,b,\*</sup>, Henriette Astrup, MD <sup>c</sup>, Lars Mørkrid, MD, PhD <sup>a,d</sup>, Helle Borgstrøm Hager, MD <sup>e</sup>, Morten Lindberg, MD, PhD <sup>e</sup>, Erik A. Eklund, MD, PhD <sup>f</sup>, Anne-Lise Bjørke-Monsen, MD, PhD <sup>a,h</sup>, Terje Rootwelt, MD, PhD <sup>a,i</sup>, Trine Tangeraa, MD, PhD <sup>j</sup>

Received: 4 July 2022 | Revised: 23 August 2022 | Accepted: 26 August 2022  
DOI: 10.1111/apa.16530

ORIGINAL ARTICLE



### Nitrous oxide in labour predicted newborn screening total homocysteine and is a potential risk factor for infant vitamin B12 deficiency

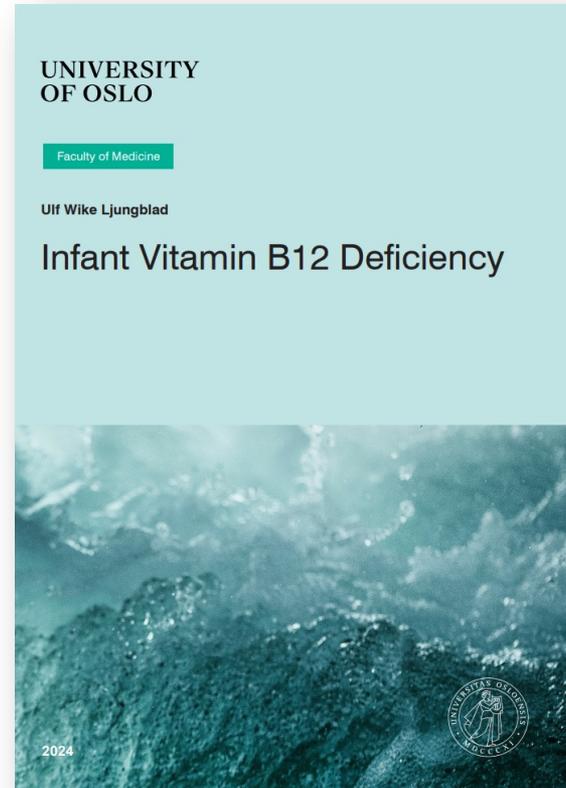
Ulf Wike Ljungblad <sup>1,2</sup> | Morten Lindberg <sup>3</sup> | Erik A. Eklund <sup>4</sup> | Ingjerd Saeves <sup>5</sup> | Anne-Lise Bjørke-Monsen <sup>6,7</sup> | Trine Tangeraa <sup>8</sup>



Article

### A Retrospective Evaluation of the Predictive Value of Newborn Screening for Vitamin B12 Deficiency in Symptomatic Infants Below 1 Year of Age

Ulf Wike Ljungblad <sup>1,2,\*</sup>, Morten Lindberg <sup>3</sup>, Erik A. Eklund <sup>4</sup>, Ingjerd Saeves <sup>5</sup>, Carlos Sagredo <sup>6</sup>, Anne-Lise Bjørke-Monsen <sup>7,8,9</sup> and Trine Tangeraa <sup>5</sup>





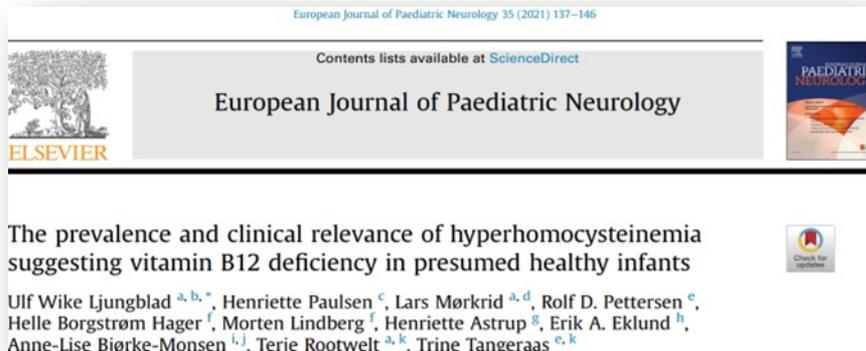
## Paper 1

Explorative prospective observational study

252 infants 3-7 months



Photos by Henriette Paulsen



# Paper 1

- 46% S-tHcy > 8 µmol/L
- Associations between S-tHcy > 8 µmol/L and tremor, parent-reported excessive sleep
- 10% had clinically relevant S-tHcy > 8 µmol/L suggesting B12 deficiency

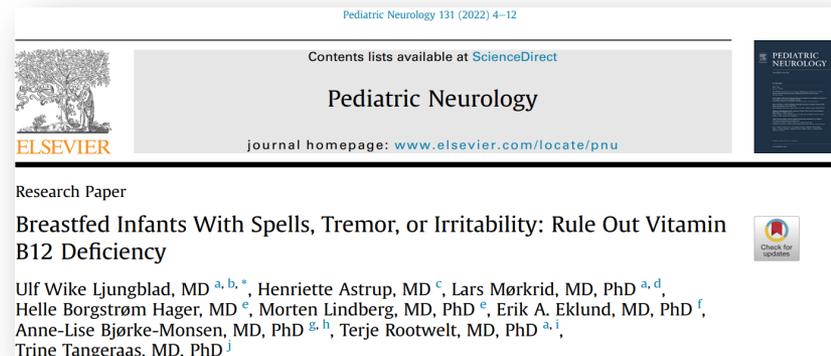


# Paper 1

- Exclusive breastfeeding increased the odds three times for tHcy  $>8 \mu\text{mol/L}$
- No increased risk for tHcy  $>8 \mu\text{mol/L}$  for infants born preterm or small for gestational age



# Paper 2



- Retrospective case-control study
- 85 cases
- 252 controls

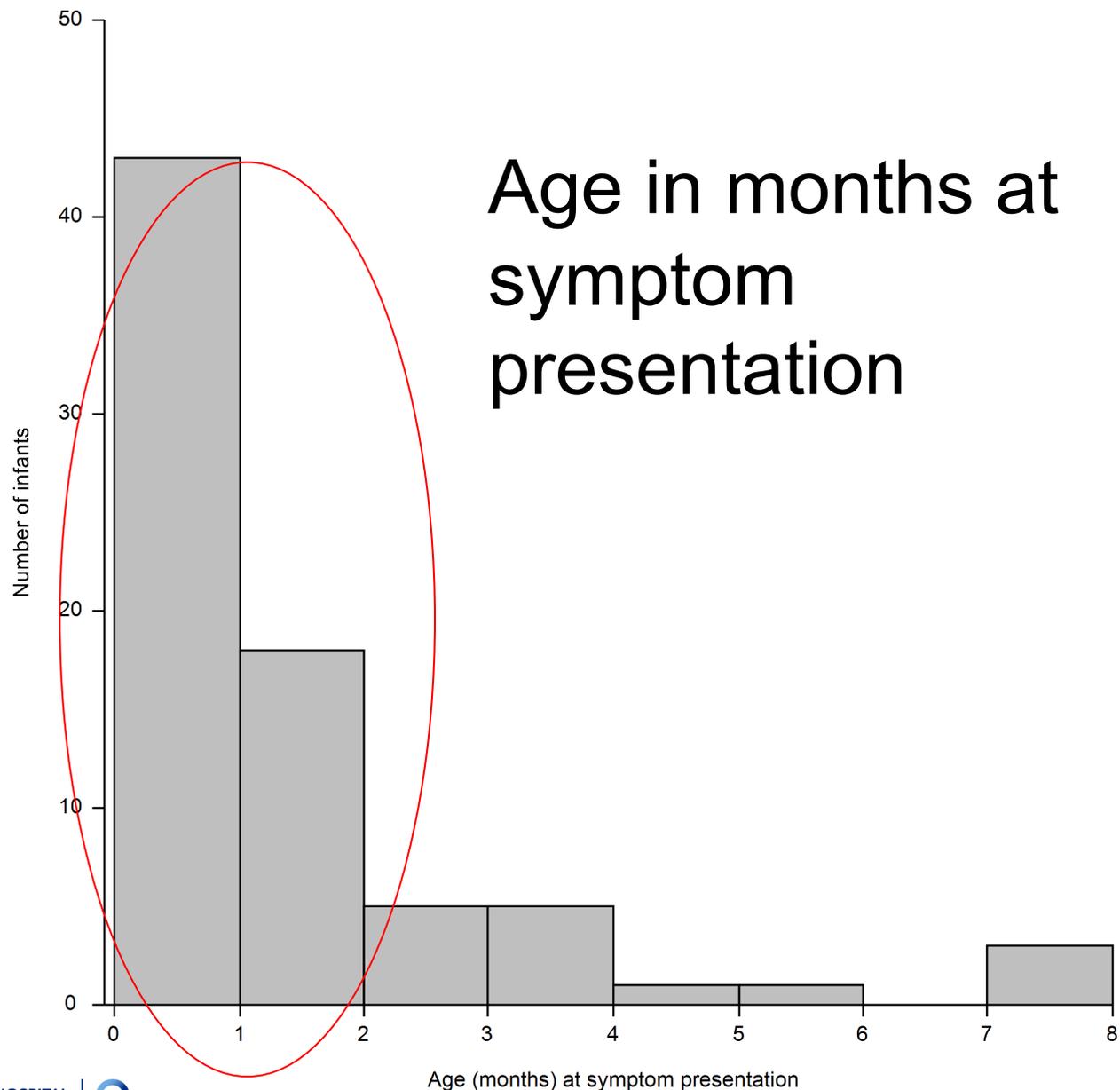
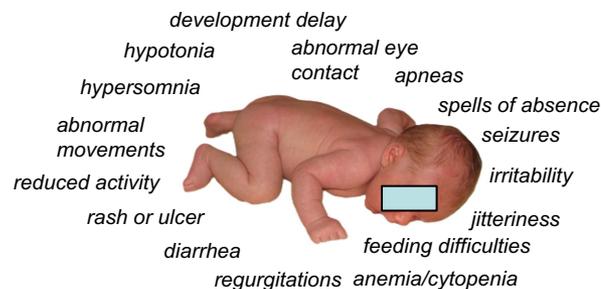


Figure 2 in Paper 2



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



## Paper 2

- No vegetarian mothers
- 25% reported earlier B12 deficiency
- Dose of nitrous oxide associated with tHcy and MMA at diagnosis
- Earlier referral age when the mother received nitrous oxide
- Exclusive breastfeeding a risk factor

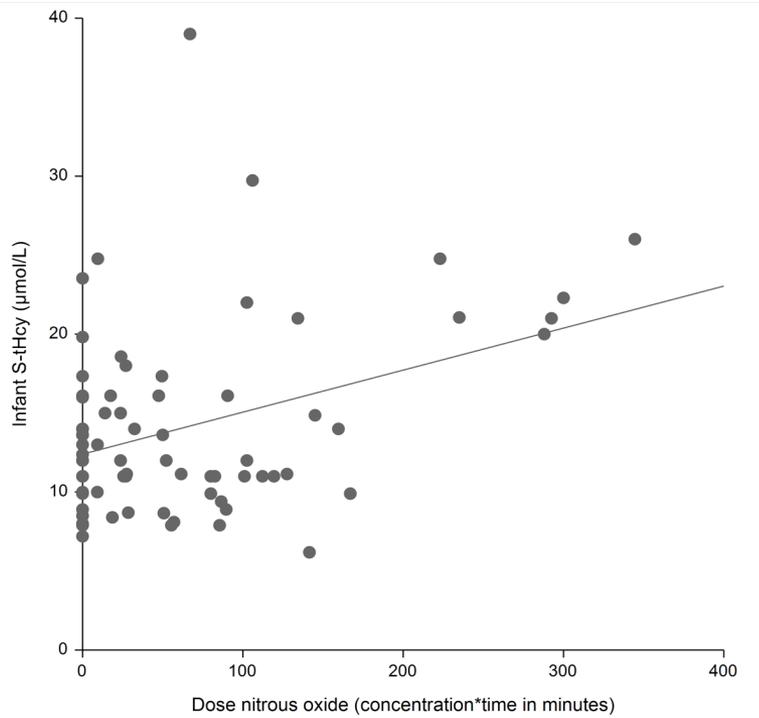


Figure 5 in Paper 2. Photos private.



months later

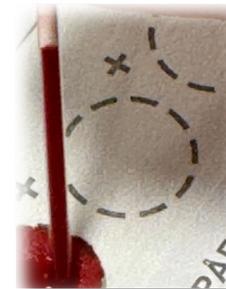




# Paper 3



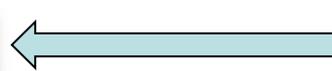
- Retrospective case-control study
- 85 cases, 252 clinical controls, and 400 dry-blood-spot-controls





## Paper 3

- B12 deficient infants had higher markers of B12 deficiency at newborn screening
- The dose of nitrous oxide to the mother in labor was the strongest predictor for total homocysteine



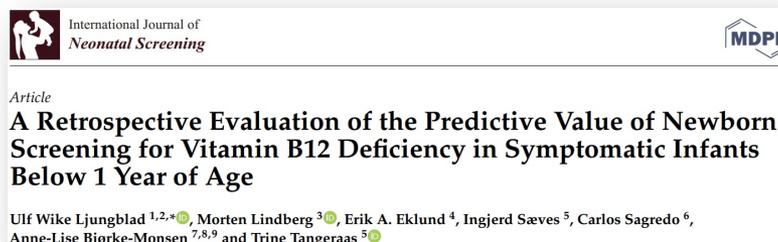
B12 deficient infants



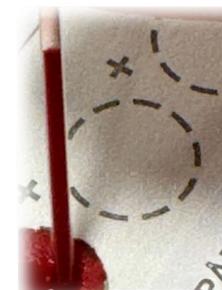
Controls



# Paper 4



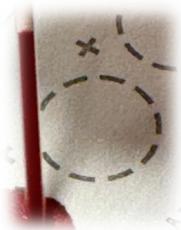
- Retrospective case-control study
- 70 clinical cases, 646 matched controls and 434 un-matched controls





# Paper 4

- Newborn screening failed to identify over 90% of infants with symptomatic B12 deficiency



Symptomatic B12  
deficient infants



Controls



Vitamin B12 deficiency is common in infants



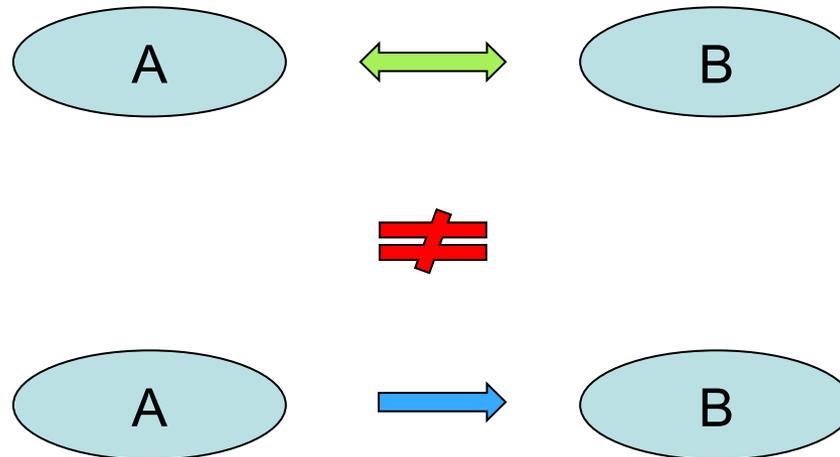
Vitamin B12 deficiency may present with serious, potentially life-threatening symptoms like spells of apneas and seizures



Nitrous oxide to the mother during labor may be a risk factor for infant B12 deficiency



Symptomatic infant B12 deficiency was missed on newborn screening in 90% of cases





Thank you for you attention!

