



# SDRM Cooperative Research: Magnesium in Covid-19

Rome, 20 November, 2021



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*Professor of Pathology*

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*Fondazione Policlinico Gemelli*

*Saint Camillus International University of Health Sciences*

*Rome - Italy*

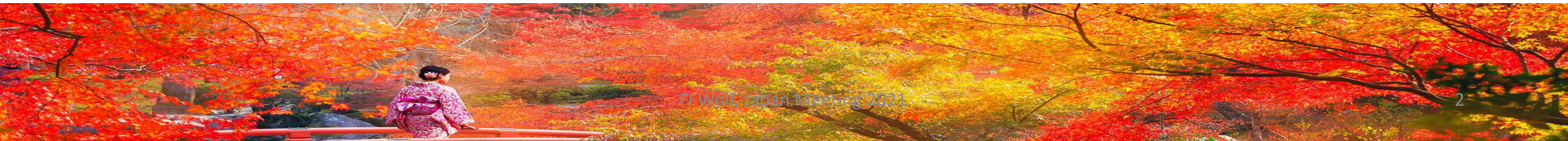
# What is SDRM?

The International  
Society for the  
Development of  
Research on  
Magnesium

[www.sdrmsociety.org](http://www.sdrmsociety.org)

*Promotes magnesium research in all branches of  
life science and medicine by increasing the  
collaboration, diffusion and exchange of  
information.*

*Official Journal:*



# INTERNATIONAL MAGNESIUM SYMPOSIA

**16th IMS**, Glasgow – Scotland 23-24 June 2022 (*R*

*Touyz, FI Wolf*)

**15th IMS**, NIH – Bethesda (USA), March 20-22, 2019

(*M Lenardo, FI. Wolf,*)

**14th IMS**, Roma - Italy, June 23-24, 2016 (*F I. Wolf*)

**13th IMS**, Merida - Mexico, October 16-19, 2012

(*F Guerrero-Romero, J Vormann*)

**12th IMS**, Iasi – Romania, September 22-25, 2009 (*M*

*Nechifor*)

**11th IMS**, Kashikojima – Japan, October 23-26, 2006

(*Yoshiki Nishizawa*)

**10th IMS**, Cairns – Australia, September 7-11, 2003 (*R*

*Vink*)

**9th IMS** - MAG 2000, Vichy - France, September 10-15,

2000 (*Y Rayssiguier*)

**8th IMS**, Heraklion-Greece, October 5-9, 1997

(*T Theophanides, J Anastassopoulou*)

**7th IMS**, Lisbon, Portugal, 1994, (*MJ Halpern*)

**6th IMS**, Indore, India, 1991, (*Bharat Chaparwal*)

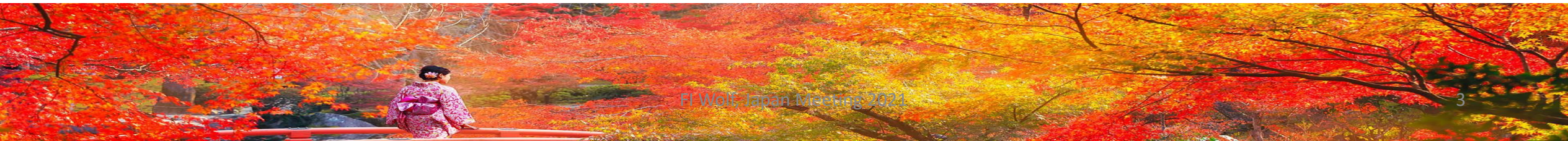
**5th IMS**, 8-12 August 1988, Kyoto, Japan, (*Yoshinori*

*Itokawa*)

# GORDON RESEARCH CONFERENCES

Magnesium in Biochemical Processes & Medicine  
California USA ([www.grc.org](http://www.grc.org))

- 2008 Mar 9-14 *William B. Weglicki, FI Wolf*
- 2005 Feb 6-11 *Juergen Vormann*
- 2002 Feb 3-8 *Klaus W. Beyenbach*
- 1999 Feb 7-12 *J.A.S. McGuigan*
- 1996 Jan 28 - Feb 2 *Mike E. Maguire*
- 1993 Feb 22-26 *Christopher H. Fry*
- 1990 Feb 26 - Mar 2 *Stanley Wallach*
- 1987 Feb 23-27 *Michael P. Ryan*
- 1984 - *Burton M. Altura*
- 1982 - *Francis Haddy*
- 1980 - *Robert Whang*
- 1979 - *Mildred S. Seelig*
- 1978 – *Ronald Elin*

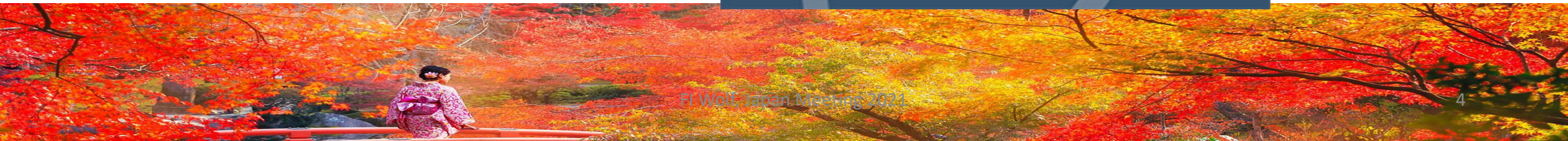


# The latest conference

Forst Online virtual Meeting

See [www.sdrmsociety.org](http://www.sdrmsociety.org)

for program and contributions



## The next event:

- *Hosting President:*  
**Rhian M Touyz**  
*Glasgow University, McGill University*



- *SDRM President:*  
**Federica I Wolf**  
*Catholic University, Saint Camillus Intl University*



# The COVID-19 pandemic: is there a role for magnesium? Hypotheses and perspectives



**Stefano Iotti<sup>1</sup>, Federica Wolf<sup>2</sup>, André Mazur<sup>3</sup>, Jeanette A. Maier<sup>4</sup>**

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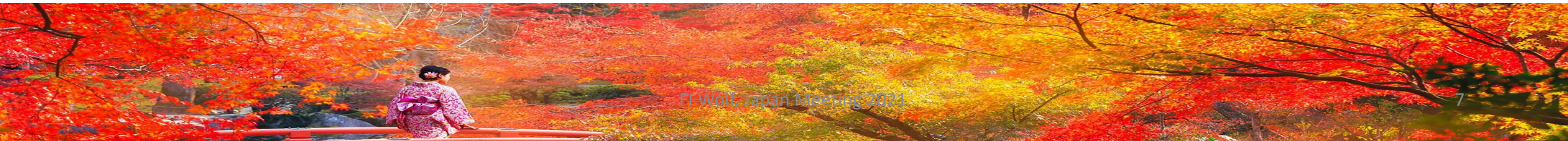
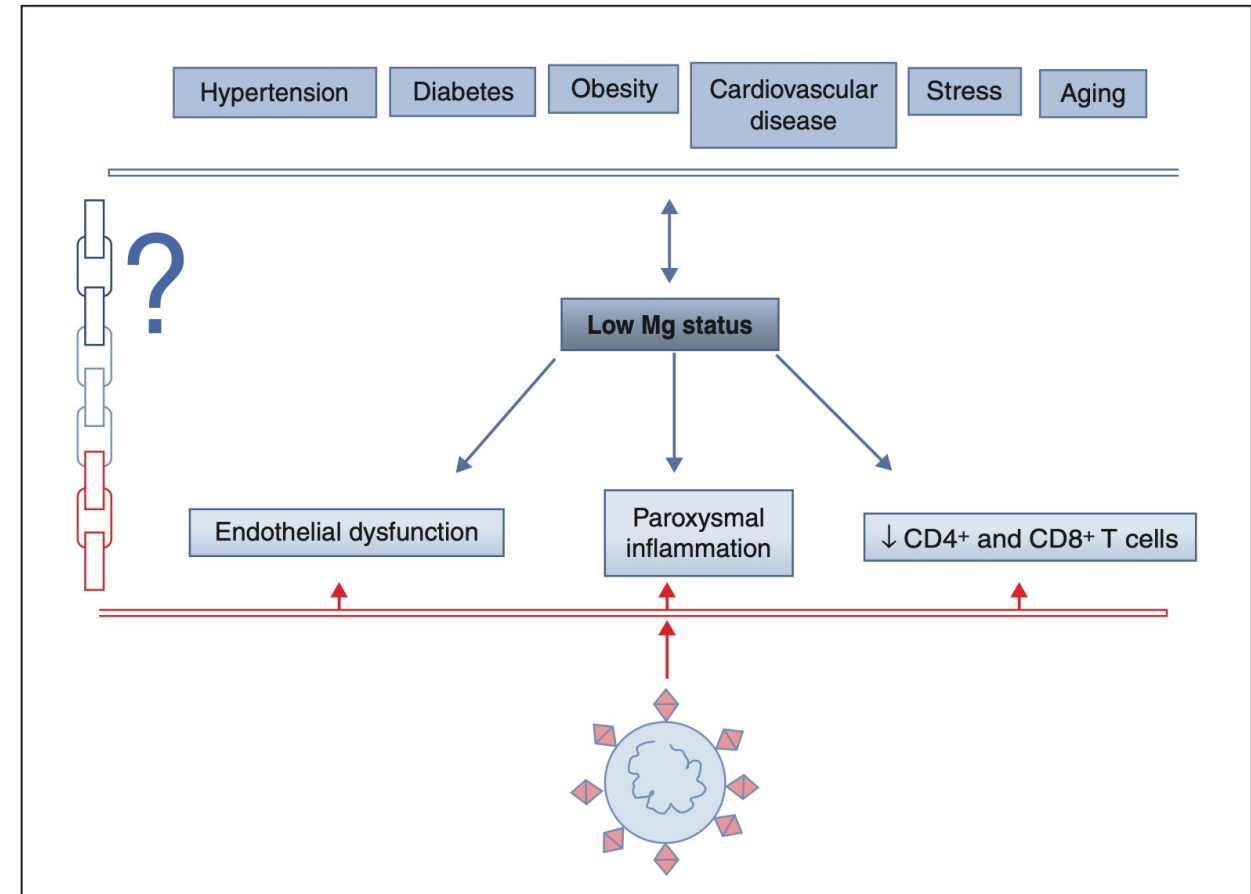
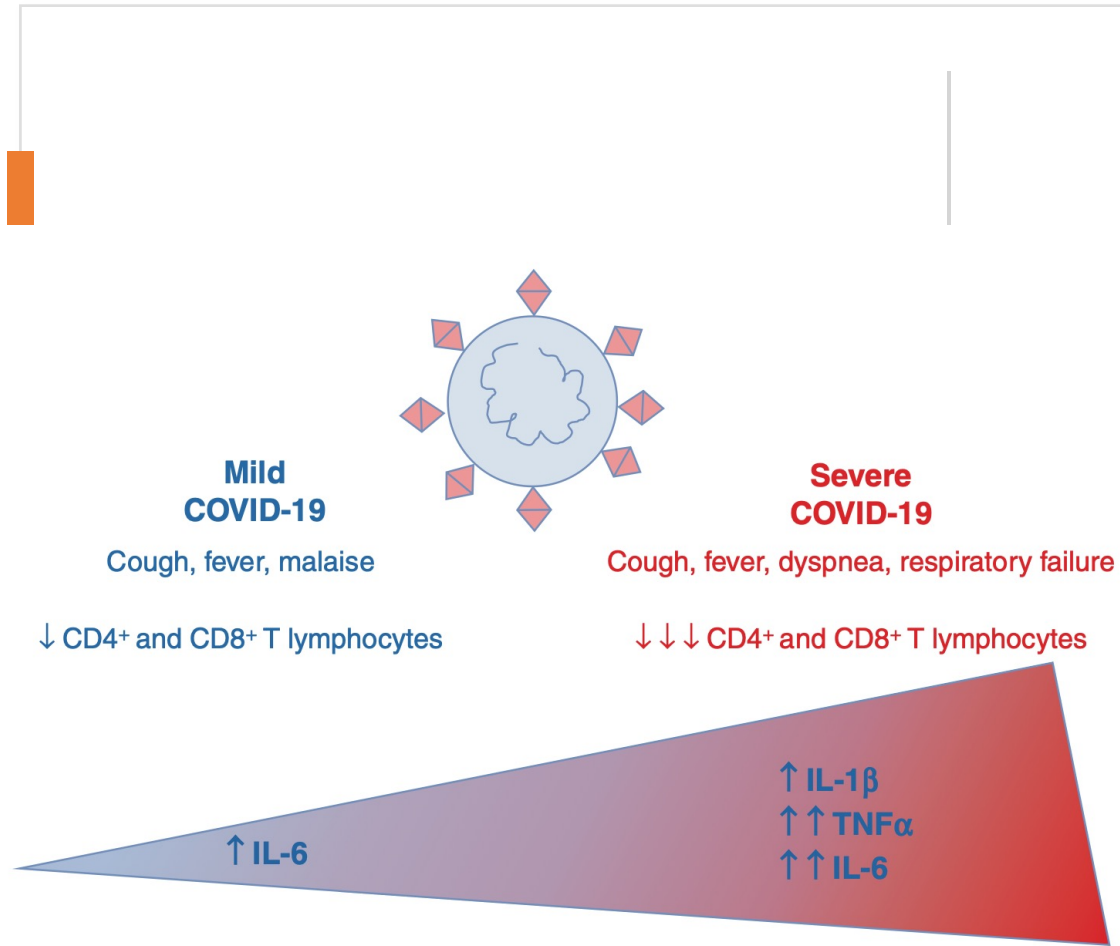
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## Editorial

# Magnesium deficiency and COVID-19 – What are the links? Some remarks from the German Society for Magnesium Research e.V.

Oliver Micke<sup>1\*</sup>, Jürgen Vormann<sup>2</sup>, and Klaus Kisters<sup>3\*\*</sup>



## **Taylor C Wallace**

**Combating COVID-19 and Building Immune Resilience: A Potential Role for Magnesium Nutrition?**

*J Am Coll Nutr* 2020;  
39(8):685-693.

doi: 10.1080/07315724.2020.1785971.



## **O Micke, J Vormann, K Kisters**

**Magnesium and COVID-19 - Some Further Comments - A Commentary on Wallace TC. Combating COVID-19 and Building Immune Resilience: A Potential Role for Magnesium Nutrition?**

*J Am Coll Nutr.* 2020;1-9.

doi:10.1080/07315724.2020.1785971.

Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B<sub>12</sub> in combination on progression to severe outcomes in older patients with coronavirus (COVID-19).

Tan CW, Ho LP, Kalimuddin S, Cherng BPZ, Teh YE, Thien SY, Wong HM, Tern PJW, Chandran M, Chay JWM, Nagarajan C, Sultana R, Low JGH, Ng HJ.

*Nutrition.* 2020 Nov-Dec;79-80:111017. doi: 10.1016/j.nut.2020.111017. Epub 2020 Sep 8.

PMID: 33039952 [Free PMC article.](#) Clinical Trial.

SARS-CoV-2: influence of phosphate and magnesium, moderated by vitamin D, on energy (ATP) metabolism and on severity of COVID-19.

van Kempen TATG, Deixler E.

*Am J Physiol Endocrinol Metab.* 2021 Jan 1;320(1):E2-E6. doi: 10.1152/ajpendo.00474.2020. Epub 2020 Nov 11.

PMID: 33174766 [Free PMC article.](#)

Magnesium and Vitamin D Deficiency as a Potential Cause of Immune Dysfunction, Cytokine Storm and Disseminated Intravascular Coagulation in covid-19 patients.

DiNicolantonio JJ, O'Keefe JH.

*Mo Med.* 2021 Jan-Feb;118(1):68-73.

PMID: 33551489 [Free PMC article.](#)

Obesity, malnutrition, and trace element deficiency in the coronavirus disease (COVID-19) pandemic: An overview.

Fedele D, De Francesco A, Riso S, Collo A.

*Nutrition.* 2021 Jan;81:111016. doi: 10.1016/j.nut.2020.111016. Epub 2020 Sep 8.

PMID: 33059127 [Free PMC article.](#) Review.

Challenges of Maintaining Optimal Nutrition Status in COVID-19 Patients in Intensive Care Settings.

Minnelli N, Gibbs L, Larrivee J, Sahu KK.





**On 2021:**




*Magnesium Research* 2021; **34** (2): 90-92

LETTER TO THE EDITOR

## The magnesium global network (MaGNet) to promote research on magnesium in diseases focusing on covid-19

Federica I. Wolf<sup>1,30</sup>, Jeanette A. Maier<sup>2,30</sup>, Andrea Rosanoff<sup>28</sup>, Mario Barbagallo<sup>3</sup>, Shadi Baniyadi<sup>4</sup>, Sara Castiglioni<sup>2,30</sup>, Fu-Chou Cheng<sup>5</sup>, Sherrie Colaneri Day<sup>28</sup>, Rebecca B. Costello<sup>28</sup>, Ligia J. Dominguez<sup>3</sup>, Ronald J. Elin<sup>6</sup>, Claudia Gamboa-Gomez<sup>7</sup>, Fernando Guerrero-Romero<sup>7</sup>, Ka Kahe<sup>8</sup>, Klaus Kisters<sup>9,29</sup>, Martin Kolisek<sup>10,29</sup>, Anton Kraus<sup>29</sup>, Stefano Iotti<sup>11,30</sup>, Andre Mazur<sup>12,30</sup>, Moises Mercado-Atri<sup>13</sup>, Lucia Merolle<sup>14</sup>, Oliver Micke<sup>15,29</sup>, Nana Gletsu-Miller<sup>16</sup>, Forrest Nielsen<sup>17</sup>, Jin O-Uchi<sup>18</sup>, Ornella Piazza<sup>19</sup>, Michael Plesset<sup>28</sup>, Guitti Pourdowlat<sup>20</sup>, Francisco J. Rios<sup>21</sup>, Martha Rodriguez-Moran<sup>7</sup>, Giuliana Scarpati<sup>19</sup>, Michael Shechter<sup>22</sup>, Yiqing Song<sup>23</sup>, Lisa A. Spence<sup>23</sup>, Rhian M Touyz<sup>21,30</sup>, Valentina Trapani<sup>1,24,30</sup>, Nicola Veronesi<sup>3</sup>, Rado van




**Global Magnesium COVID-19 Project**  
**Video Link for Meeting #15**  
Wednesday, October 13, 2021

Link for video Meeting Recording:  
<https://us02web.zoom.us/j/84461212693?pwd=OWp2dUAGOG6WODG6>

Access Passcode: Py?VK8@0

**Lei Fan, MD, MPH**  
Postdoctoral fellow, Division of Epidemiology, Department of Medicine  
Vanderbilt University Medical Center



**Potential role of Mg in SARS-CoV-2 entry and coagulation cascade via epigenetic changes of transmembrane serine protease 2 (TMPRSS2)**

European Journal of Nutrition

<https://doi.org/10.1007/s00394-021-02704-y>

## REVIEW



# The relevance of magnesium homeostasis in COVID-19

**Valentina Trapani<sup>1,2</sup>  · Andrea Rosanoff<sup>3</sup> · Shadi Baniyadi<sup>4</sup> · Mario Barbagallo<sup>5</sup> · Sara Castiglioni<sup>6</sup> · Fernando Guerrero-Romero<sup>7</sup> · Stefano Iotti<sup>8</sup> · André Mazur<sup>9</sup> · Oliver Micke<sup>10</sup> · Guitti Pourdowlat<sup>11</sup> · Giuliana Scarpati<sup>12</sup> · Federica I. Wolf<sup>1</sup> · Jeanette A. Maier<sup>6</sup>**

Received: 21 June 2021 / Accepted: 6 October 2021

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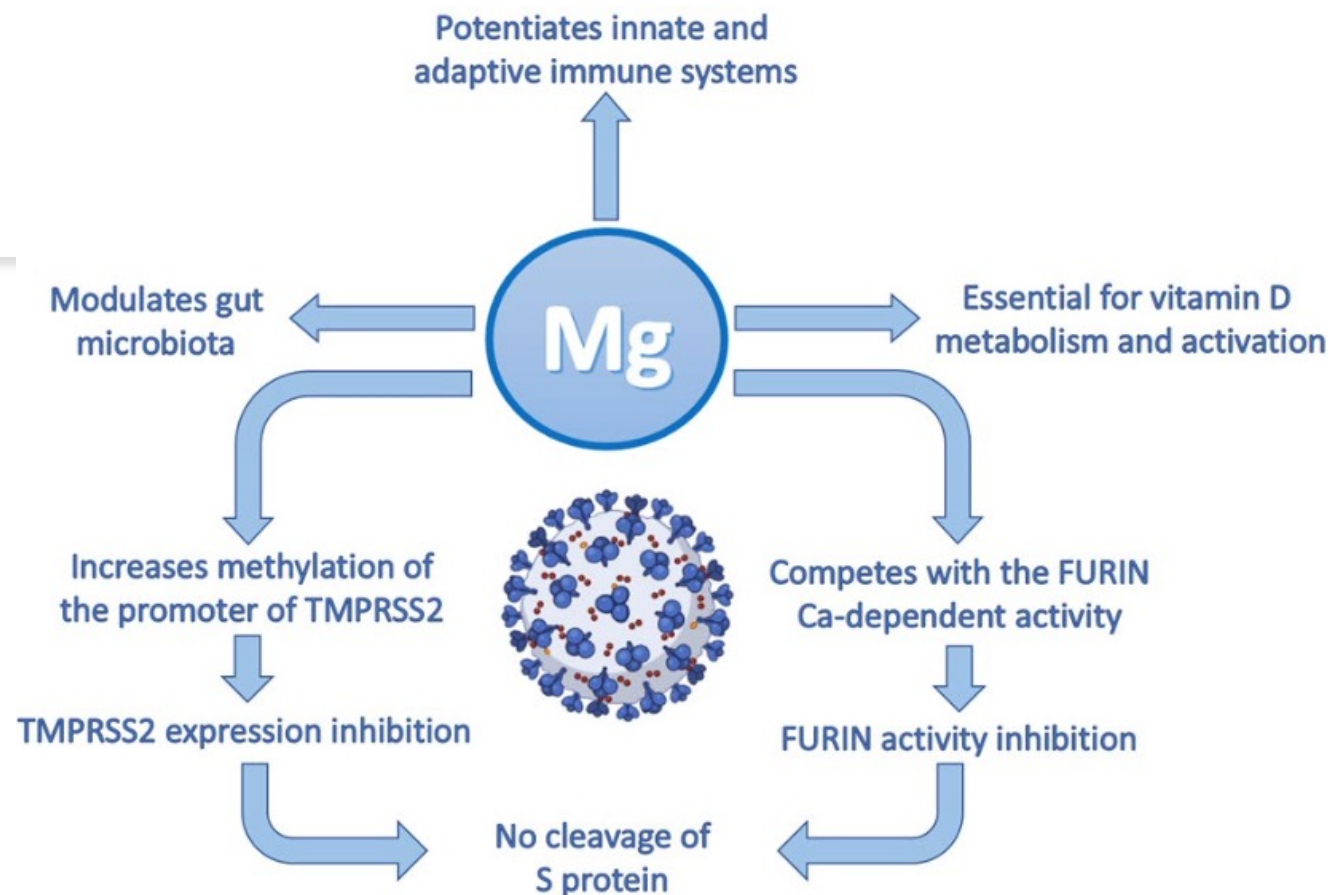
## Links between magnesium derangements and COVID-19 pathogenesis

### Background:

Magnesium, a metabolite

Magnesium deficit in aging and non-communicable chronic diseases

Magnesium in infectious diseases



Article

## Dietary Magnesium Alleviates Experimental Murine Colitis through Modulation of Gut Microbiota

Federica Del Chierico <sup>1,†</sup>, Valentina Trapani <sup>2,†</sup>, Valentina Petito <sup>2</sup>, Sofia Reddel <sup>1</sup>, Giuseppe Pietropaolo <sup>2,§</sup>, Cristina Graziani <sup>2</sup>, Letizia Masi <sup>2</sup>, Antonio Gasbarrini <sup>2,3</sup>, Lorenza Putignani <sup>4</sup>, Franco Scaldaferri <sup>2,3,\*</sup> and Federica I. Wolf <sup>2,5,\*</sup>

## Magnesium status and supplementation influence vitamin D status and metabolism: results from a randomized trial

Qi Dai, et al. *Am J Clin Nutr* 2018;108:1249–1258



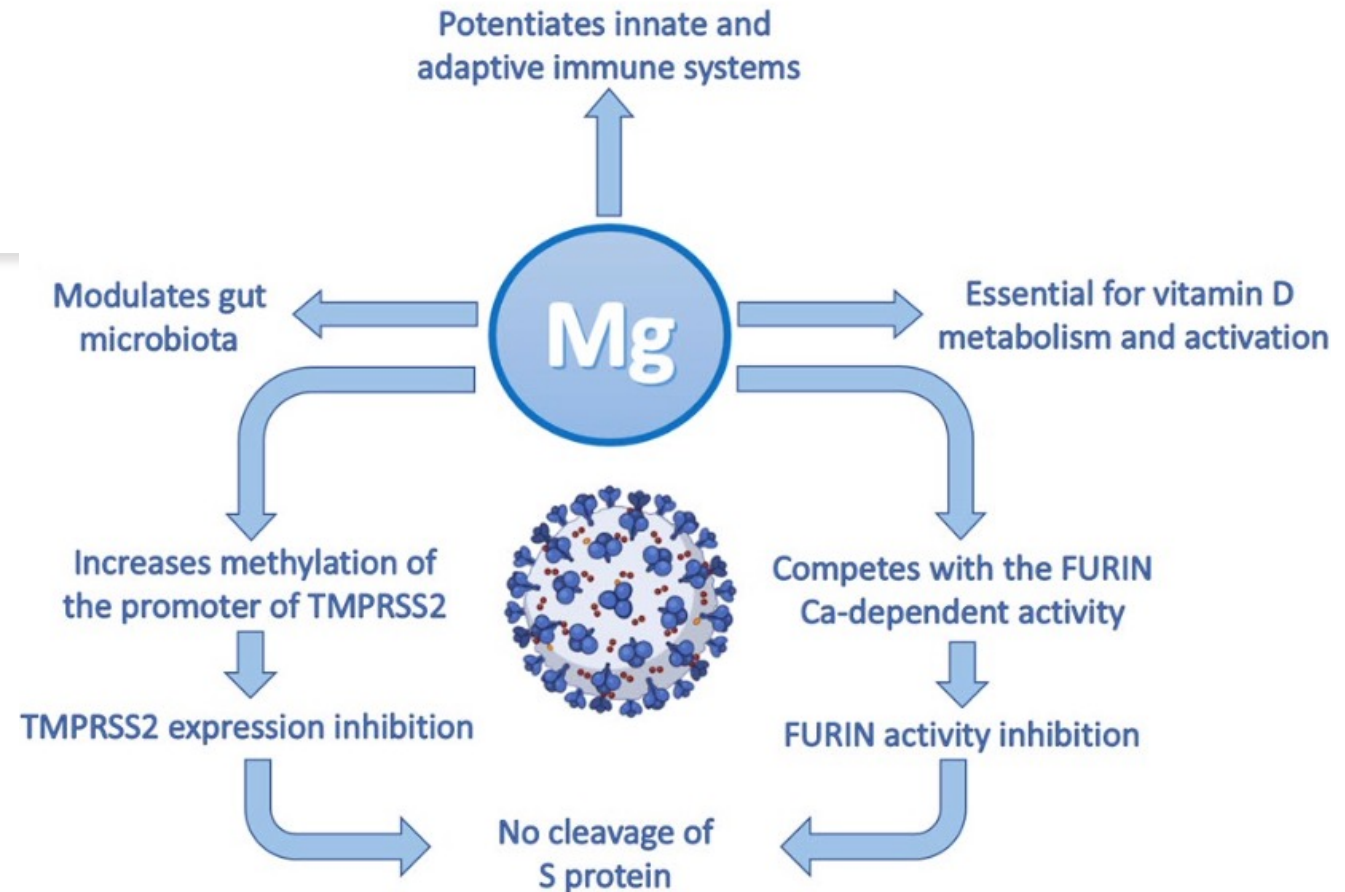
Seminars in Cell & Developmental Biology  
Volume 115, July 2021, Pages 37–44



## Magnesium and inflammation: Advances and perspectives

Jeanette A. Maier <sup>a</sup>, Sara Castiglioni <sup>a</sup>, Laura Locatelli <sup>a</sup>, Monica Zocchi <sup>a</sup>, André Mazur <sup>b</sup>

## Links between magnesium derangements and COVID-19 pathogenesis



# Magnesium in COVID-19: clinical studies

**Table 1** Existing clinical studies showing alterations of magnesium levels in COVID-19 patients

Study Design	Number of patients	Outcome	F
Retrospective	300	Severe cases have lower magnesium levels than mild and moderate cases	
Retrospective	459	Low magnesium levels are associated to mortality	
Prospective	300	48% of hospitalized patients are hypomagnesemic, but hypermagnesemia is more prevalent in ICU cases	
Prospective	200	In pregnant women, SARS-CoV2 infection was associated to higher magnesemia in the first and third semester in comparison to non-infected subjects	
Cross-sectional	58	An altered magnesium status (either hypomagnesemia or hypermagnesemia) was more frequent in ICU cases	
Retrospective	90	Patients show levels of calcium and magnesium lower than controls	
Retrospective	320	Serum calcium and magnesium concentration were significantly lower in hypokalemic than normokalemic patients	
Case report	1	Persistent hypokalemia and hypomagnesemia, which continued for more than 5 months after the initial infection and its resolution	



**Table 2** Ongoing clinical studies investigating the role of magnesium in COVID-19

Study Design	Clinical Center	Number of Patients	Outcome
Interventional RCT [84]	Masih Daneshvari Hospital, Shahid Dr. Labbafinejad Hospital, Shahid Sadoughi Hospital, Iran	100	Improvement of respiratory function and symptoms upon inhalation of $\text{MgSO}_4$
Interventional RCT	Mexican Social Security Institute at Durango, Mexico	100	Reduction of the probability of infection and the need for hospitalization and/or mortality upon administration of $\text{MgCl}_2$ plus vitamin D
Interventional	University of Minnesota, USA	NA	Efficacy of Mg supplementation for preventing sudden cardiac death in hypertensive patients
Prospective	AOU San Giovanni di Dio e Ruggi D'Aragona, University of Salerno, Italy	100	Correlation between total and ionized serum Mg levels and outcomes in ICU patients
Prospective	National Research Institute of Tuberculosis and Lung Diseases, Iran	200	Correlation between serum Mg/Ca level and CRP in ICU patients
Retrospective and Prospective [85]	Academy of Nutrition and Dietetics / George Mason University, USA	250	Correlation between nutrition standard care practices and outcomes in ICU patients



## ... Ongoing Clinical Studies

Retrospective	University of Milan – Ospedale Sacco, Italy	430	Correlation between Mg levels and the course of COVID-19
Retrospective	AUSL-IRCCS Reggio Emilia, Italy	241	Correlation between Mg levels and COVID-19 outcomes
Retrospective [86]	University Hospital of Puebla, Mexico	118	Correlation between renal function, serum magnesium levels and mortality in T2D patients
Retrospective	Comenius University in Bratislava –Biomedical Centre Martin at Jessenius Faculty of Medicine, and the Hospitals of Žilina self-governing region, Slovakia	300	Correlation between Mg levels (and of other bio-elements) and the course of COVID-19
Retrospective	Indiana University, USA	NA	Associations between nutritional status of vitamin D, iron, and magnesium and disease severity of COVID-19
Cross-sectional	Mexican Social Security Institute at Durango, Specialty Hospital from the National Medical Center Century XXI, Mexican Social Security Institute at Mexico City, Mexico	450	Correlation between hypomagnesemia and COVID-19 mortality



- **Discussed issues:**

- **LIMITATIONS:**

- Paucity
  - Secondary outcomes
  - Different methods to measure serum magnesium, most of the time one measurement «snapshot» at admittance.
  - Debate on the significance of serum magnesium as a good biomarker of Mg status
  - Lack of reference values prior to disease.
- Observational nature of investigations
  - Lack of consensus on reference values

## **SUGGESTIONS:**

There is an association between **deranged magnesium status** and **Covid-19 severity**:

- Most of the studies report **hypomagnesemia** associated to **more severe cases**
- Some report **Hypermagnesemia** in **critically ill patients** (sepsis, Multiorgan failure)



# Open Questions:

- *Magnesium deficiency is a risk factor to developing Covid-19?*
- *Does infection lower magnesium levels?*
- *Do magnesium levels affect the clinical course of the disease?*
- *Magnesium supplementation is a prophylactic or a therapeutic measure?*

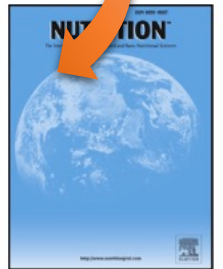
- One study



Contents lists available at [ScienceDirect](#)

Nutrition

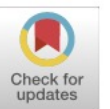
journal homepage: [www.nutritionjrn.com](http://www.nutritionjrn.com)



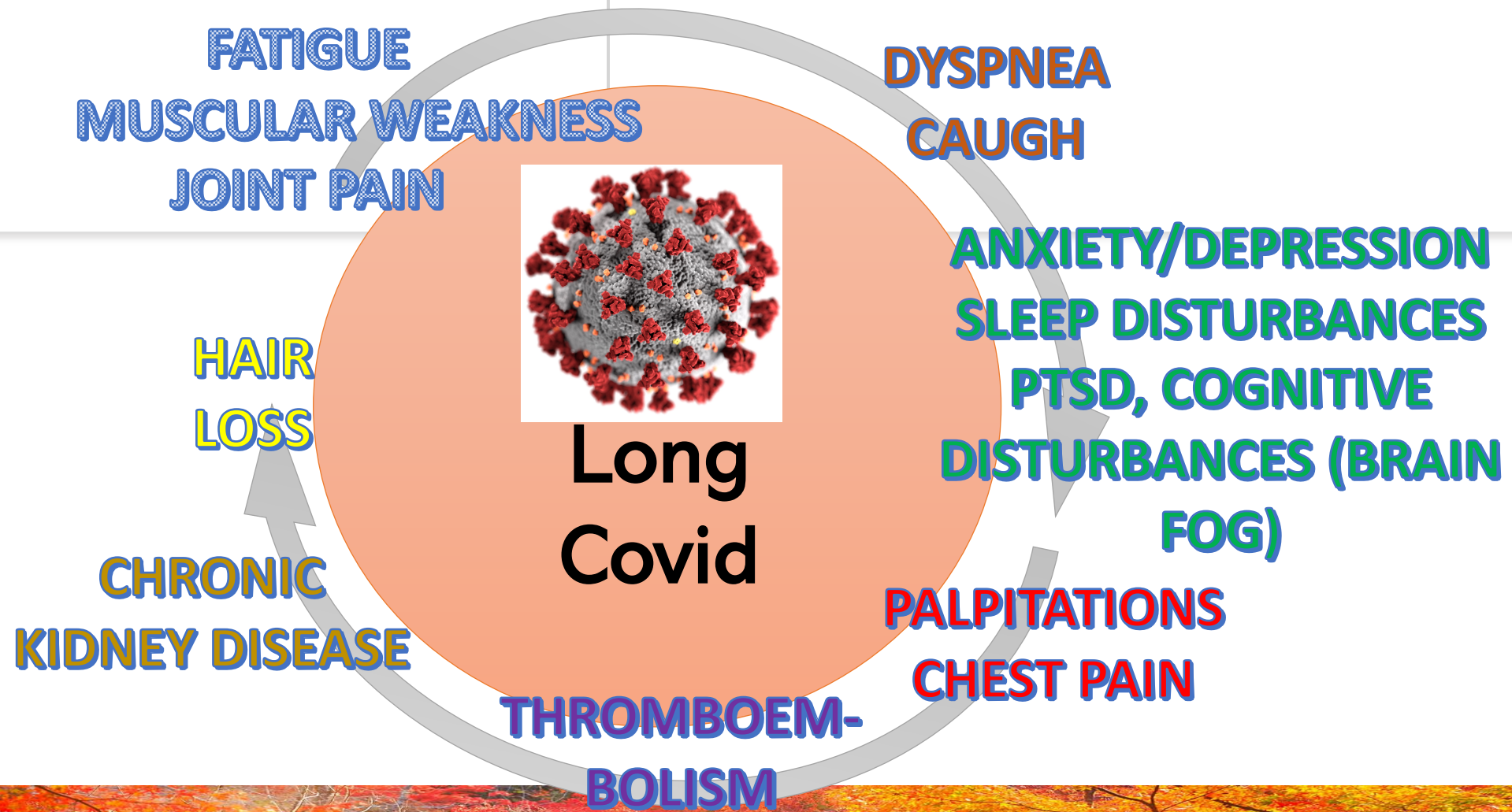
Applied nutritional investigation

Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B<sub>12</sub> in combination on progression to severe outcomes in older patients with coronavirus (COVID-19)

Chuen Wen Tan M.R.C.P., F.R.C.Path <sup>a,1</sup>, Liam Pock Ho F.R.C.P.A. <sup>a,b,c,1</sup>,



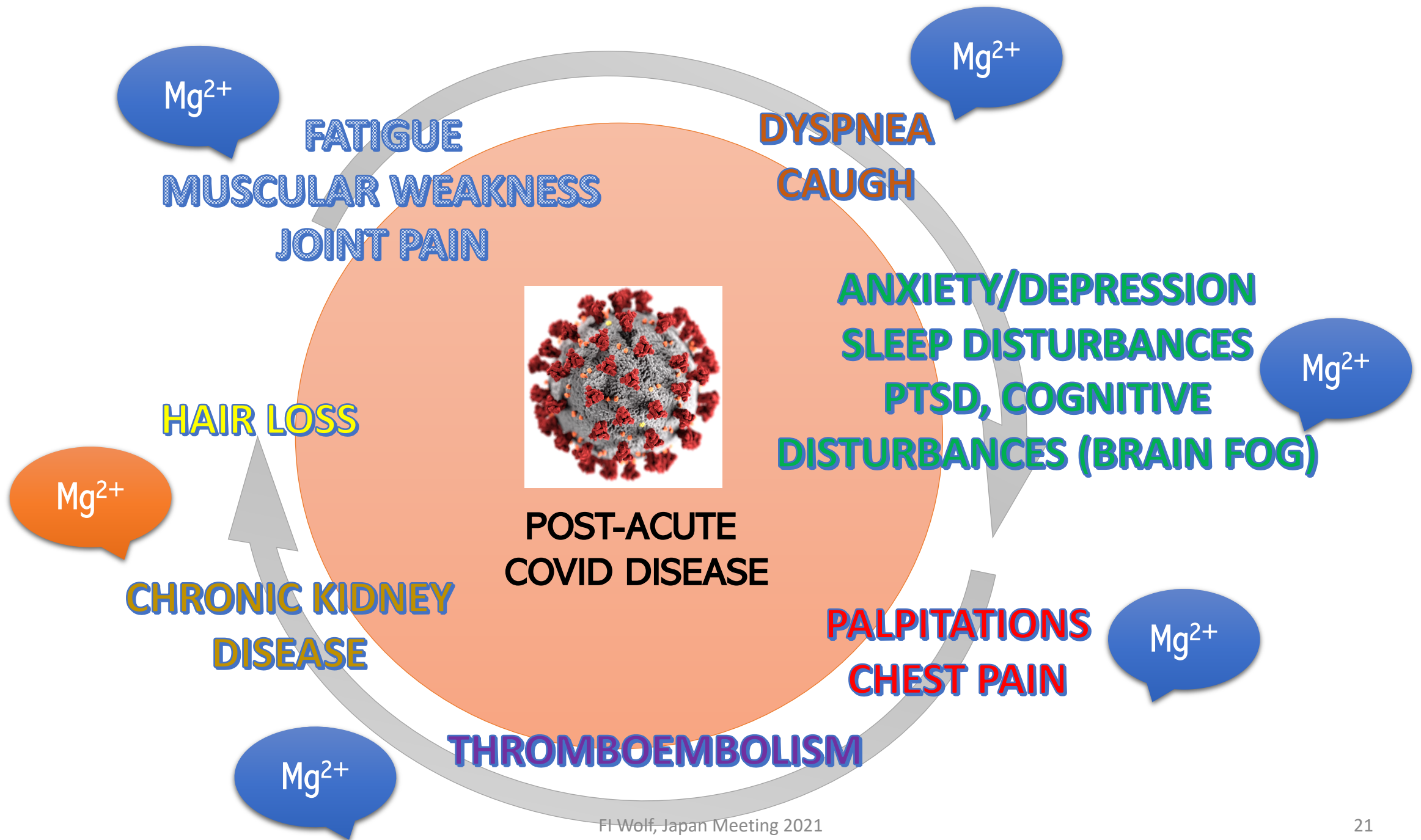
# Magnesium and Post-Acute COVID-19 Syndrome - Long Covid



# Pathophysiology of Post-Acute Covid-19 Syndrome – Long Covid-19

- Direct virus-induced alterations,
- Immunologic aberration and inflammatory damage in response to the acute infection,
- Ischemia due to microvascular thromboembolism, immobility and metabolic derangements,
- Metabolism deregulation occurs in Post Traumatic Stress Disorder (PTSD)
- Chronic fatigue, dyspnea, pain and cough suggest alterations in the brain:
- SARS-CoV-2 neuro-invades through sensory neurons to enter the central nervous system (CNS).
- Neuroinflammatory events driven by the cytokine storm are likely to affect various regions of the CNS.



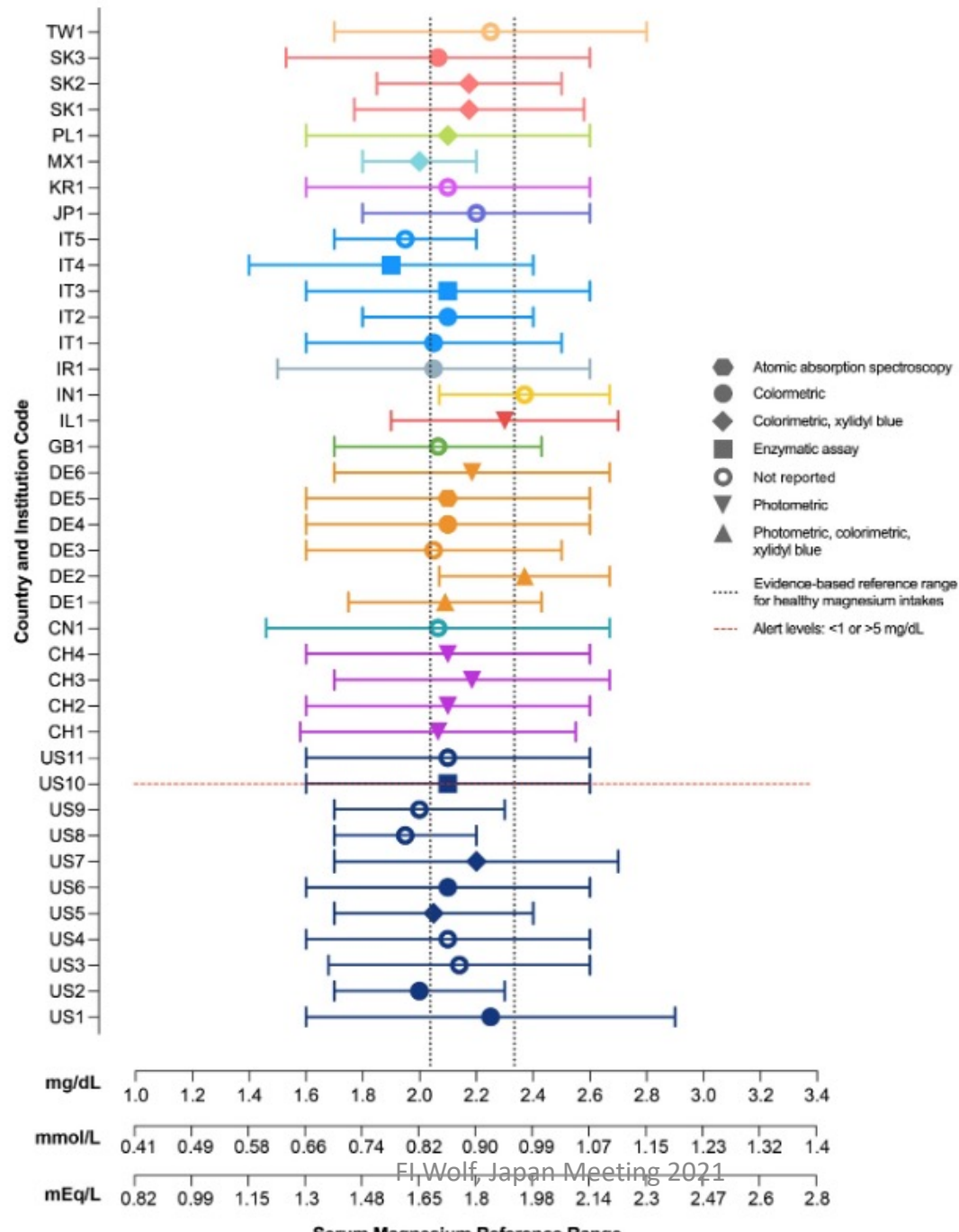


## Next step:

- We investigated the adequacy and variability of the international serum Magnesium reference range:
- We collected data worldwide on the evaluation methods and reference ranges for serum magnesium, and considered their variability indicative of the global non-homogeneous reference ranges.
- This impacts on the underestimation of borderline, asymptomatic hypomagnesemia widely diffused in developed countries (Chronic Latent Magnesium Deficiency).
- CLMD is considered an important risk factor for long term health.

*See Costello R et al. The Case for an Evidence-Based Reference Interval for Serum Magnesium: The Time Has Come *Advances in Nutrition* 2016 7(6):977-99 DOI:10.3945/an.116.012765*

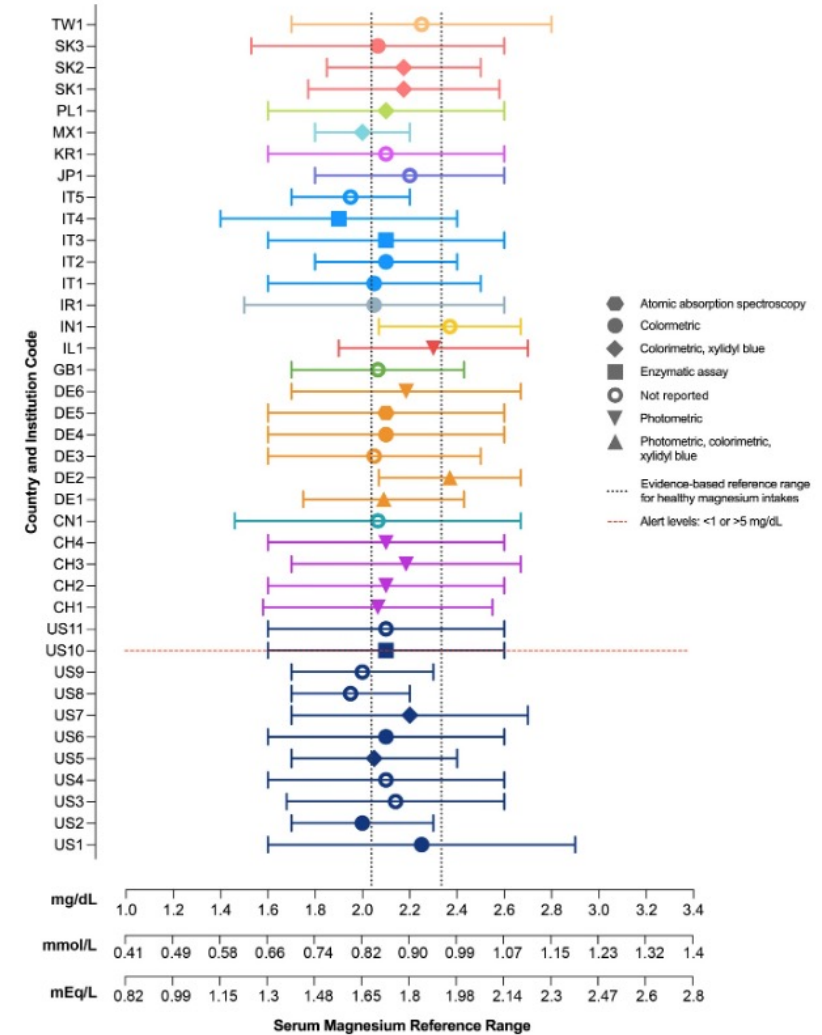




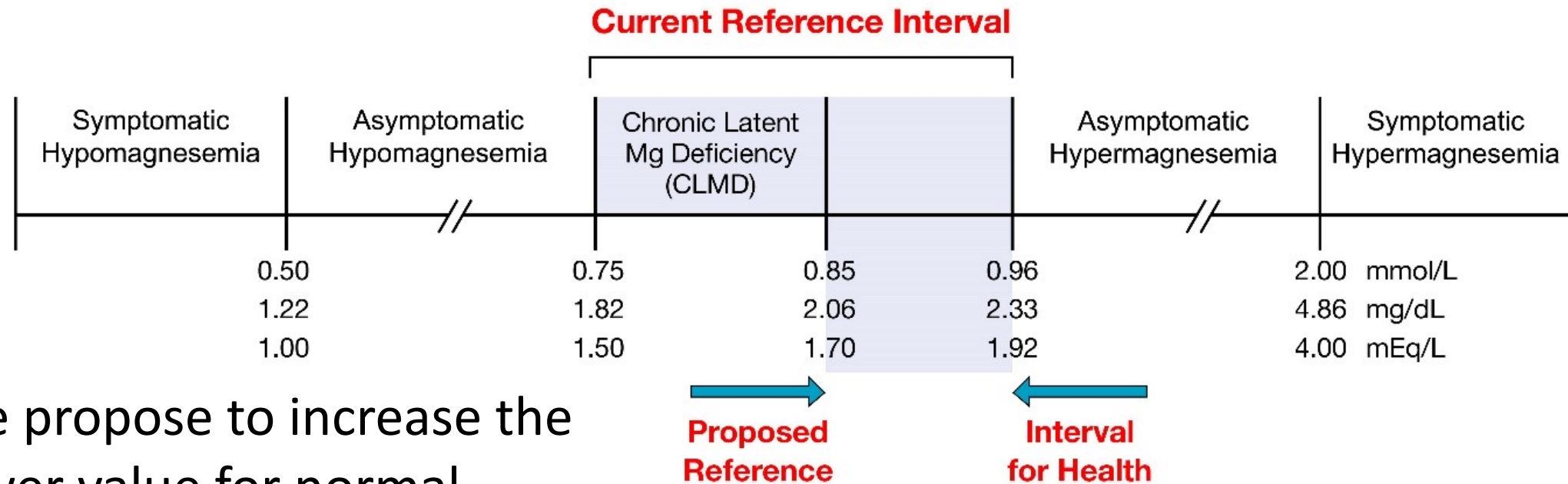
*Rosanoff A and MaGNet,  
submitted for publication*

- **Discussion:**

- the data we collected is a small but indicative sample of serum magnesium reference range variability worldwide.
- Data show there is no consensus on global serum magnesium reference ranges.
- Data also show a tendency to underestimate hypomagnesemia (CLMD), a sign of high health risk.

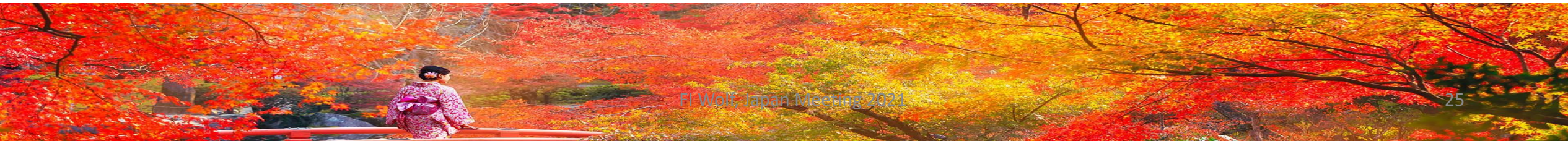


# Conclusion, Recommendation, Consensus



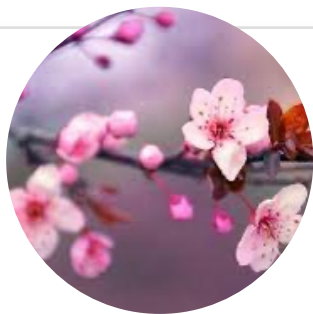
- We propose to increase the lower value for normal serum magnesemia from 0.75 to 0.85 mmol/L.

*Costello R et al. Adv Nutrition, 2016*



# Summary

- SDRM AIMS, HYSTORY AND PROJECTS
- RECENT AGREEMENT ON THE MAGNESIUM GLOBAL NETWORK MaGNet
- ACTIVITIES TO ORGANIZE AND ADVERTISE INTERNATIONAL MAGNESIUM SYMPOSIA AND OTHER SCIENTIFIC MEETINGS
- LATEST PUBLICATIONS:
- MAGNESIUM AND COVID-19
- MAGNESIUM AND POST-COVID DISEASE
- INTERNATIONAL CONSENSUS ON LOW NORMAL MAGNESIUM VALUE
- ***YOU ARE CORDIALLY INVITED TO JOIN OUR GROUPS (SDRM, MaGNet)***



# Acknowledgments

- *Prof. Jean Durlach †*
- **Prof. Andrè Mazur**
- *Dr Yves Rayssiguier*



*Prof Stefano Iotti* – Bologna  
**Prof. Jeanette Maier** –  
Milano



*Dr Juergen Vormann* -  
German Magnesium Society



*Dr Mildred Seeling †*  
*Dr. William B Weglicky*  
**Dr. Andrea Rosanoff**



MaGNet group





## A warm thank to my group:

- **Giuseppe Pietropaolo** PhD
- **Francesca Luongo** post-Doc
- **VALENTINA TRAPANI** Assistant Professor

**Mariapaola Marino MD** Assistant Professor  
**Valentina Petito** Assistant Professor  
**Franco Scaldaferri MD** Associate Professor

*THANK YOU FOR YOUR ATTENTION AND.....*



*Looking forward meeting you in Glasgow*