

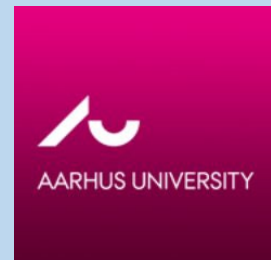
# Psychological effects and risk of comorbidity in Myasthenia Gravis



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# Disclosures

Received research support, travel support, speaker honoraria and served as consultant on advisory boards

- Octapharma,
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- Novo,
- Alexion,
- Sanofi Genzyme
- UCB Pharma
- Amicus Pharmaceuticals
- Lundbeck

# Depression in chronic disease and in MG

- Having a chronic disease is associated with an increased prevalence of depression
  - 54% increased life time prevalence and a
  - 62 % increased "6 months prevalence"compared with otherwise healthy subjects having a life time prevalence of major depression 7-17% and a 30 day prevalence of 5%

(Blazer et al 1994, Kessler et al 1994)

- In Myasthenia Gravis studies on depression have reported
  - A prevalence of depression of 33% (Magni et al 1988, Twork et al 2010)
  - Twofold increased prevalence compared with pts in primary care (Alanazy 2019)

# Depression in MG

Depression is a prognostic indicator of poor Health Related QoL in MG

In MG, depression is associated with

decreased motivation for self-care,

significant limitations in physical abilities

increased mortality rates

increased somatic complaints,

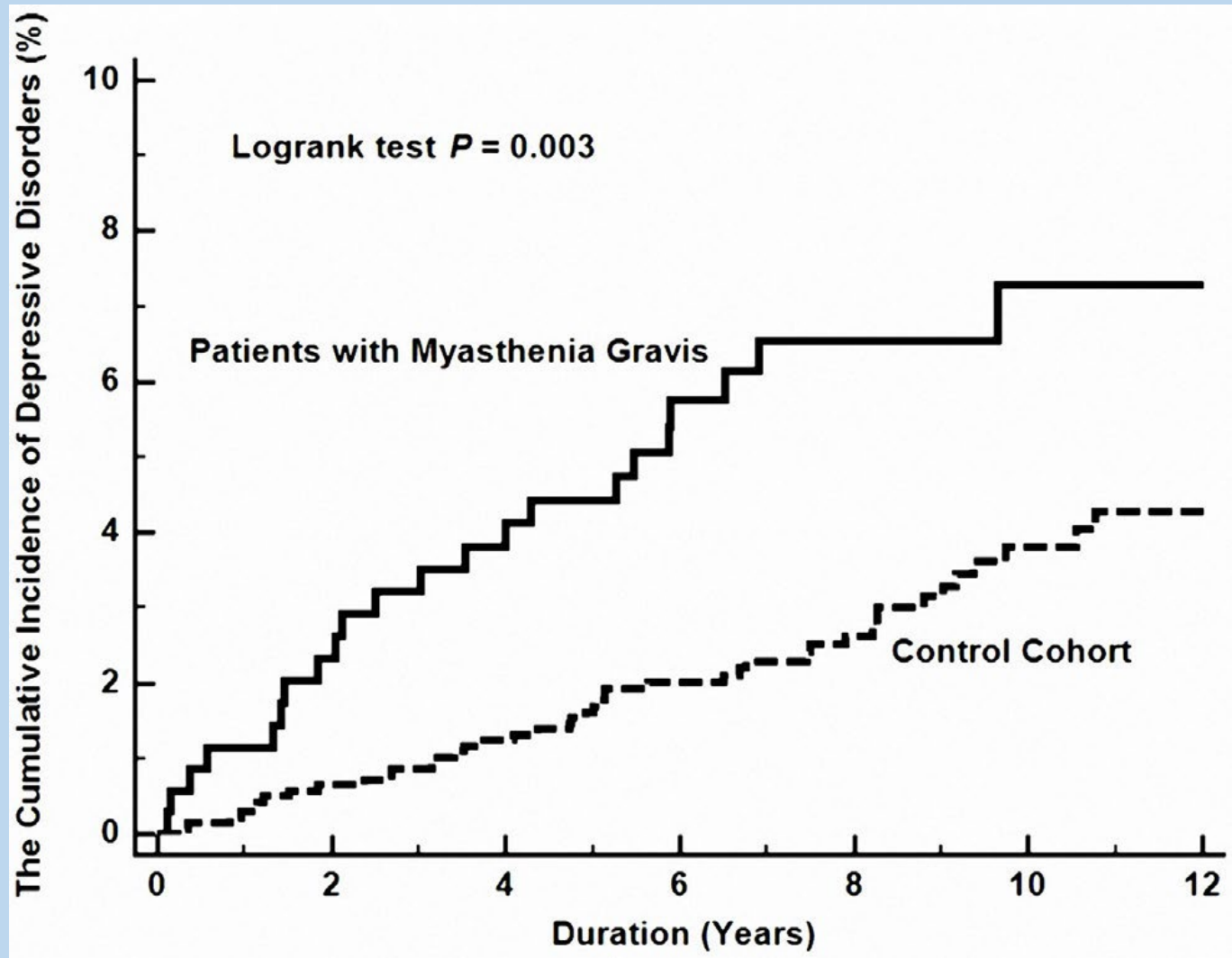
more frequent ambulatory visits

higher healthcare costs

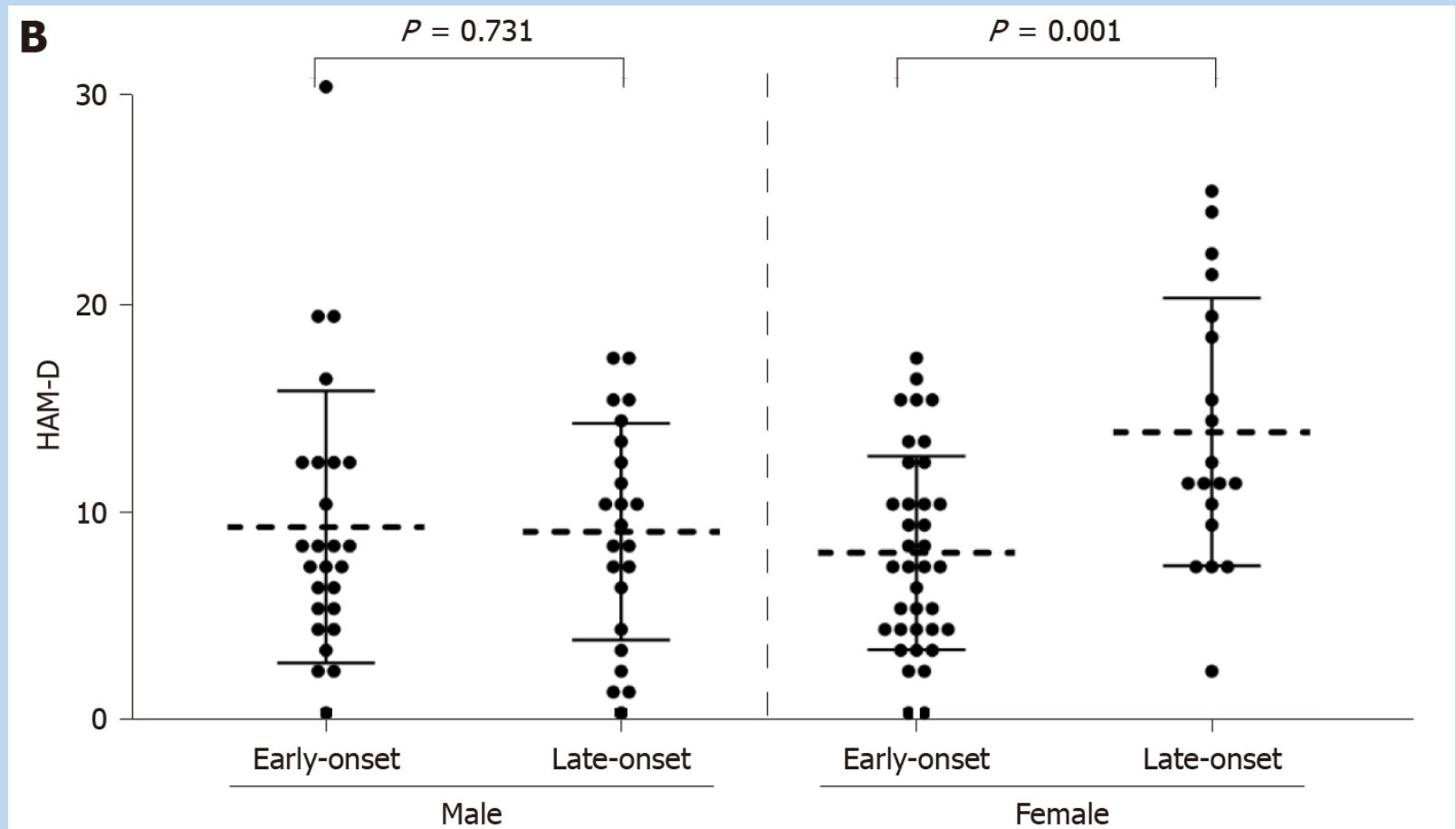


# Cumulative risk of depression in newly diagnosed MG

Study from Taiwan



# Depression in early vs late onset MG in females and males



# Anxiety in MG

Few studies on anxiety in MG

## Prevalence

- Poul et al found a prevalence of anxiety of **46%** (Hamilton Anxiety Rating Scale) (2000)
- Anxiety is related to low Health Related QoL in MG (Basta et al, 2012)

MG is a chronic and unpredictable disorder - predisposing to anxiety

In particular respiratory symptoms cause anxiety (Paul et al, 2000)

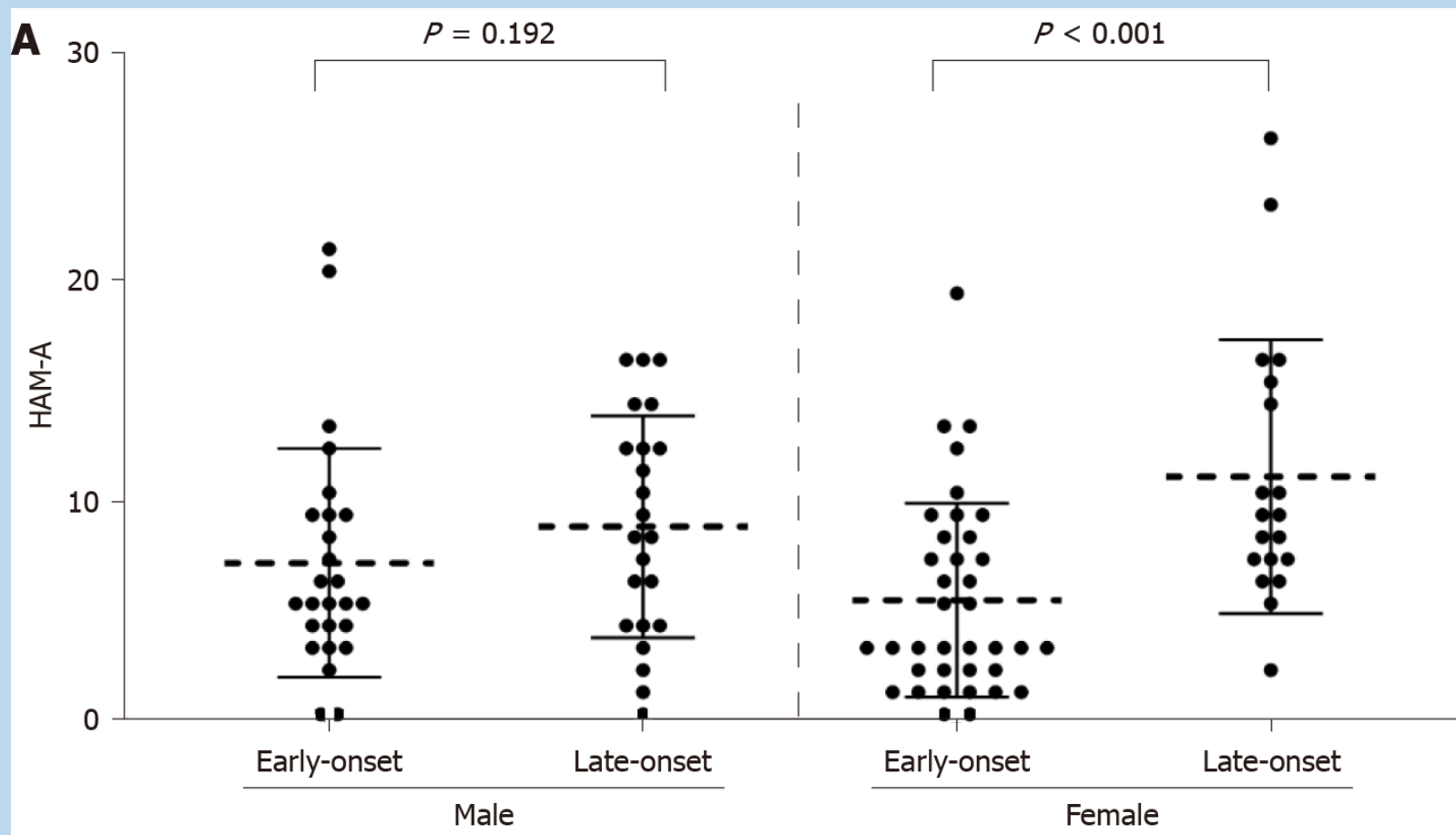
Avoidance of social situations due to risk of embarrassment related to compromised

- speech,
- communication,
- facial expression,
- swallowing abilities

In some pts this may lead to excessive advanced planning.



# Anxiety in early vr late in males vr females





# Effects of MG Treatment on Mood

**Corticosteroids** can provoke psychiatric morbidity

Long-term use of corticosteroides has been linked to depression, anxiety, and psychosis in two large meta-analyses of MG.

(Pretorius 2004 and Warrington et al 2006)

In a Japanese study, Suzuki et al found that a mean daily **dose of 8.1 mg of prednisolone** was the most significant independent factor associated with depression in MG (Suzuki et al, BMJ Open. 2011)

Steroids can cause **insomnia** - an essential feature of depression and anxiety, further obscuring the etiology of mood disorders in MG treated with corticosteroids.

# Other Factors Affecting Psychiatric Comorbidities in MG

Lower Health Related QoL can induce emotional stress by:

1. Low acceptance of disease
2. Poor coping strategies
3. Lack of social support
4. Old age at onset of MG
5. Lower education and occupation related to heavy labor
6. Career changes due to MG related symptoms

# Diagnosing depression and anxiety in the MG clinic

You will probably **not** find it - if you do not look for it !

MG QoL15 captures some aspects of mood problems

## MG QoL 15

### Questions

1. I am frustrated by my MG
2. I have trouble using my eyes
3. I have trouble eating because of MG
4. I have limited my social activity because of my MG
5. My MG limits my ability to enjoy hobbies and fun activities
6. I have trouble meeting the needs of my family because of my MG
7. I have to make plans around my MG
8. My occupational skills and job status have been negatively affected by MG
9. I have difficulty speaking due to MG
10. I have trouble driving due to MG
11. I am depressed about my MG
12. I have trouble walking due to MG
13. I have trouble getting around public places because of my MG
14. I feel overwhelmed by my MG
15. I have trouble performing my personal grooming needs

# How to treat psychological problems ?

## Psychoactive Medicines given to pts with MG

- SSRI antidepressants are sparsely studied in MG but appears to be safe and probably effective.
- Tricyclic antidepressants and some neuroleptics may impair neuromuscular transmission (Kramer, 2000)
- Benzodiazepines may impair ventilation which can be critical in severely affected MG patients.
- Lithium may induce occurrence of MG (Neil, 1976)

# Treatment of insomnia and anxiety

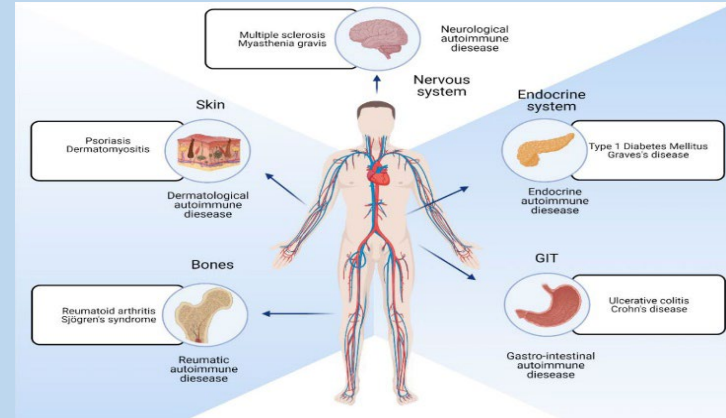
**TABLE 1.** Common medications for treating insomnia and acute anxiety in patients with myasthenia gravis

Drug	Reported effects
Alpha-1 blockers	Orthostatic hypotension
Antihistamines	Case reports of triggering decompensation in myasthenia gravis
Benzodiazepines	Generally contraindicated; potential to cause respiratory depression in patients with preexisting respiratory impairments
Gabapentin	Case reports of triggering decompensation and unmasking previously undiagnosed myasthenia gravis
Melatonin	Well tolerated; no known adverse effects of particular concern to myasthenic patients
Mirtazapine	Myasthenia observed in <1% of patients in premarketing evaluation, but no existing case reports of triggering decompensation
Quetiapine	Case reports of various atypical antipsychotics triggering decompensation in myasthenia gravis; orthostatic hypotension
Ramelteon	Respiratory effects in patients with preexisting respiratory impairments not definitively known
Suvorexant	Respiratory effects in patients with preexisting respiratory impairments not definitively known
Trazodone	Orthostatic hypotension
Tricyclic antidepressants	Theoretical risk of neuromuscular blockade demonstrated in vitro; does not appear to be replicated in vivo (no reports of triggering decompensation)
Z drugs	Potential to cause respiratory insufficiency in patients with preexisting respiratory impairments
Herbal supplements	Lack of high-quality literature on the safety of unregulated supplements; caution should be advised

# Risk of comorbidity in Myasthenia Gravis



Diabetes



Autoimmune disorders



Hypertension



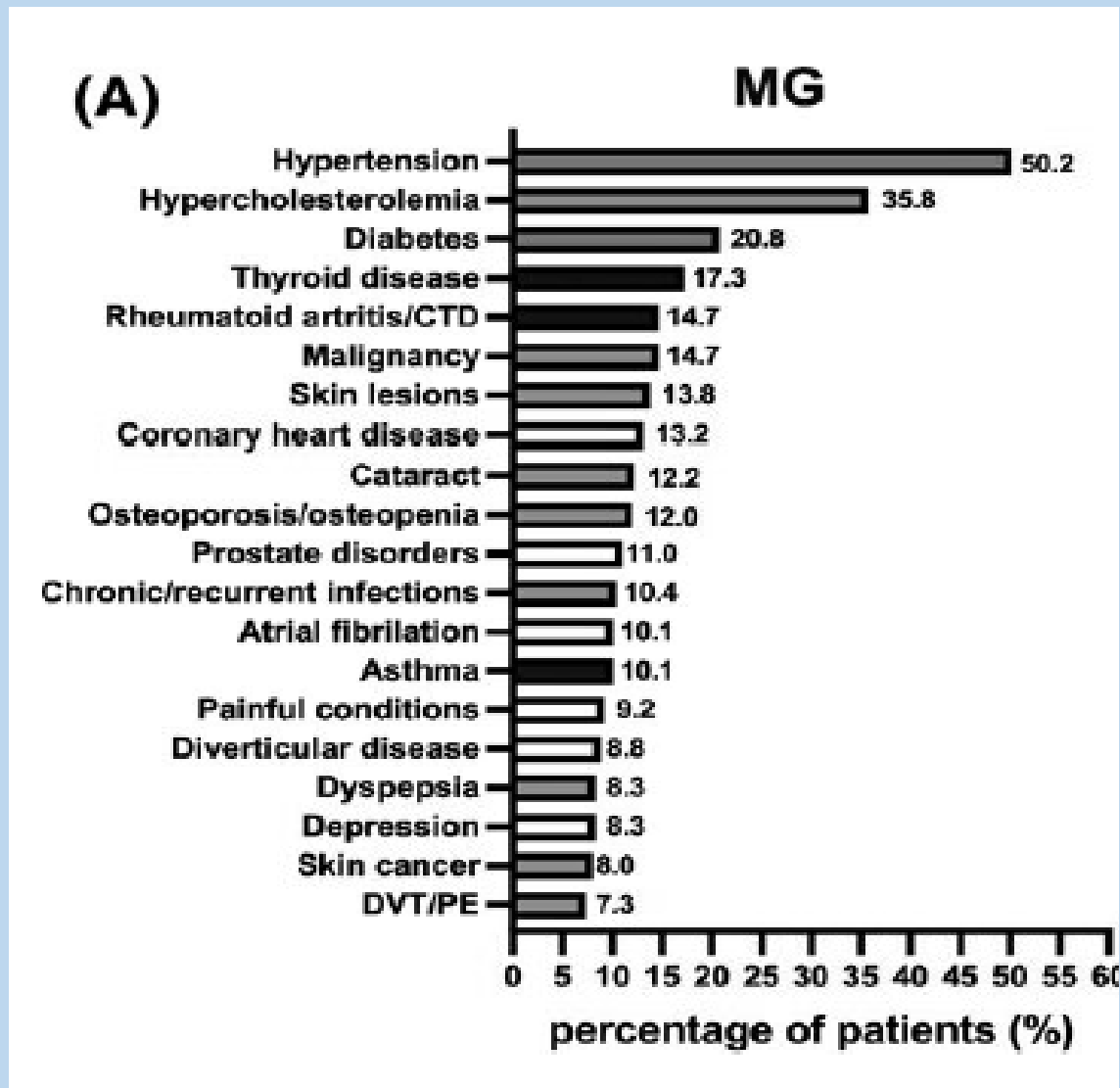
Obesity

# Comorbidities in MG - large UK study

**Table 2** Comorbidities in the study population with myasthenia gravis ( $N = 1149$ )

Comorbidity	No. of patients (%)	
	Baseline (pre-index to index) period	Follow-up (post-index) period
Myocardial infarction	83 (7.2)	169 (14.7)
Congestive heart failure	44 (3.8)	152 (13.2)
Peripheral vascular disease	61 (5.3)	79 (6.9)
Cerebrovascular disease	106 (9.2)	92 (8.0)
Dementia	13 (1.1)	70 (6.1)
Chronic pulmonary disease	129 (11.2)	236 (20.5)
Rheumatologic disease	37 (3.2)	58 (5.0)
Peptic ulcer disease	50 (4.4)	9 (0.8)
Mild liver disease	16 (1.4)	37 (3.2)
Moderate or severe liver disease	3 (0.3)	13 (1.1)
Diabetes without chronic complications	154 (13.4)	231 (20.1)
Diabetes with chronic complications	43 (3.7)	56 (4.9)
Hemiplegia or paraplegia	14 (1.2)	22 (1.9)
Renal disease	128 (11.1)	265 (23.1)
Malignancy	99 (8.6)	193 (16.8)
Metastatic solid tumor	14 (1.2)	62 (5.4)
HIV/AIDS	0 (0.0)	1 (0.1)
Hypertension	437 (38.0)	172 (15.0)
Ankylosing spondylitis	145 (12.6)	88 (7.7)
Psoriasis	50 (4.4)	25 (2.2)
Psoriatic arthritis	3 (0.3)	6 (0.5)
Crohn's disease	7 (0.6)	4 (0.3)
Ulcerative colitis	10 (0.9)	12 (1.0)
Systemic lupus erythematosus	7 (0.6)	5 (0.4)

# Comorbidities in Myasthenia Gravis - Poland

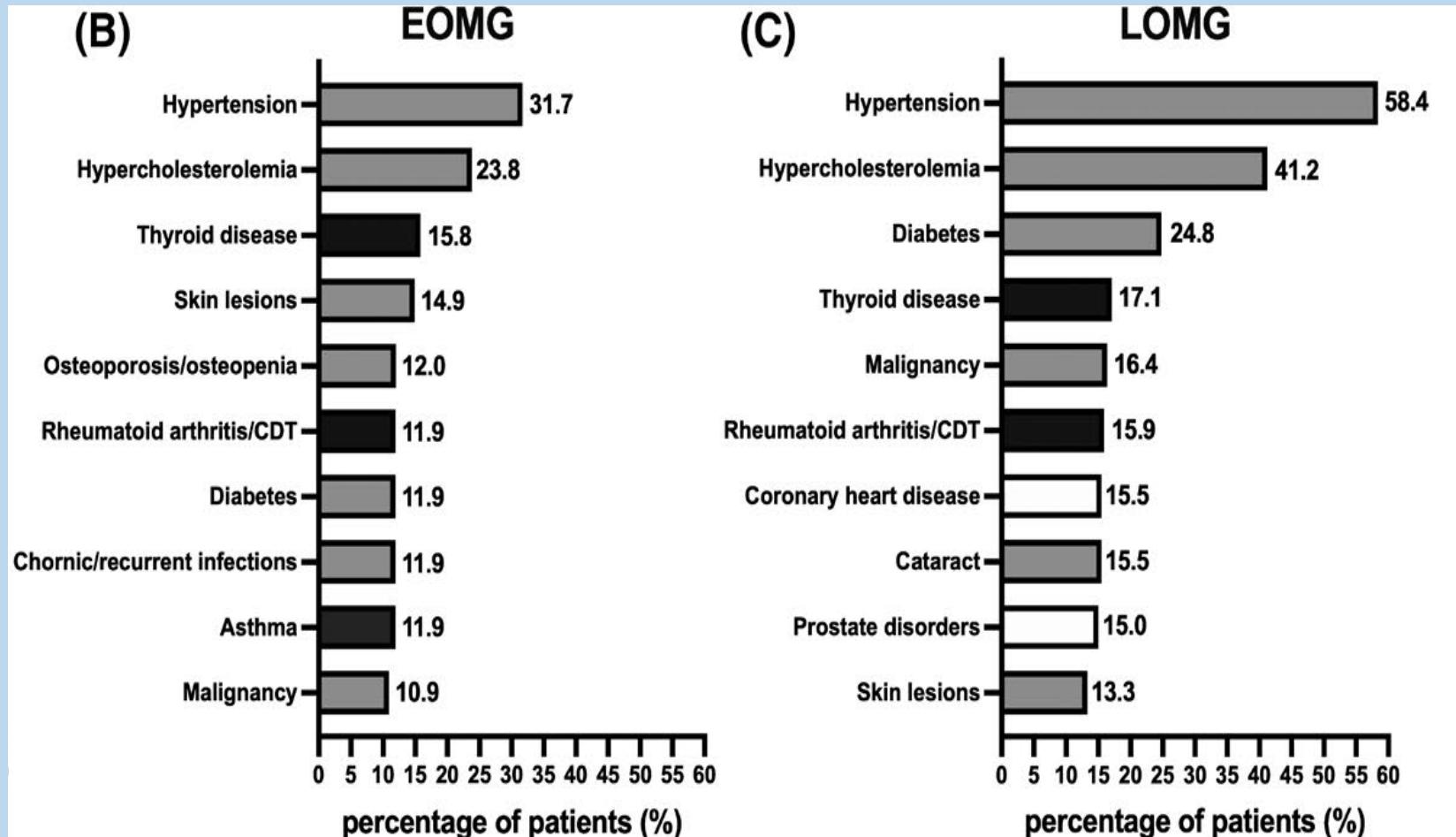




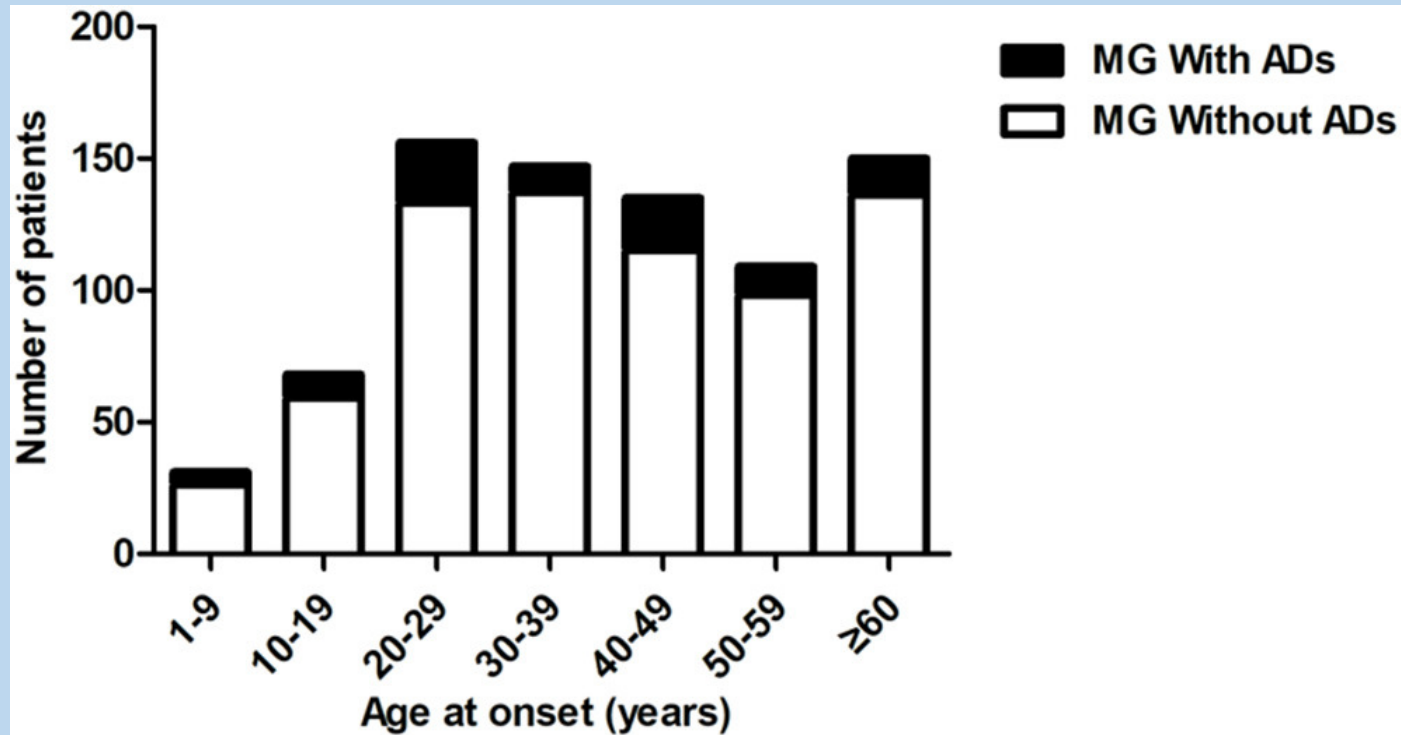
# Comorbidities – relation to age at onset

Early Onset

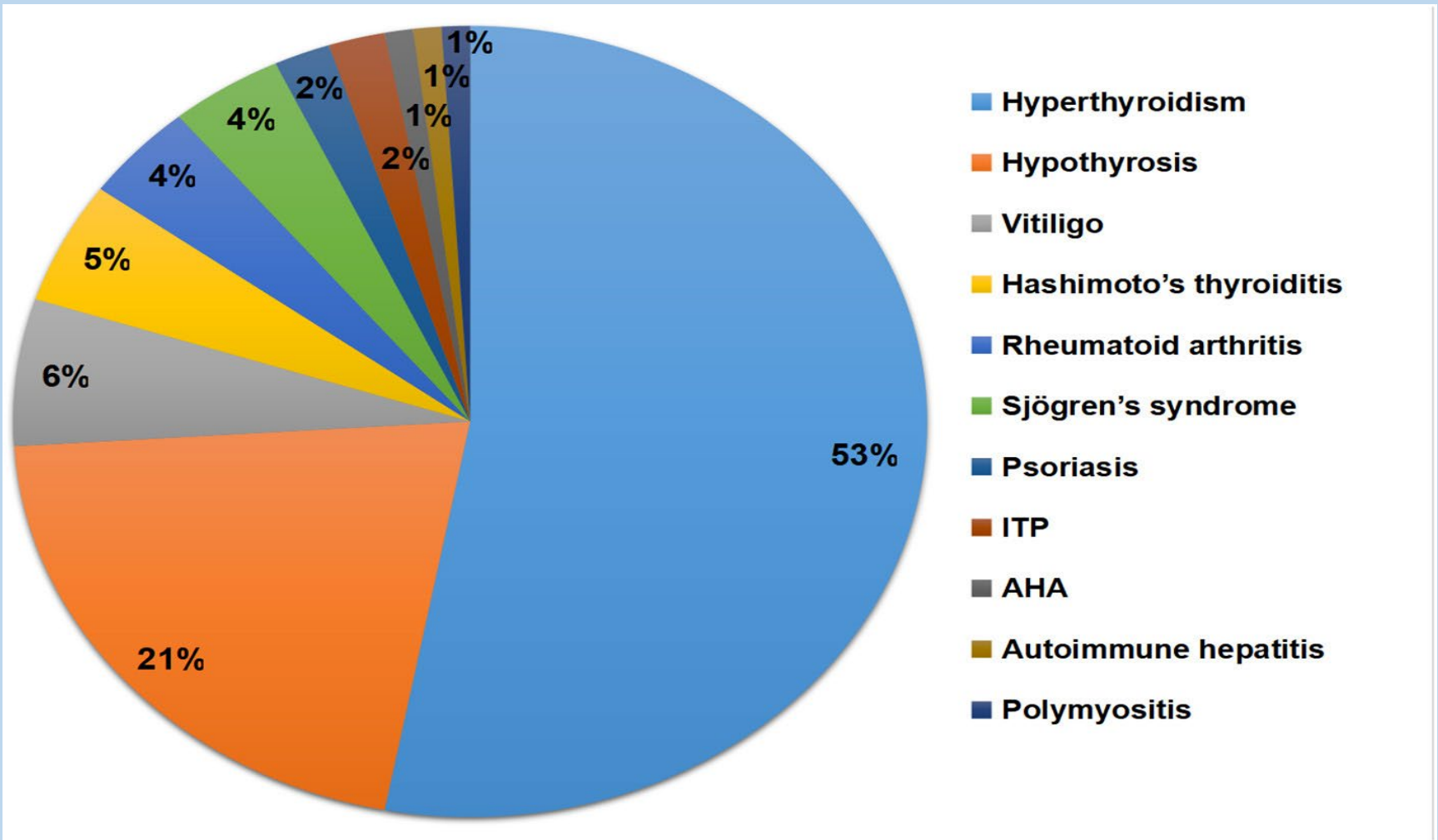
Late onset



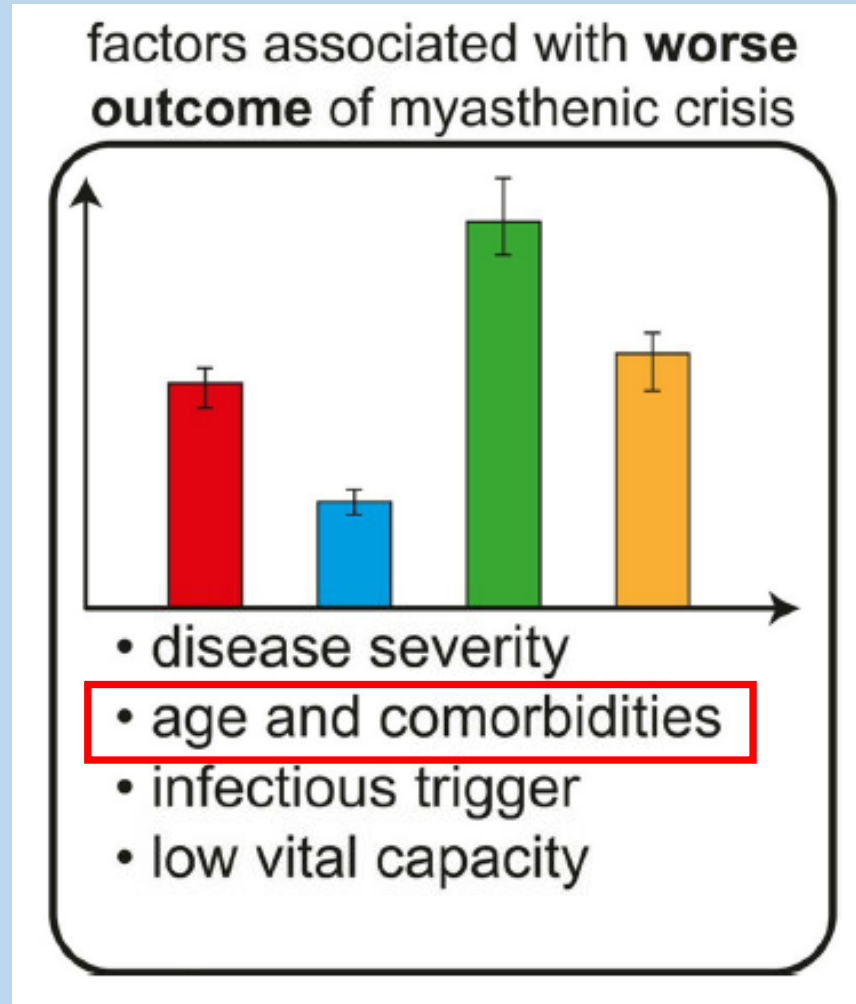
# Percentage of comorbid autoimmune disorders



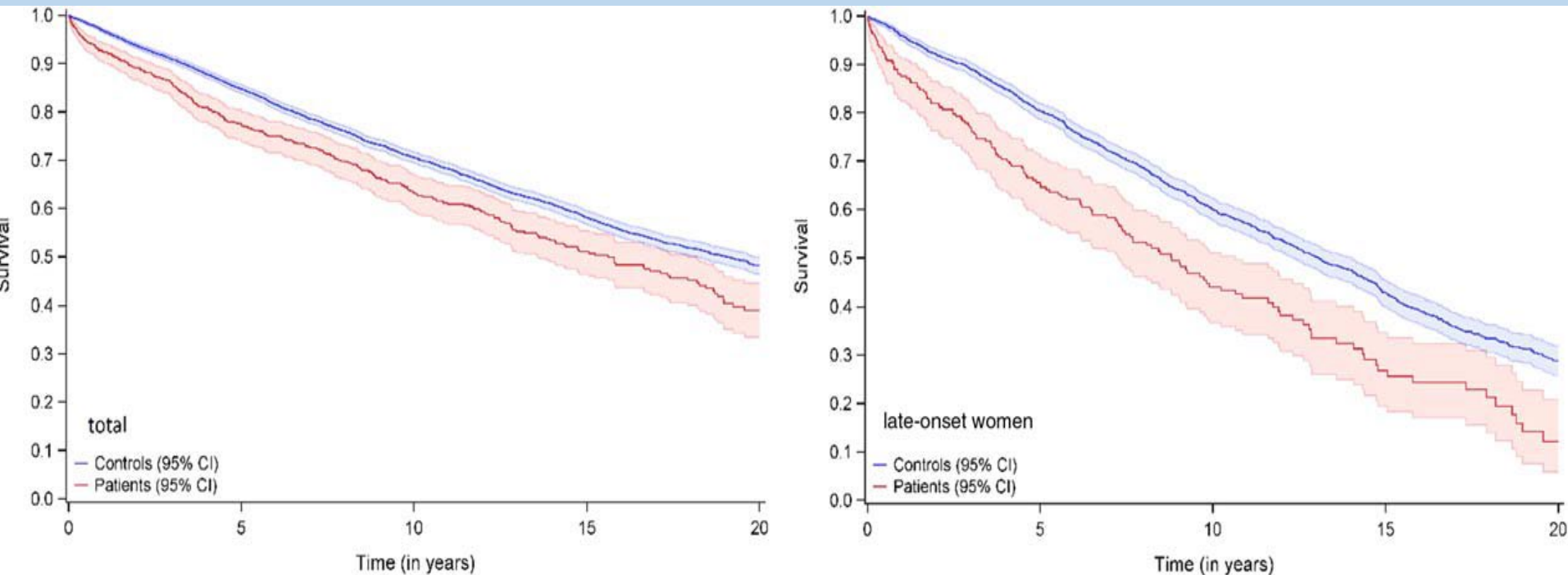
# Autoimmune comorbidities



# Comorbidities – effect on Myasthenic crisis



# Mortality in Myasthenia Gravis in Denmark



## **MORTALITY IN MYASTHENIA GRAVIS: A NATIONWIDE POPULATION-BASED FOLLOW-UP STUDY IN DENMARK**

JULIE S. HANSEN, MD,<sup>1</sup> DITTE H. DANIELSEN, MD,<sup>1</sup> FINN E. SOMNIER, MD, PhD,<sup>2</sup> TRINE FRØSLEV, PhD,<sup>3</sup> JOHANNES JAKOBSEN, MD, PhD,<sup>1</sup> SØREN P. JOHNSEN, MD, PhD,<sup>3</sup> and HENNING ANDERSEN, MD, PhD<sup>1</sup>

# Population-Based Study of Nonelective Postpartum Readmissions in Women With Stroke, Migraine, Multiple Sclerosis, and Myasthenia Gravis

Barbara M. Decker, MD, MSCE, Dylan Thibault, MS, Kathryn A. Davis, MD, MSTR, and Allison W. Willis, MD, MS

*Neurology*® 2022;98:e1545-e1554. doi:10.1212/WNL.0000000000200007

**Table 5** 30-Day and 90-Day Readmissions

Readmissions	N (%)	<i>p</i> Value	OR (95% CI)	<i>p</i> Value	AOR (95% CI)	<i>p</i> Value
<b>30-day</b>						
Controls	80,911 (1.1)		Ref		Ref	
Previous stroke	217 (2.9)	<0.0001	2.99 (2.46–3.63)	<0.0001	2.38 (1.95–2.90)	<0.0001
Migraine	1,405 (1.7)	<0.0001	1.71 (1.57–1.86)	<0.0001	1.63 (1.49–1.77)	<0.0001
MS	123 (1.8)	0.0004	1.86 (1.45–2.40)	<0.0001	1.63 (1.25–2.11)	<0.0001
MG	36 (4.3)	0.0025	4.69 (2.79–7.88)	<0.0001	3.96 (2.37–6.65)	<0.0001

# Increased risk of motor neuron disease in MG

## Autoimmune disease preceding amyotrophic lateral sclerosis

An epidemiologic study

Martin R. Turner, PhD  
Raph Goldacre, BA  
Sreeram Ramagopalan,  
DPhil  
Kevin Talbot, DPhil  
Michael J. Goldacre,  
FFPH

Neurology® 2013;81:1222-1225

**Table** Preceding autoimmune diseases in relation to ALS

Exposure	No. observed	Expected no.	RR (95% CI)	p Value
Myasthenia gravis <sup>a</sup>	36	7.2	5.02 (3.51-6.96)	<0.001

25-fold increased coincidence of MG and ALS

## Amyotrophic lateral sclerosis and myasthenia gravis: association or chance occurrence?

Silvia de Pasqua<sup>1</sup> · Francesco Cavallieri<sup>2</sup> · Roberto D'Angelo<sup>3</sup> · Fabrizio Salvi<sup>4</sup> ·  
Nicola Fini<sup>2</sup> · Roberto D'Alessandro<sup>4</sup> · Rita Rinaldi<sup>3</sup> · Antonio Fasano<sup>2</sup> ·  
Jessica Mandrioli<sup>2</sup>

Neurol Sci (2017) 38:441-444

# Clinical profile and impact of comorbidities in patients with very-late-onset myasthenia gravis

**TABLE 2** Comorbidities

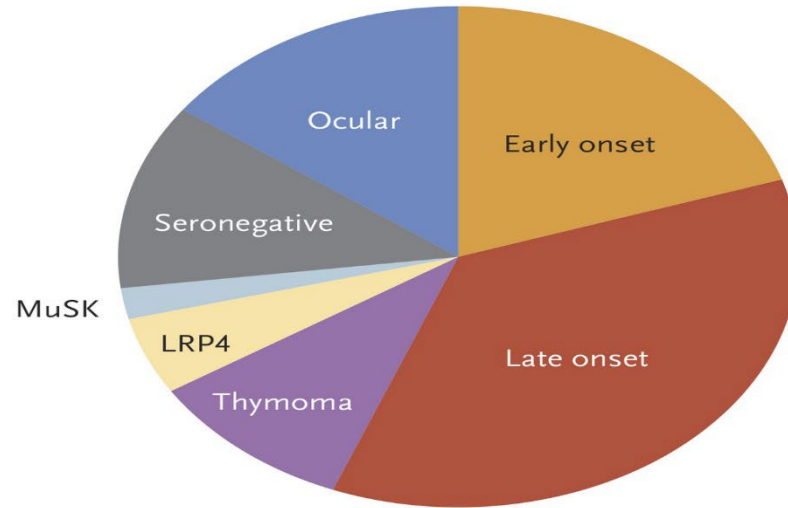
Comorbidities	Number (%)
None	12 (11%)
Single comorbidity	25 (22.9%)
Multiple comorbidities	72 (66.1%)
Cardiorespiratory	36 (33%)
Musculoskeletal disorders	16 (14.7%)
Neurological	20 (18.3%)
Cancer	17 (15.6%)
Diabetes mellitus	16 (14.7%)
Endocrine disorders (thyroid and parathyroid)	17 (15.6%)
Other disorders (psychiatric, cirrhosis)	12 (11%)

**Discussion:** Our study shows that patients with very-late-onset MG had a good prognosis and treatment response. None of the comorbidities had an impact on the severity of myasthenic symptoms or on outcome in these patients.

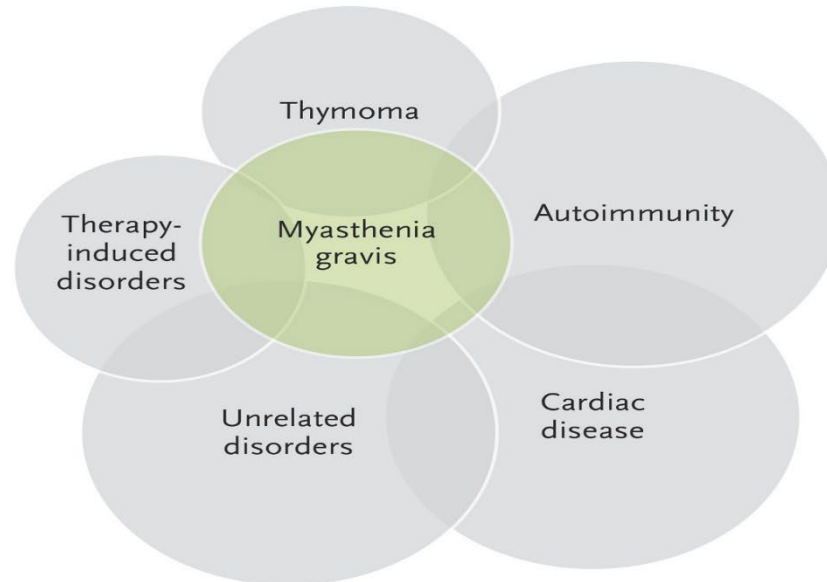


# Thymoma

## A Myasthenia Gravis Subgroups



## B Coexisting Conditions



# Thymoma

The current treatment for localized thymic epithelial tumors is surgical removal.

## **Challenge:**

20–30% of thymomas and 70–80% of thymic carcinomas are unresectable, recurrent, or metastatic at the time of detection.

The standard therapy for these patients is chemotherapy, but the effect is limited.

# Conclusions

- Pts with MG have an increased risk of developing anxiety and depression.
- Depression and anxiety may be treated as in other patient groups – however evidence is lacking and care has to be taken for some medications.
- Pts with MG have many comorbidities – especially in older patient groups - additional challenge in treatment including MG crisis.
- Treatment of MG may cause comorbidities – especially corticosteroids (diabetes, hypertension, obesity, osteoporosis, insomnia etc)
- Thymoma is seen more frequently in MG pts and may be a major challenge.

Thank you for your attention





# International Consensus Guidance for Management of Myasthenia Gravis

## 2020 Update

**Table 1** Drugs to Avoid or Use With Caution in MG<sup>a</sup>

Drug	Comment
<b>Aminoglycoside antibiotics (e.g., gentamycin, neomycin, and tobramycin)</b>	Used for gram-negative bacterial infections. May worsen MG. Use cautiously if no alternative treatment available.
<b>Beta-blockers</b>	Commonly prescribed for hypertension, heart disease, and migraine but potentially dangerous in MG. May worsen MG. Use cautiously.
<b>Botulinum toxin</b>	Presynaptic neuromuscular junction blocker. Avoid use.
<b>Chloroquine and hydroxychloroquine</b>	Used to treat/prevent malaria and for certain autoimmune diseases. May precipitate de novo MG or worsen preexisting MG. Use only if necessary and observe for worsening.
<b>Corticosteroids</b>	A standard treatment for MG but may cause transient worsening within the first 2 weeks. Monitor carefully for this possibility.
<b>Desferrioxamine (deferoxamine)</b>	Chelating agent used for hemochromatosis. May worsen MG.
<b>D-Penicillamine</b>	Used for Wilson disease and rarely for rheumatoid arthritis. Strongly associated with causing MG. Avoid use.
<b>Fluoroquinolone antibiotics (e.g., ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin)</b>	Commonly prescribed broad-spectrum antibiotics that are associated with worsening MG. The US FDA has designated a “black-box” warning for these agents in MG. Use cautiously, if at all.
<b>Immune checkpoint inhibitors (e.g., ipilimumab, pembrolizumab, atezolizumab, and nivolumab)</b>	Used for certain cancers. Can precipitate de novo MG or worsen preexisting MG. Use with caution as determined by oncologic status.
<b>Iodinated radiologic contrast agents</b>	Older reports document increased MG weakness, but modern contrast agents appear safer. Use cautiously and observe for worsening.
<b>Macrolide antibiotics (e.g., erythromycin, azithromycin, and clarithromycin)</b>	Commonly prescribed antibiotics for gram-positive bacterial infections. May worsen MG. Use cautiously, if at all.
<b>Magnesium</b>	Potentially dangerous if given intravenously, i.e., for eclampsia during late pregnancy or for hypomagnesemia. Use only if absolutely necessary and observe for worsening.
<b>Procainamide</b>	Used for irregular heart rhythm. May worsen MG. Use with caution.
<b>Quinine</b>	Occasionally used for leg cramps. Use prohibited except in malaria in the United States.
<b>Statins (e.g., atorvastatin, pravastatin, rosuvastatin, and simvastatin)</b>	Used to reduce serum cholesterol. May rarely worsen or precipitate MG. Evaluate closely for worsening MG when statin treatment is commenced.