Living with myasthenia gravis

Updates on psychosocial issues and training

Friday September 30 - Saturday October 1, 2022
Musholm, Denmark

MUSKELSVINDFONDEN

The National Rehabilitation Center for Neuromuscular Diseases

HELSE VEST

Myasthenia Gravis
Pregnancy and giving birth

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Disclaimers

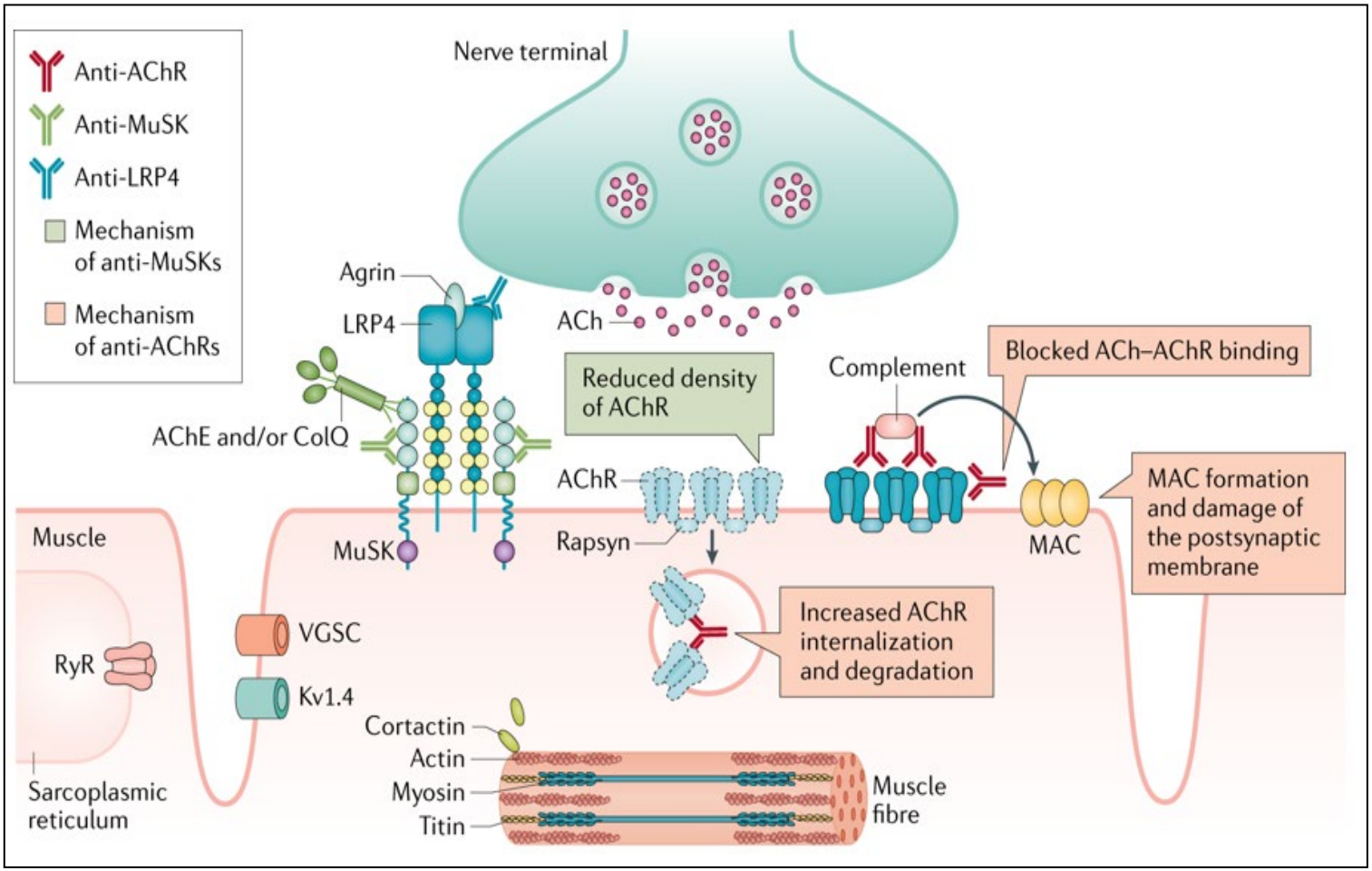
Nils Erik Gilhus has received consultative or speaker's honoraria from;

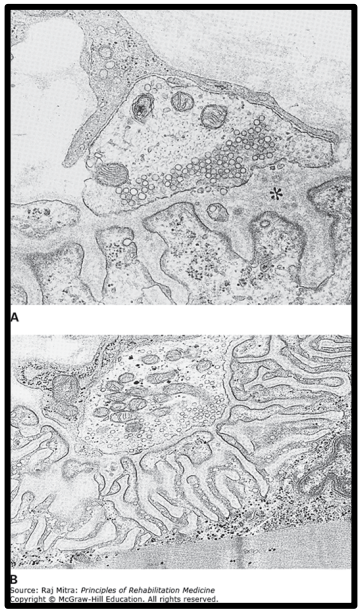
- Argenx
- Ra Pharma
- Alexion
- Octapharma
- UCB
- Merck
- Roche
- Immunovant
- Janssen

HELSE VEST

UNIVERSITAS BERGENSIS

Pathophysiology of MG at the neuromuscular junction

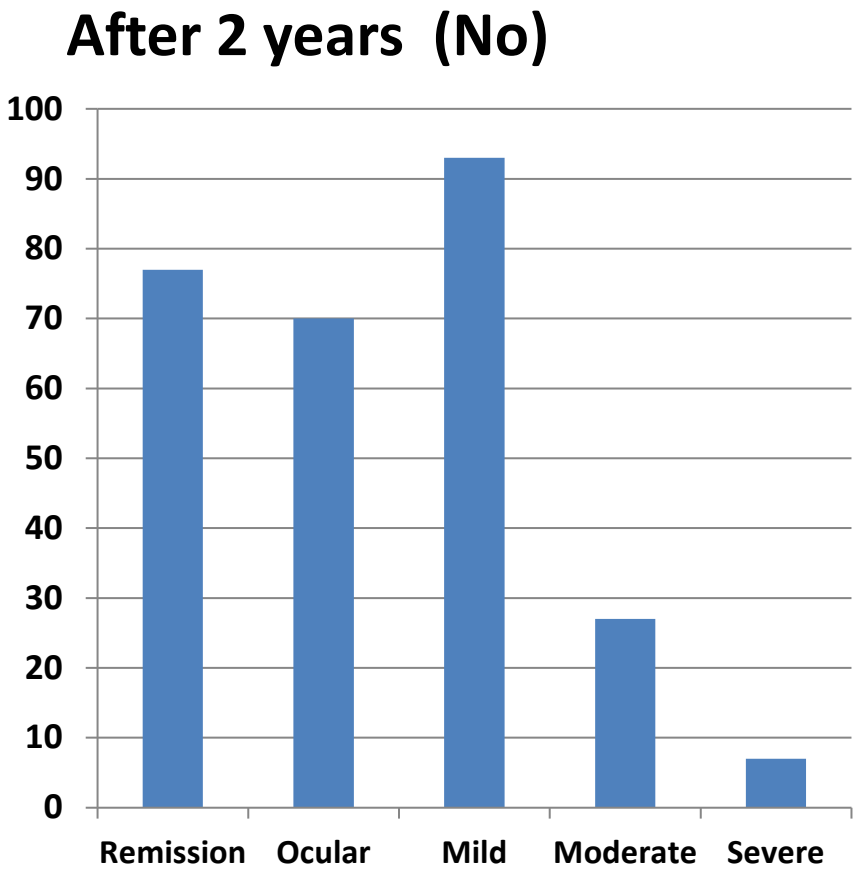


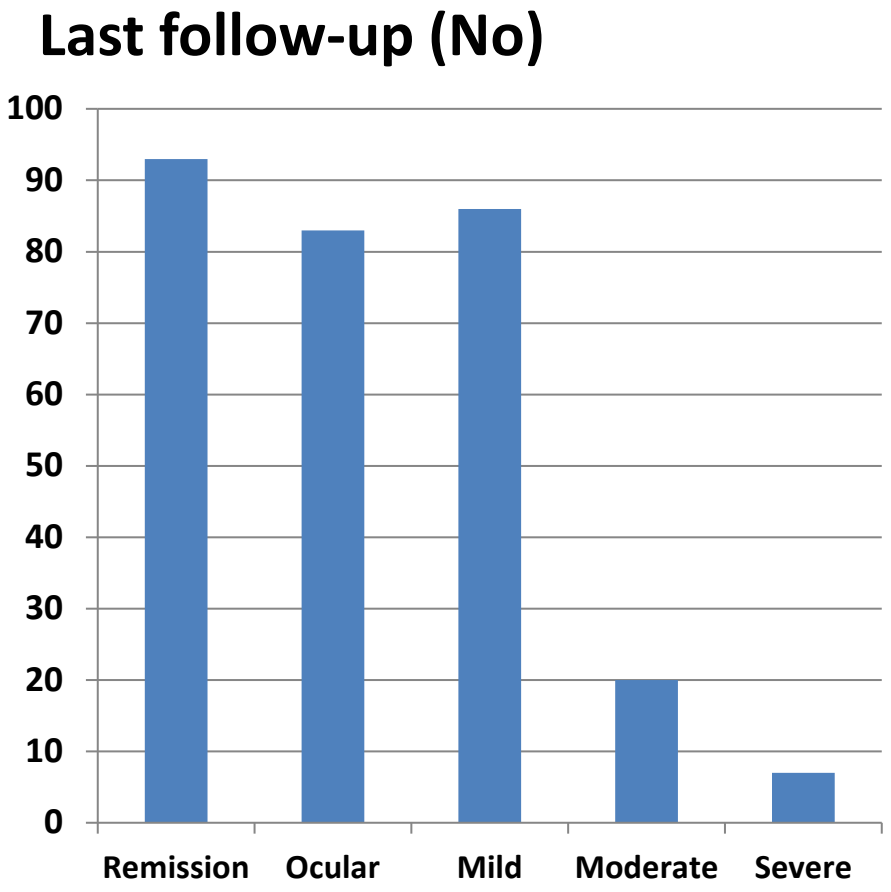


From Engel A 1972

Gilhus, N. E. et al. (2019) Myasthenia gravis.
Nature Rev. Dis. Primers

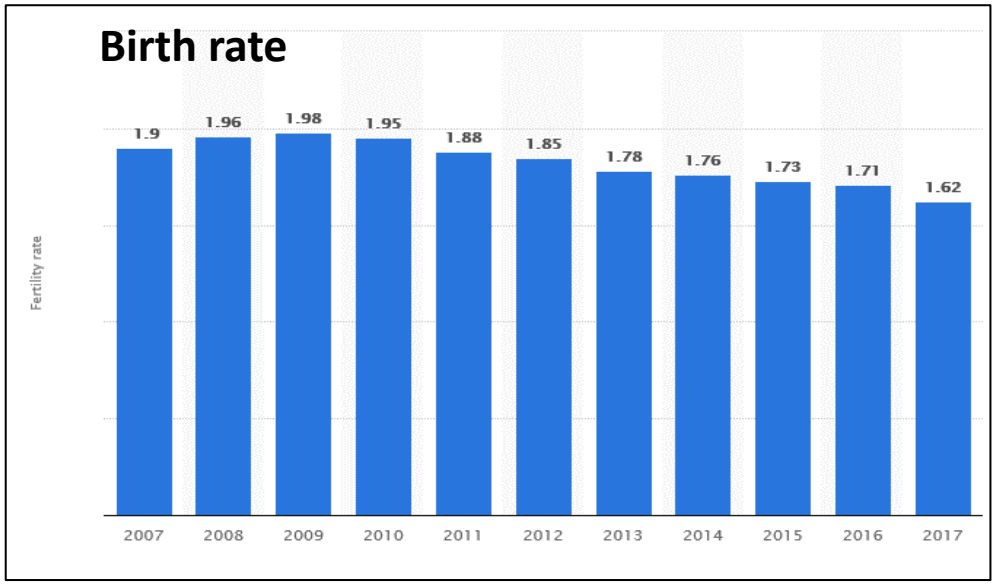
MG outcome in a single centre cohort

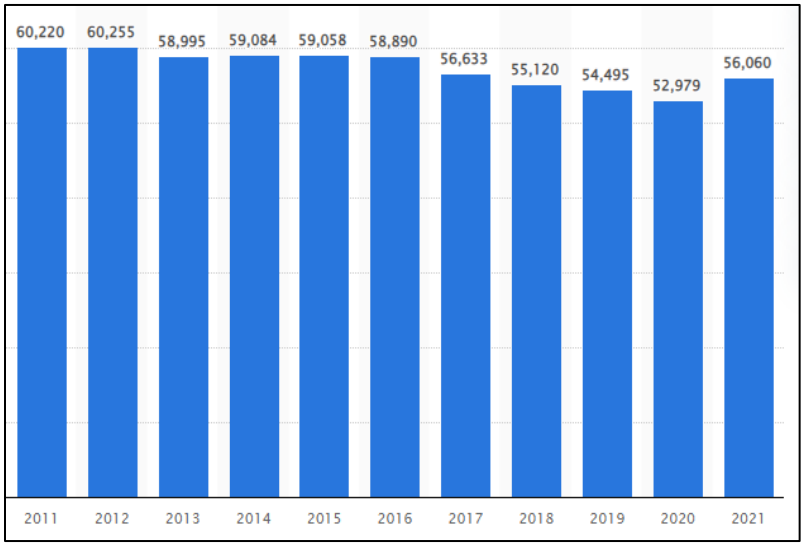


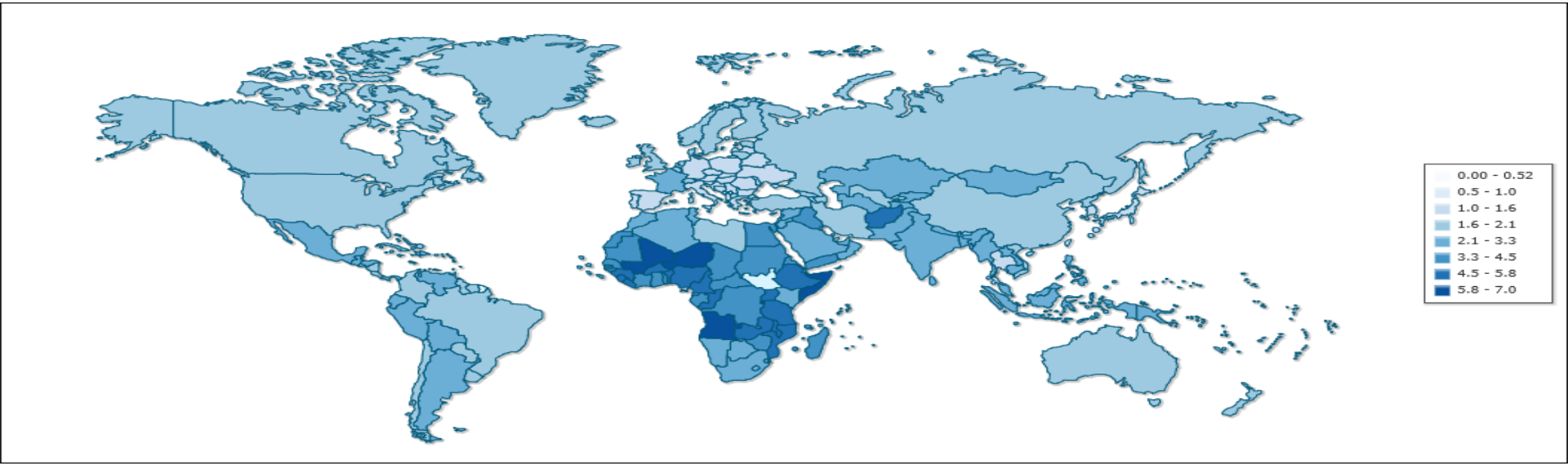


Andersen et al 2016 (Duke, USA)

Births in Norway and the world

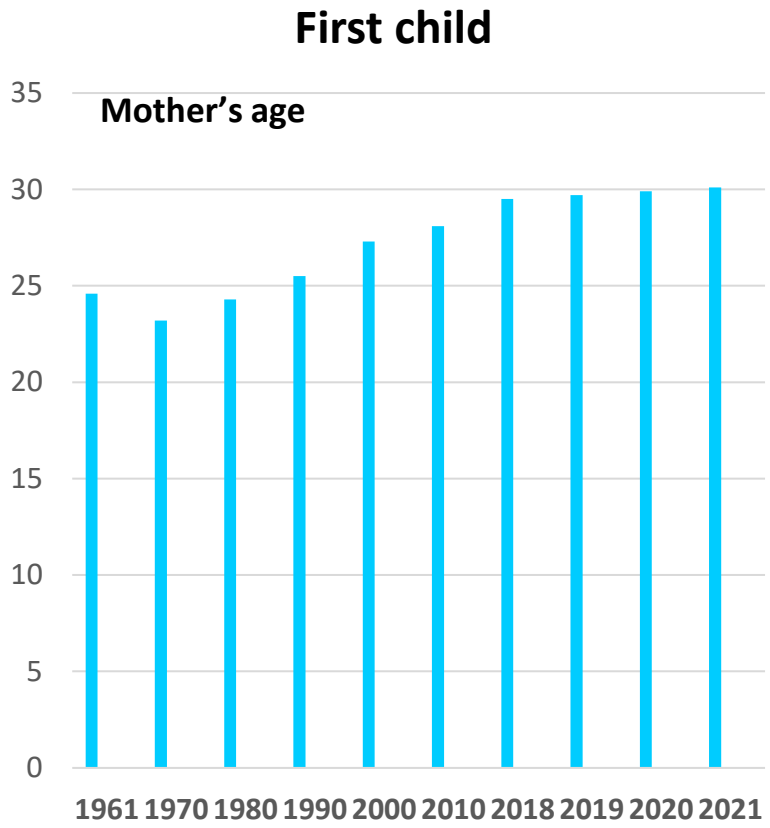


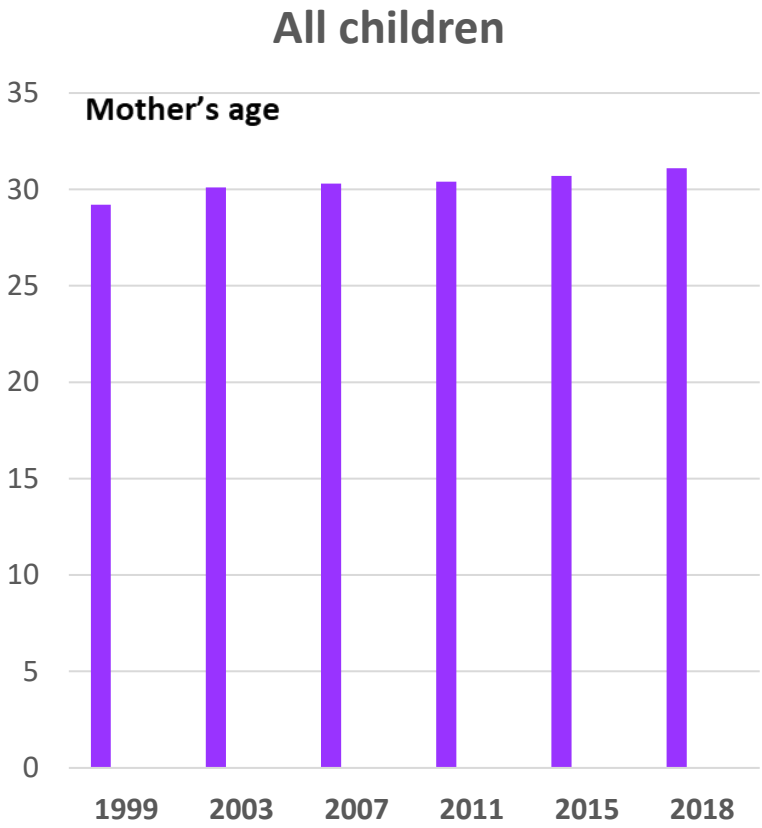




Mother's age when giving birth is increasing

Data from Norway





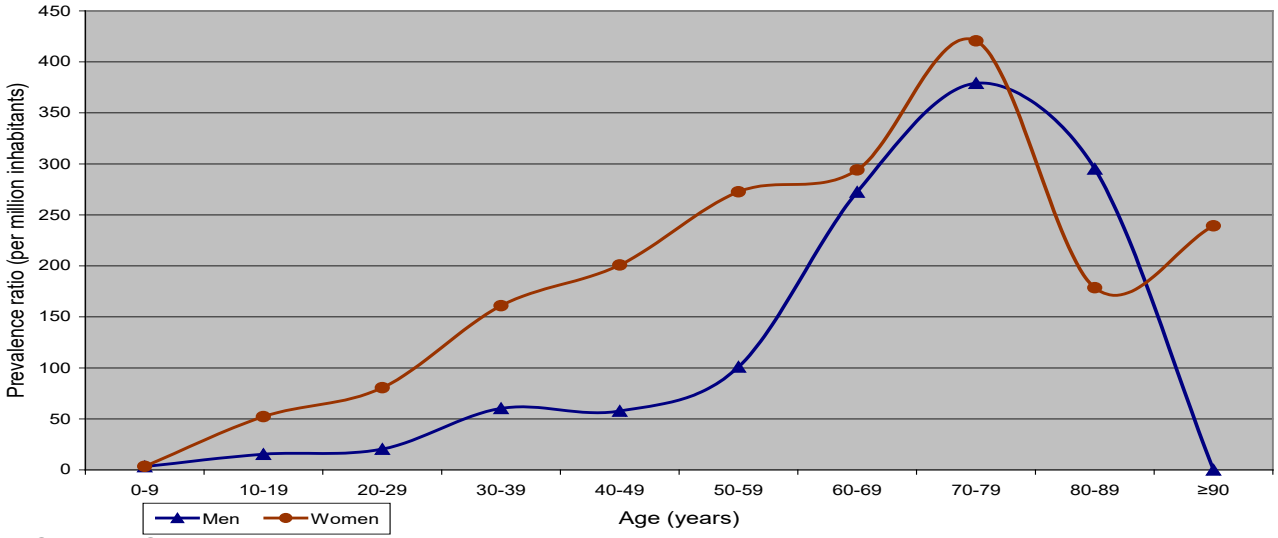
Myasthenia gravis and pregnancy

- Epidemiology
- Physiology
- Heredity
- Health of mother
- Health of child

- Councelling
- Investigations
- Follow-up
- Therapy
- Monitoring
- Support

MG prevalence and incidence in Norway

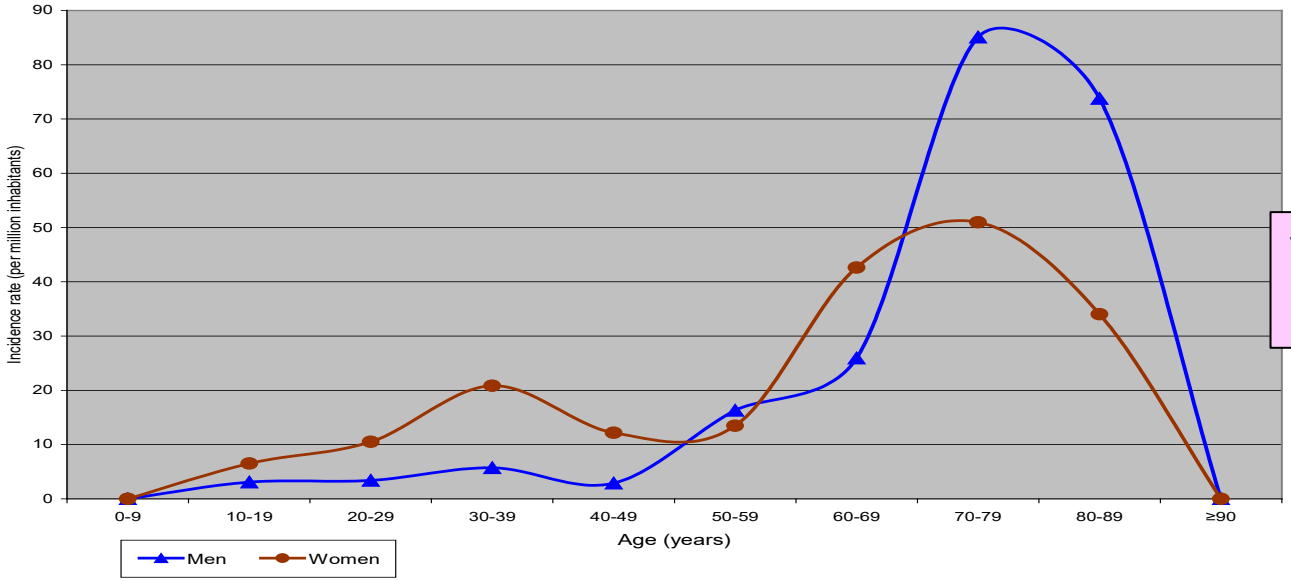
PREVALENCE:



Andersen et al 2011

Prevalence: 200 per million

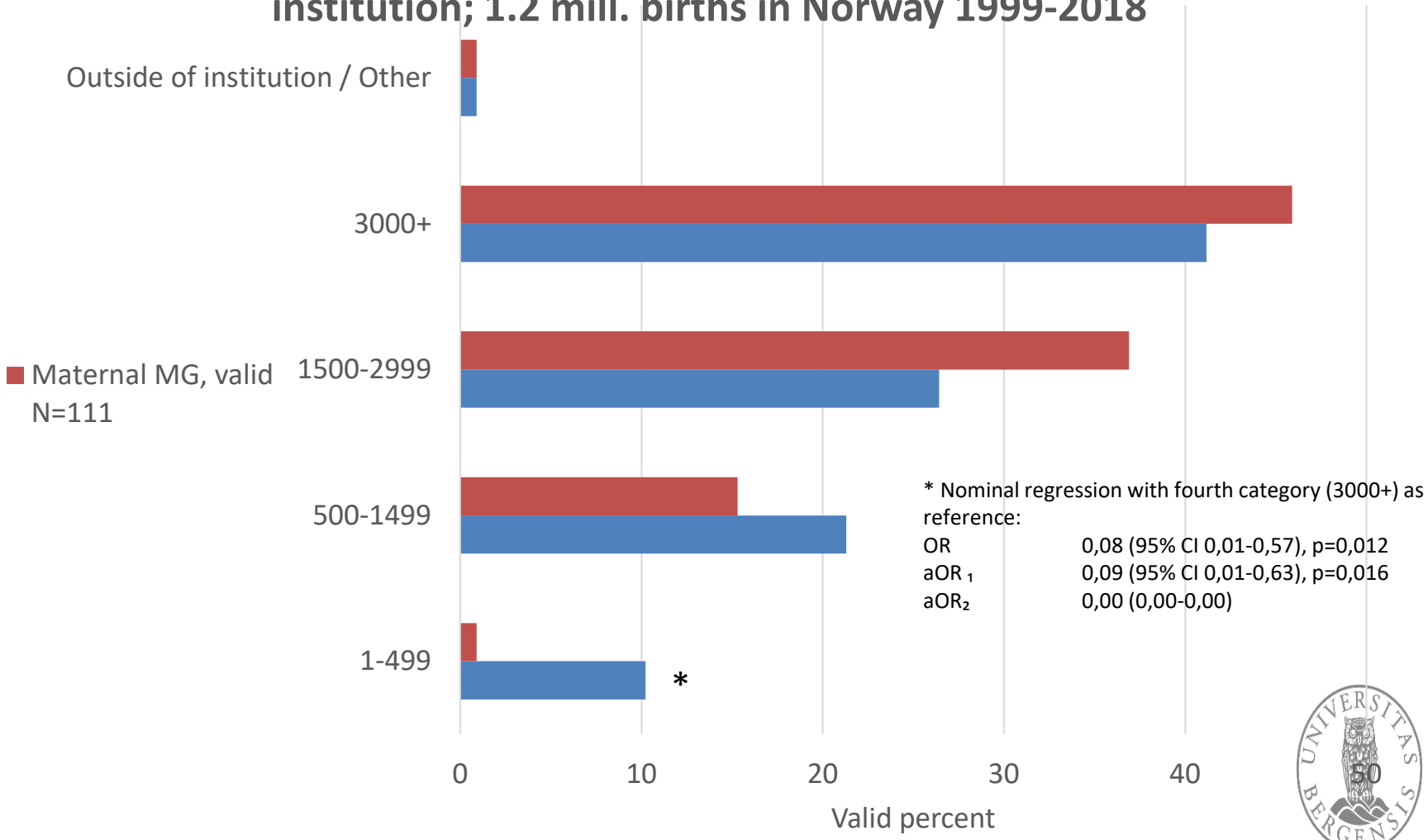
INCIDENCE:



Incidence: 10 per million

Younger MG populations in other countries

Place of delivery categorized by: size of maternity clinic (deliveries per year)/ deliveries outside institution; 1.2 mill. births in Norway 1999-2018



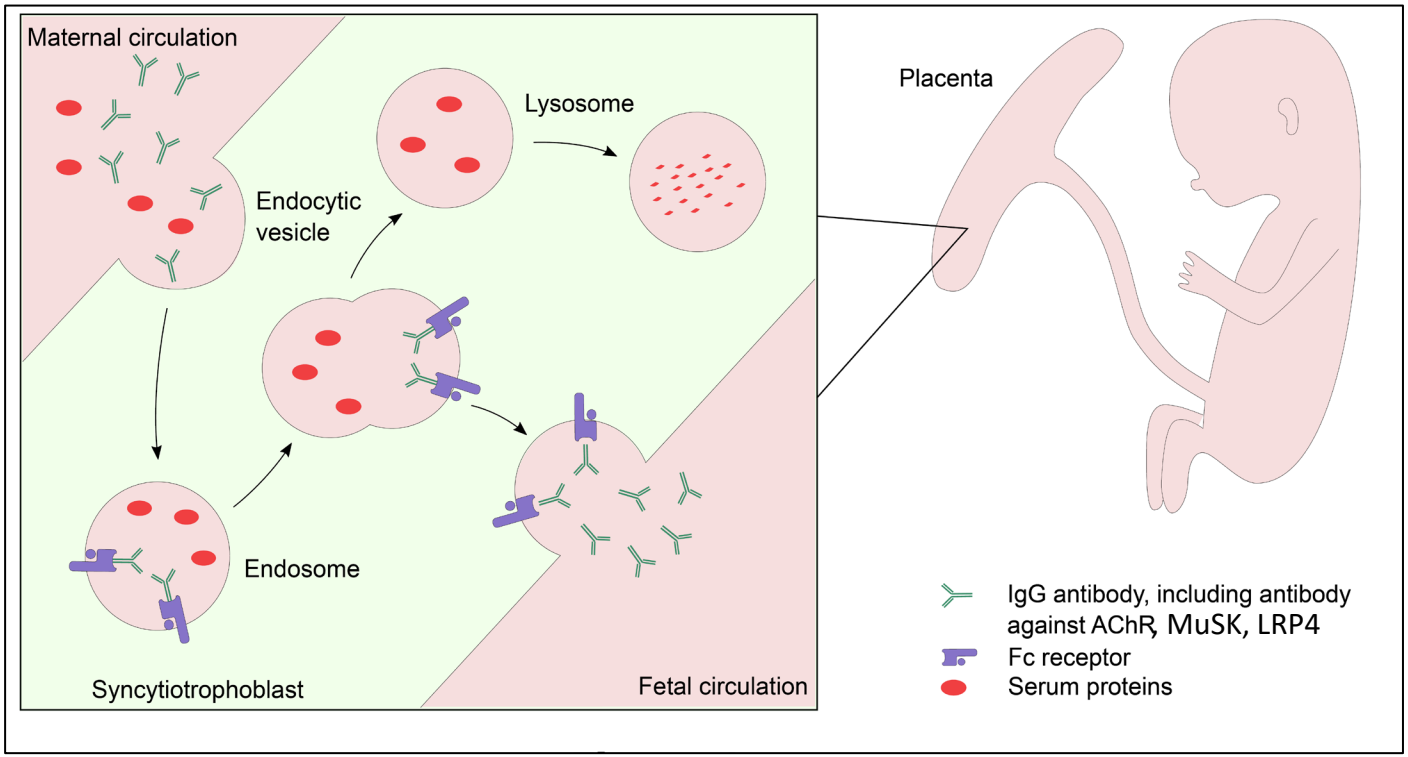
* Nominal regression with fourth category (3000+) as reference:

OR	0,08 (95% CI 0,01-0,57), p=0,012
aOR $_1$	0,09 (95% CI 0,01-0,63), p=0,016
aOR$_2$	0,00 (0,00-0,00)

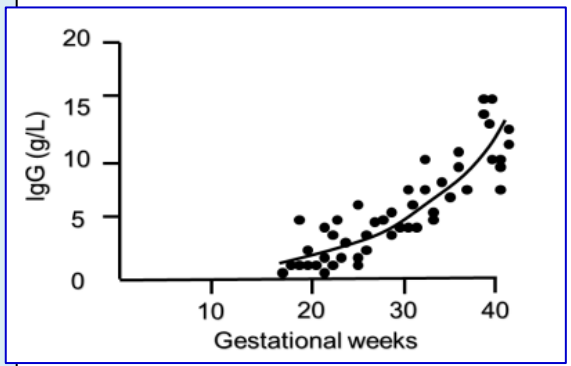
IgG transfer from mother to child

Consequences for MG antibodies

Consequences for mo.ab. therapy

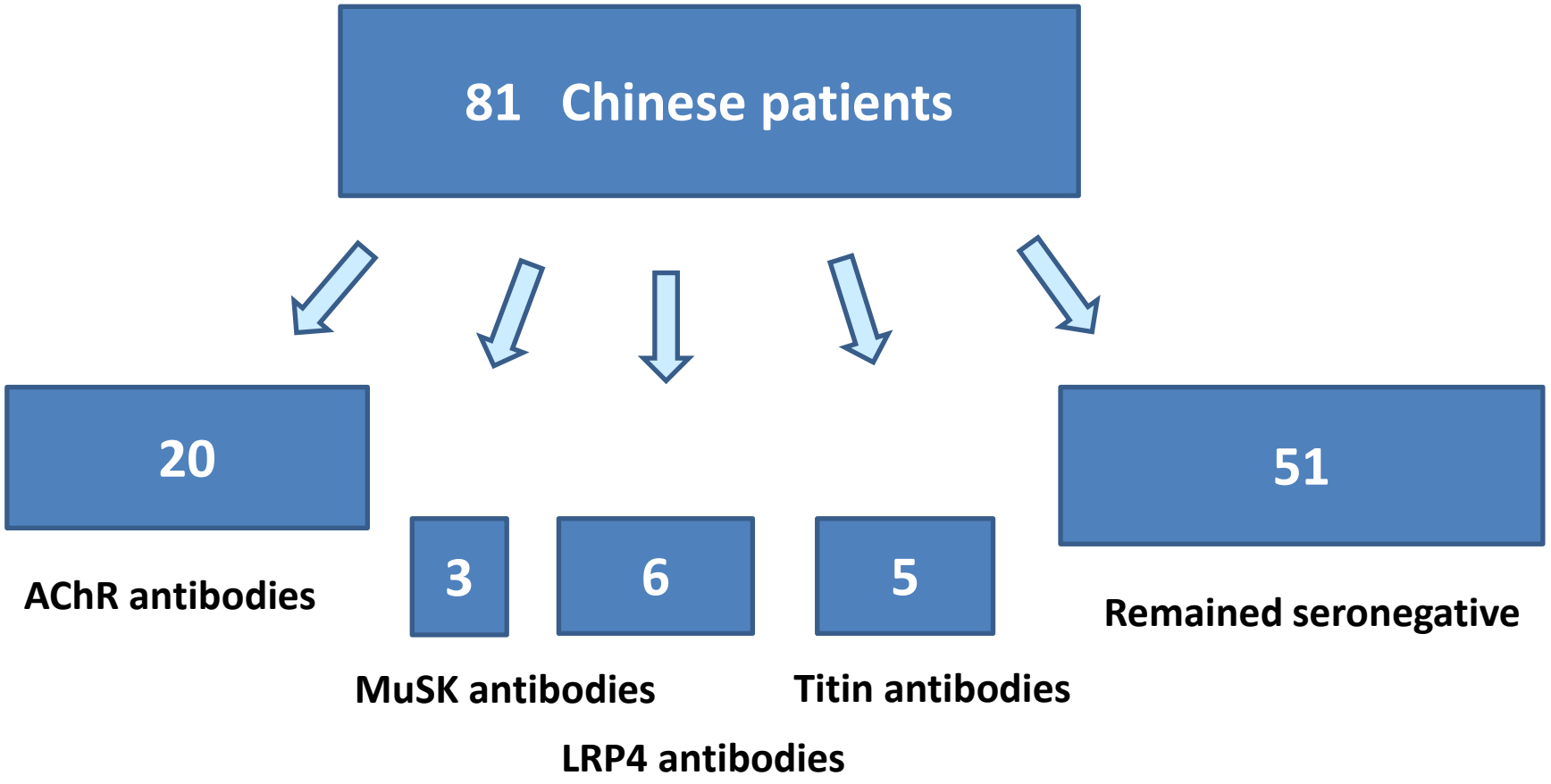


- ✓ Starts at week 13
- ✓ 10 % of mother's conc. at week 20
- ✓ 50 % of mother's conc. at week 32
- ✓ > 100% at mothers conc. at delivery



No MG antibodies in commercial tests

Sensitive testing:



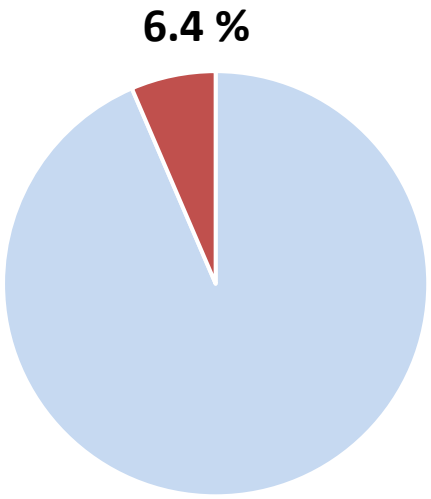
Hong et al
Eur J Neurol 2017

Sensitive AChR-ab RIA *Sensitive MuSK-ab CBA* *Sensitive titin-ab RIA*
Sensitive AChR-ab CBA *Sensitive LRP4-CBA*

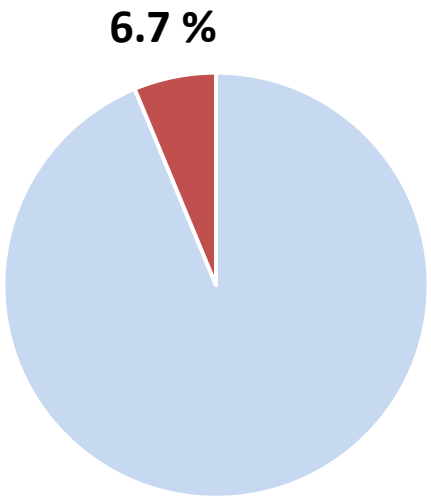
Neonatal myasthenia

- Incidence 10 %
- Not related to mother's MG severity or antibody concentration
- Previous neonatal myasthenia increases the risk
- Described for AChR, MuSK, LRP4, «antibody-negative»
- Antibodies against fetal AChR γ increase the risk
- Transient; during 2 first days and lasting max 6 weeks
- Usually mild; sucking, crying, swallowing, hypotonia
- Respiration, aspiration
- No treatment, anti-AChE-treatment, IvIg / plasma exchange
- No permanent weakness
- Giving birth requires intensive care neonatal facilities

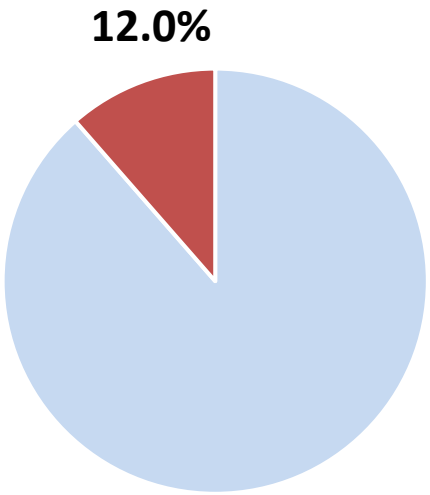
Neonatal myasthenia occurence



Jovandaric et al 2016



Braga et al 2016



Ducci et al 2017

- **Diagnostic sensitivity**
- **All children have antibodies**
- **Monitoring for at least 5 days**

MG birth defects and neonatal complications;
127 MG vs. 1.9 mill. references

	MG	Reference	
Total	21.3 %		
Severe defects	3.9 %	1.9 %	p< 0.05
Transferred pediatrics	21.3 %	2.0 %	p < 0.001
Perinatal mortality	2.4 %	1.4 %	p = 0.7

4 children with severe skeletal anomalies consistent with ***arthrogryposis***

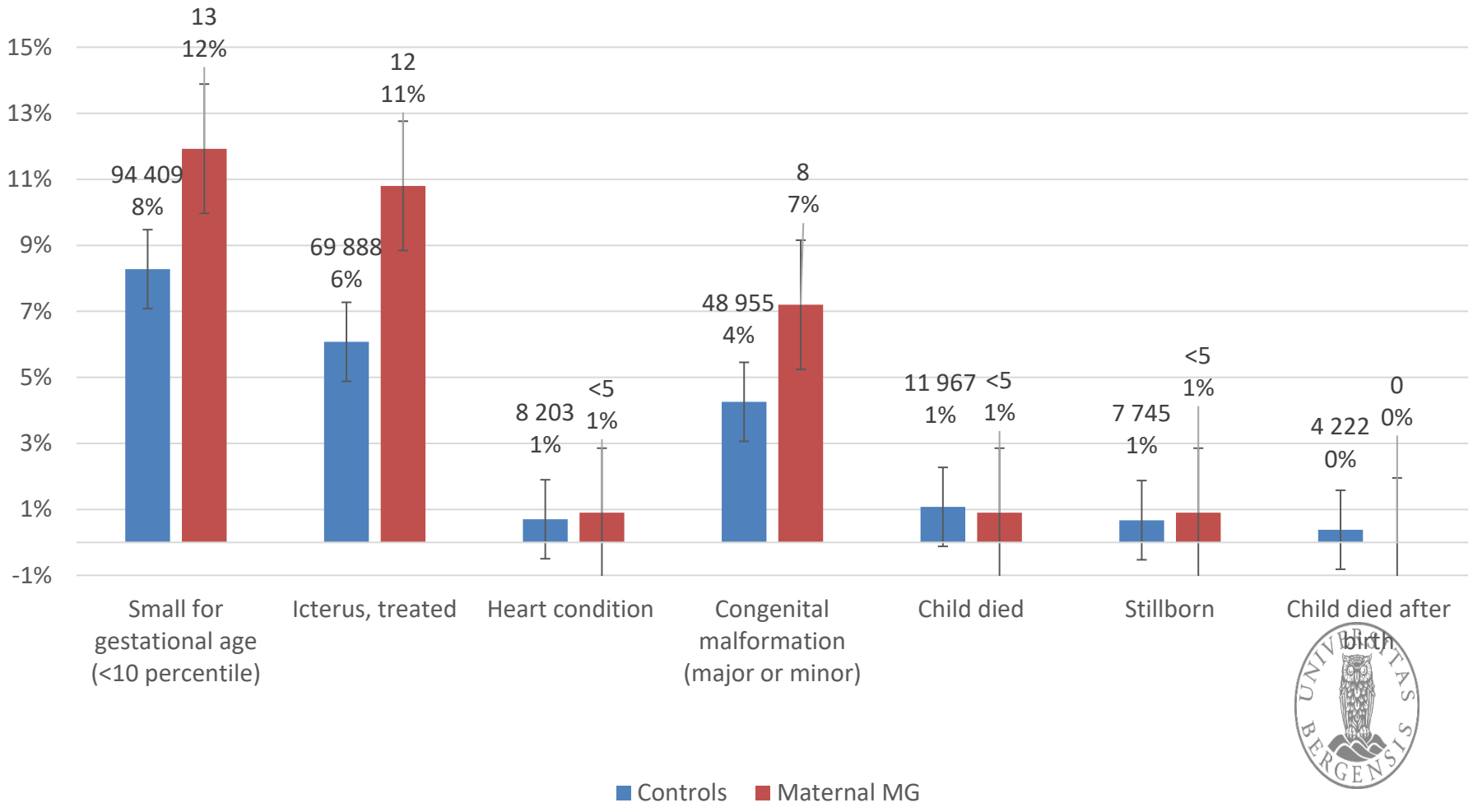
Linked to; Neonatal MG, twins, AChR ab.

Not linked to; MG severity

Preclinical MG; 49 births

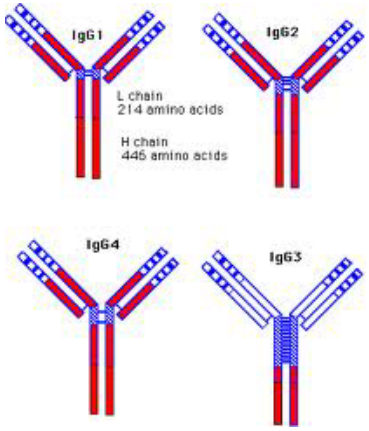
Hoff et al 2003, 2004, 2006

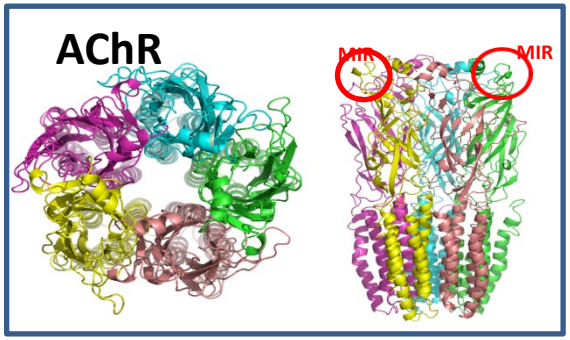
Adverse neonatal outcomes 1999-2018, Norway



Arthrogryposis and persistent myopathy

- Single case reports, rare conditions
- Induced by muscle antibodies
- Antibodies against fetal antigenic epitopes
- Risk if in previous pregnancy
- IvIg or plasma exchange during pregnancy
- Muscle function in children of MG mothers?



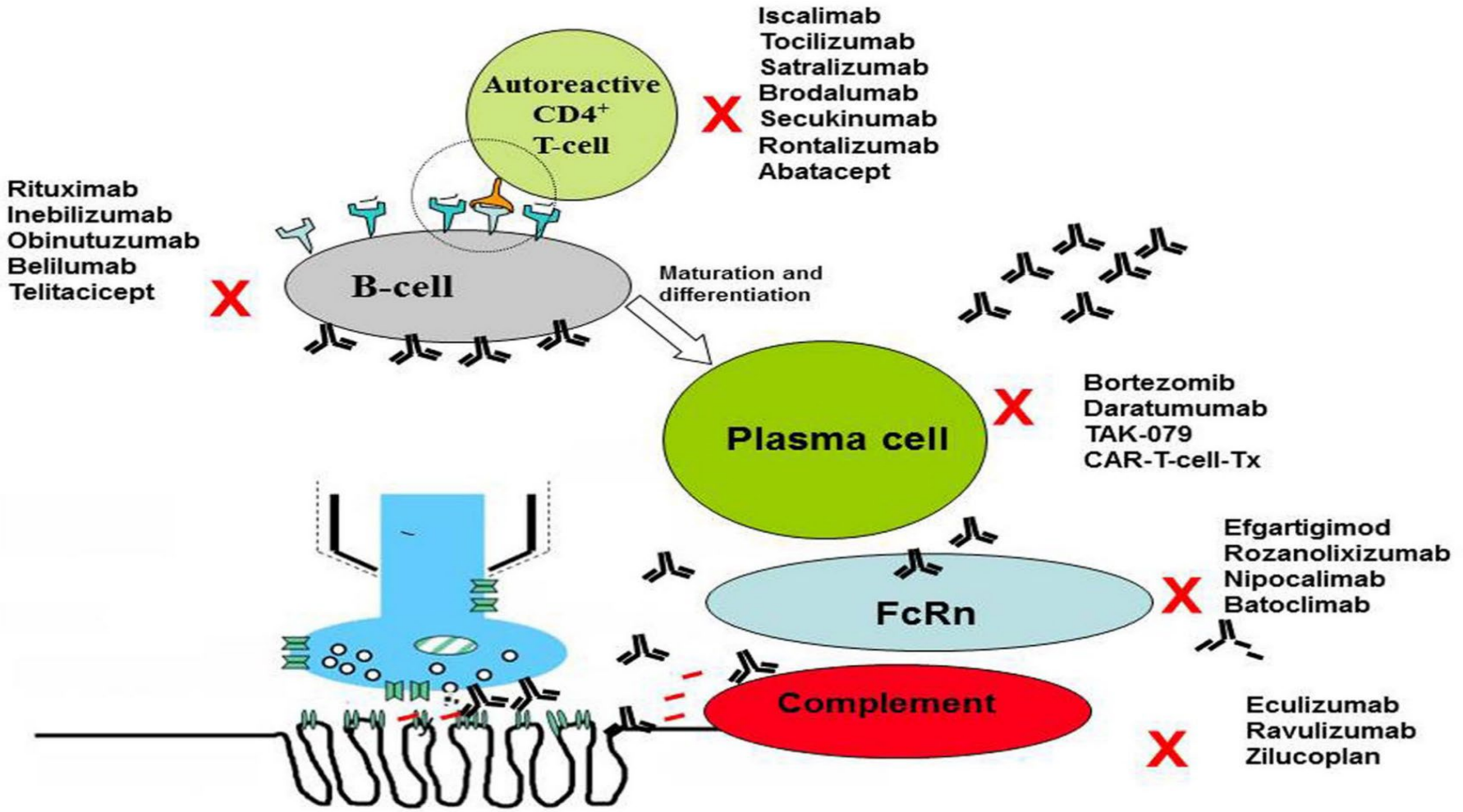


Drugs in pregnancy

- Safe drugs: pyridostigmine, prednisone / prednisolone, azathioprine, Ivlg
- Drugs with teratogenic potential: mycophenolate mofetil, methotrexate, cyclophosphamide
- Rituximab: Not 3 (6) months before and in pregnancy
- Monoclonal antibodies
- New drugs
- Folic acid 0.4 mg daily (as for others)

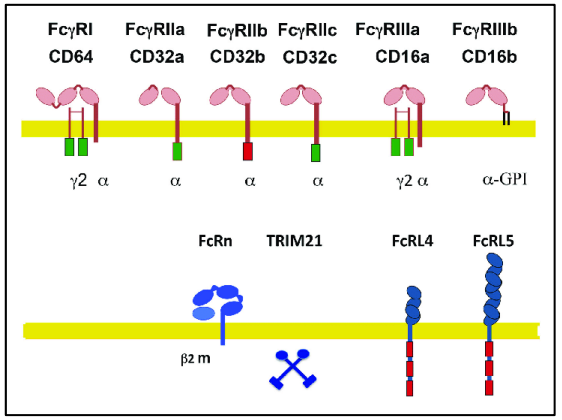
- ❑ **Females in reproductive age**
- ❑ **Females before reproductive age**
- ❑ **Females planning pregnancy**
- ❑ **In pregnancy**

New immunotherapies in myasthenia gravis

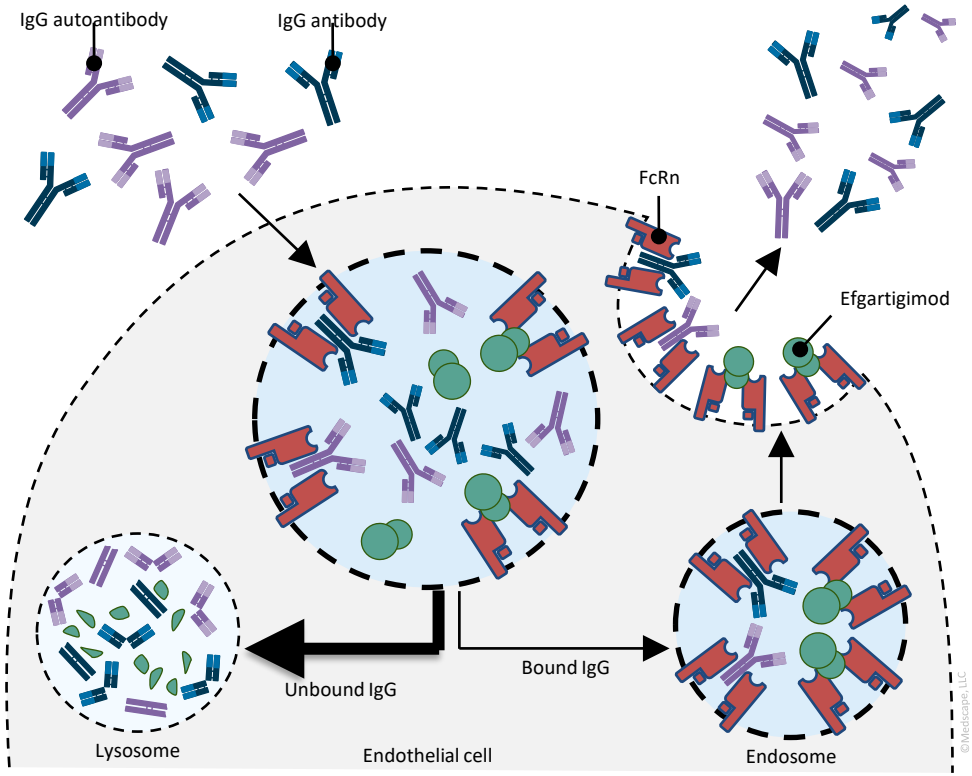


Schneider-Gold and Gilhus, Ther Adv Neurol Dis 2022

FcRn blockers inhibit IgG recycling



- **Outcompete endogenous IgG, prevent recycling, promote IgG lysosomal degradation**
- **Targeted reduction of all IgG subtypes**
- **No impact on IgM, IgA, or albumin**



Breastfeeding

- Recommended and encouraged
- Maternal IgG in milk 2 % of serum
- Recommended also after symptomatic antibody transfer
- Advised against with mycophenolate mofetil, methotrexate, cyclophosphamide
- Rituximab probaly safe. Concentration in breast milk 1 : 200 of serum
- New drugs, monoclonal antibodies
- Timing of drug intake and breastfeeding

Mother's intake → Mother's absorption → Excretion to breast milk →

Child's absorption from gut to blood → Child's absorption to organ

Genetic councelling in MG

- First-degree relatives; 10 – 100x increased risk of MG
- Spain; 3.5% had a first or second degree relative *(Salvado et al 2016)*
- Finland:

Siblings	**11 / 264**
Mother - Child	**2 / 264**
Cousins	**6 / 264**

(Pirskanen et al 1977)

- Autoimmunity in general; 10 – 20x increased risk in children
- Total risk versus relative risk
- Monozygotic twins can be discordant
- HLA
- Non-HLA
- No recommended genetic markers

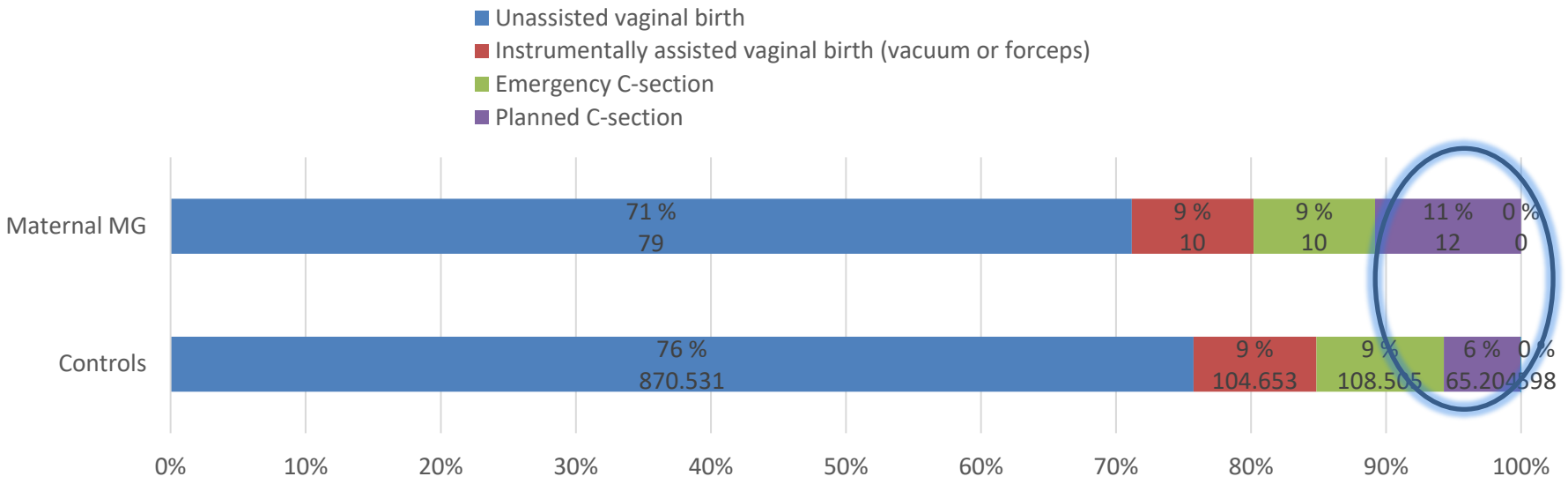
Pregnancy and giving birth in MG

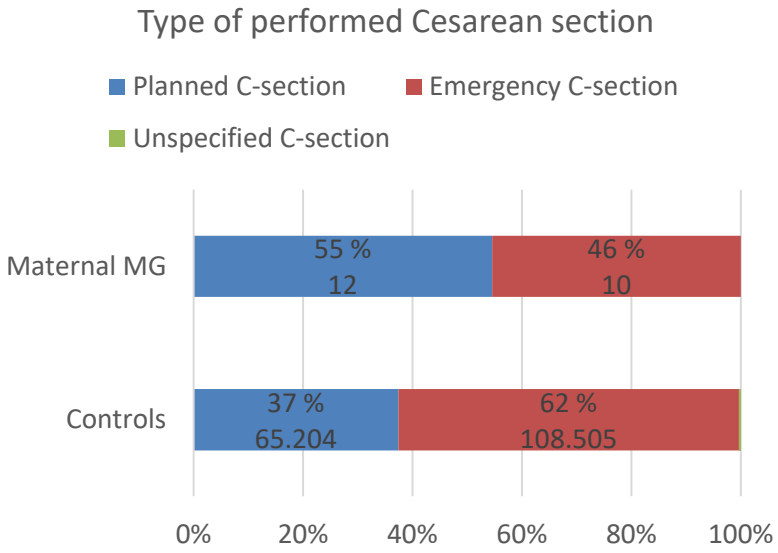
- No increased rate of preeclampsia
- No increased rate of umbilical cord complications
- No increased bleeding

	MG	Control
Mean birth weight	3 483g	3 485g
Caesarean section (CS)	17.3%	8.6%
Acute CS	7.4%	4.0%
Elective CS	9.9%	4.6%
Vaginal intervention	8.7%	6.3%

Hoff et al 2003

Mode of delivery Norway 1999-2018





Myasthenia gravis worsening and improvement during pregnancy; a meta-analysis

Worsening

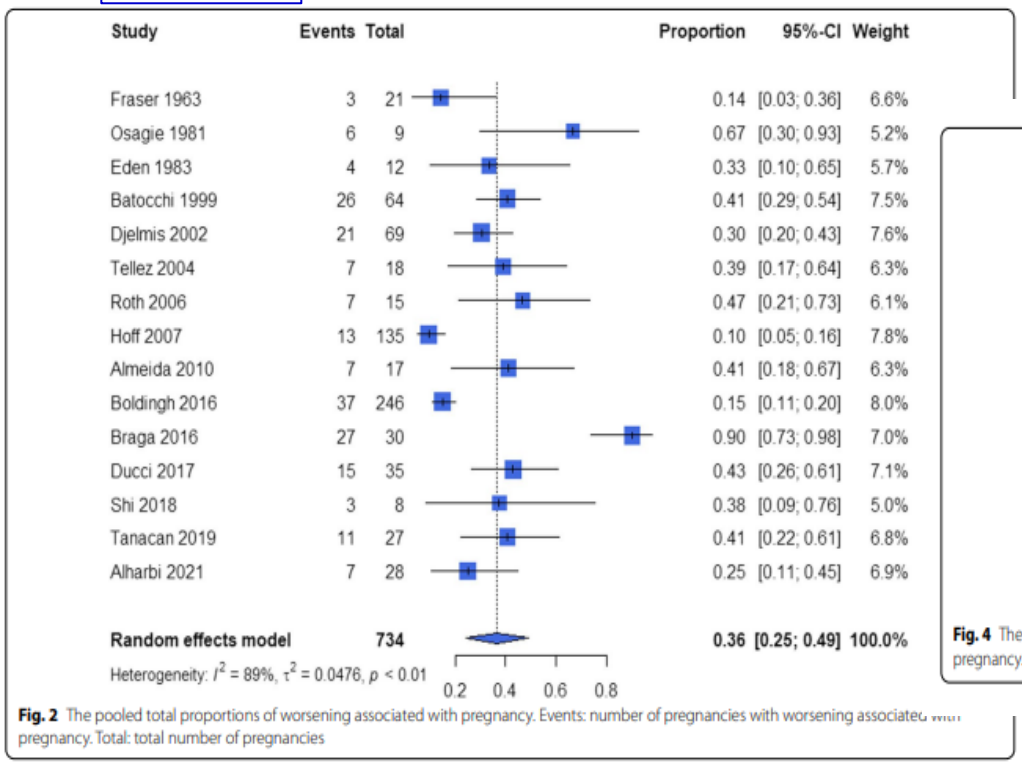


Fig. 2 The pooled total proportions of worsening associated with pregnancy. Events: number of pregnancies with worsening associated with pregnancy. Total: total number of pregnancies

Improvement

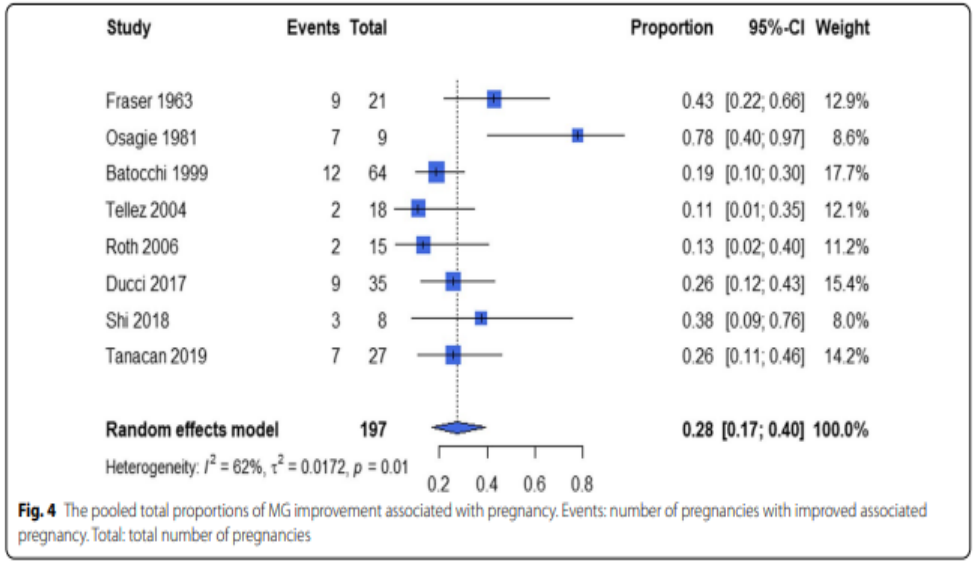
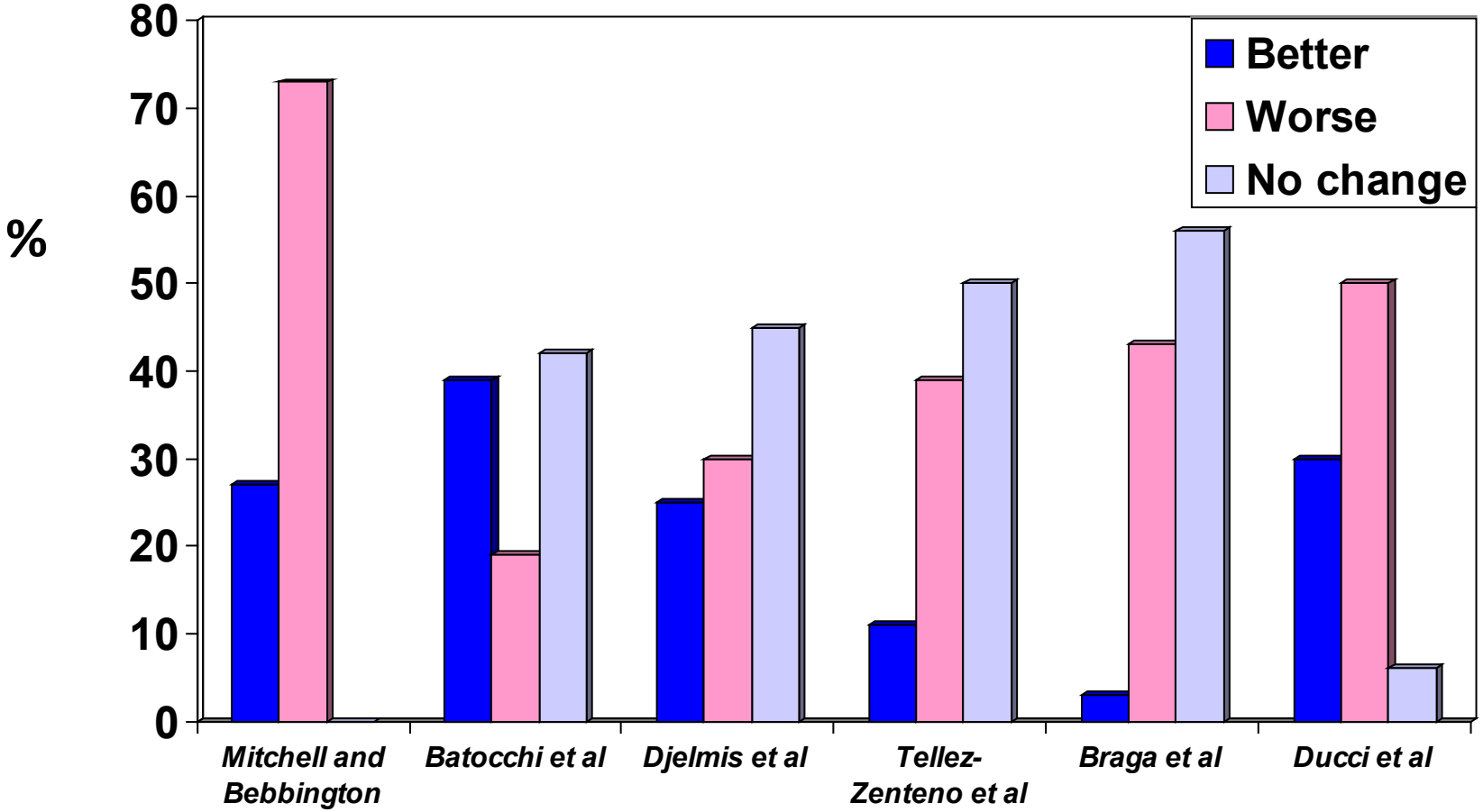


Fig. 4 The pooled total proportions of MG improvement associated with pregnancy. Events: number of pregnancies with improved associated pregnancy. Total: total number of pregnancies

Su et al. Orph J Rare Dis 2022;17:52

Mother's MG during pregnancy



- *Moderate and unpredictable effects*
- *If worsening, in first trimester*
- *One pregnancy did not predict the next*
- *Worsening in puerperium common*

Myasthenia gravis and pregnancy

- Epidemiology
- Physiology
- Heredity
- Health of mother
- Health of child

- ✓ Councelling
- ✓ Investigations
- ✓ Follow-up
- ✓ Therapy
- ✓ Monitoring
- ✓ Support