



DIRECTORATE-GENERAL FOR INTERNAL POLICIES

POLICY DEPARTMENT  
ECONOMIC AND SCIENTIFIC POLICY **A**

Economic and Monetary Affairs

Employment and Social Affairs

**Environment, Public Health  
and Food Safety**

Industry, Research and Energy

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# Autoimmune Diseases – Modern Diseases

Study for the ENVI Committee



**DIRECTORATE GENERAL FOR INTERNAL POLICIES**  
**POLICY DEPARTMENT A: ECONOMIC AND SCIENTIFIC POLICY**

# **WORKSHOP**

## **Autoimmune Diseases – Modern Diseases**

**Brussels, 25 September 2017**

**PROCEEDINGS**

### **Abstract**

This report summarises the presentations and discussions of a workshop on “Autoimmune Diseases – Modern Diseases”, held at the European Parliament in Brussels on Monday 25 September 2017. The aim of the workshop was to provide background and technical information and advice to the members of the ENVI Committee on the latest findings and trends in the field of autoimmune diseases, specifically concerning treatment and prevention of such diseases.

The current state of play of autoimmune diseases in Europe was highlighted during the first part of the workshop. Presentations focused on the public health prospective, and the possible causes of autoimmune diseases.

The second part of the workshop focused on treatment and prevention of autoimmune diseases. This included presentations looking at the situation outside the US, and a focus on the lupus as a case study.

This document was requested by the European Parliament's Committee on Environment, Public Health, and Food Safety.

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## LIST OF ABBREVIATIONS

<b>ADs</b>	Autoimmune Diseases
<b>AARDA</b>	American Autoimmune Related Disease Association
<b>DALY</b>	Disability-adjusted life year
<b>DG EMPL</b>	Directorate General for Employment, Social Affairs, & Inclusion
<b>DG SANTE</b>	Directorate General for Health and Food Safety
<b>EC</b>	European Commission
<b>EEA</b>	European Economic Area
<b>EP</b>	European Parliament
<b>EU</b>	European Union
<b>MEP</b>	Member of European Parliament
<b>MS</b>	Member States
<b>NCDs</b>	Non-communicable diseases
<b>WHO</b>	World Health Organisation

## EXECUTIVE SUMMARY

On 25 September 2017, the European Parliament's Committee on Environment, Public Health and Food Safety (ENVI) held a workshop on "Autoimmune diseases – Modern Diseases". The workshop was hosted by Mr Alojz PETERLE (MEP), Co-Chair of the Health Working Group within the ENVI Committee.

The Chair, Mr Peterle, opened the workshop by highlighting the fact that there has been a significant increase in autoimmune diseases (ADs) diagnosed over the last decade, caused by either genetics or environmental factors; for example, lifestyle choices or pollution. The public health scale of the problem is significant, so a better understanding of ADs, their causes and the relationships between different types is crucial in order to improve their diagnoses, prevention and management.

The first part of the workshop focused on the state of play of autoimmune diseases in Europe. Dr HAYES, Senior Advisor at the World Health Organisation (Brussels) opened the session by outlining autoimmune diseases from a public health perspective. She started by drawing parallels with the battle on non-communicable diseases. She noted how one of these diseases (diabetes) had successfully caught the attention of policy-makers and the United Nations, and went on to introduce some of the actions that were taken as a result. Dr Hayes turned the discussion to autoimmune diseases (specifically musculoskeletal diseases) that have an impact similar to that of cancer on people's life expectancy and quality of life (disability-adjusted life years). She presented several tools and policy actions implemented by the WHO to reduce this condition and outlined the progress made promoting autoimmune diseases in the policy sphere and generally. Dr Hayes finished her presentation by offering some recommendations to further increase policy attention with regard to autoimmune diseases, including the importance of visionary leadership and effective representation, policy cohesion, policy windows, and effective interventions.

Professor LERNER, Senior Scientist at B. Rappaport School of Medicine, Technion-Israel Institute of Technology and Aesku-KIPP Institute, Germany, focused his presentation on the possible triggers of autoimmune diseases. He also noted that the rate of these diseases has increased in recent years and stressed that there are various types of disease that fall into the category of autoimmune diseases. Prof. Lerner highlighted the effects of various impacts on different domains/organs in the body, focusing in particular on intercellular tight junctions. He explained how various foods and drugs affect the microbiome, taking gluten as an example. He also explained the role of horizontal gene transfer, which can be a cause for concern when humans consume foods with bacteria which then transfers genetic material that can trigger an autoimmune disease.

The second part of the workshop focused on the treatment and prevention of autoimmune diseases. Professor BACH, Permanent Honorary Secretary at the Académie des Sciences in Paris, began his presentation by giving an overview of the statistics for the United States of America, noting that for many such diseases, there is a large disparity between the number of male and female patients. He explained that the causes of autoimmune diseases tend to be either environmental or genetic, expanding further on the environmental factors. He noted that globally, autoimmune diseases are more prevalent in developed countries, for reasons including diet, lifestyle, health systems and, notably, hygiene. Prof. Bach finished his presentation by giving an overview of therapy for autoimmune diseases. He noted that immunosuppression therapy has changed drastically in recent decades, monoclonal antibody therapy remains expensive and autoantigen therapy has been showing positive results in recent research.

The final speaker of the afternoon was Ms LERSTRØM, chair of LUPUS EUROPE, who spoke on the prevention and treatment of autoimmune diseases, focusing specifically on lupus. Lupus is a chronic inflammatory disease that can affect many different body systems - including joints, skin, kidneys, blood cells, brain, heart and lungs. She started by introducing the disease, noting that symptoms are different for different people. Next, she discussed some of the common triggers (e.g. sun exposure) experienced by sufferers and the mental impact these can have on the patient. Ms Lerstrøm then explained some of the treatment options, noting that the medications used are similar to those used to treat other autoimmune diseases. She also mentioned the possibility of using biologics, which are expensive yet not effective on all patients. Ms Lerstrøm stressed that with only one new compound developed in more than 50 years, current treatment is simply not good enough. Ms Lerstrøm ended her presentation by reinforcing the role of patient groups, and specifically LUPUS EUROPE.

In his closing remarks, the Chair Mr Peterle thanked the speakers and stressed the importance of a “health in all policies” approach. He noted that more can be achieved by working together and that there are various steps that can/are being taken, particularly with regard to supporting patient organisations.

## EU POLICY CONTEXT

The immune system is a complex network of cells and molecules that work together to protect the body against various diseases<sup>1</sup>. However, in certain circumstances, the immune system may also attack and damage the body's own tissues, organs and cells, resulting in autoimmune diseases (ADs)<sup>2</sup>.

Almost any part of the body can be targeted by the immune system, including the heart, brain, nerves, muscles, skin, eyes, lungs, the digestive tract and blood vessels<sup>3</sup>. A broad range of ADs exist given that they vary according to the part of the body that is being targeted by the immune system. Common ADs include rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, psoriasis, and celiac diseases<sup>4</sup>. The symptoms that AD patients develop are wide-ranging, making it extremely complex for physicians to make a diagnosis. Moreover, ADs are typically treated by different specialists depending on the organ involved rather than as a group as such<sup>5</sup>.

Only 67 ADs had been identified by 1992<sup>6</sup>, but the number of discoveries is increasing rapidly<sup>7</sup>. To date, the American Autoimmune Related Disease Association (AARDA) has classified more than 100 ADs<sup>8</sup>, making it the third most common type of disease in the United States<sup>9</sup>. In fact, ADs affect 5 to 10% of the global population, particularly women, who are two to ten times more likely to suffer from an AD than men<sup>10</sup>. Some of the ADs are within the top 10 leading causes of death among women aged 65 and older<sup>11</sup>.

While AD symptoms can be treated – generally by reducing immune system activity -, there is currently no cure for autoimmunity<sup>12</sup>, which results in great direct and indirect costs for society. According to the AARDA, if all the 100 ADs discovered to date were considered together, the estimated cost to society would range from 80 to 100 billion dollars<sup>13</sup>. Furthermore, the causes triggering ADs are currently unknown. A publication issued by the World Health Organization (WHO) in 2006 pointed out that: '*[a]utoimmune diseases are multifactorial. Both intrinsic factors (e.g. genetics, hormones, age) and environmental factors (e.g. infections, diet, drugs, environmental chemicals) may*

<sup>1</sup> Parker J & Parker P, 2002, 'The official patient's sourcebook on autoimmune diseases', Tiffany LaRoche.

<sup>2</sup> Nature.com, official webpage, available at: <https://www.nature.com/subjects/autoimmune-diseases> (accessed July 2017).

<sup>3</sup> Scanlin A., 2014, 'Autoimmune Diseases: The Growing Impact', *BioSupply Trends Quarterly*, available at: [http://www.bstquarterly.com/Assets/downloads/BSTQ/Articles/BSTQ\\_2014-04\\_AR\\_Autoimmune-Disease-The-Growing-Impact.pdf](http://www.bstquarterly.com/Assets/downloads/BSTQ/Articles/BSTQ_2014-04_AR_Autoimmune-Disease-The-Growing-Impact.pdf) (accessed July 2017).

<sup>4</sup> Parker J & Parker P, 2002, 'The official patient's sourcebook on autoimmune diseases', Tiffany LaRoche.

<sup>5</sup> Cooper G., et al., 2009, 'Recent Insights in the Epidemiology of Autoimmune Diseases: Improved Prevalence Estimates and Understanding of Clustering of Diseases', *Journal of Autoimmunity*, 33(3-4), 197–207, available at: <http://doi.org/10.1016/j.jaut.2009.09.008> (accessed July 2017).

<sup>6</sup> AARDA, 2010, Comprehensive Report on the Global State of Autoimmune Diseases, available at: <https://www.aarda.org/> (accessed July 2017).

<sup>7</sup> Lerner A, et al., 2015 'The World Incidence and Prevalence of Autoimmune Diseases is Increasing', *International Journal of Celiac Disease*, 3(4), 151-155, available at: <http://pubs.sciepub.com/ijcd/3/4/8/#> (accessed July 2017).

<sup>8</sup> AARDA, official webpage, available at: <https://www.aarda.org/diseaselist/> (accessed July 2017).

<sup>9</sup> Rubtsova K., et al., 2017, 'B cells expressing the transcription factor T-bet drive lupus-like autoimmunity', *Journal of Clinical Investigation*, 127 (4), available at: <https://www.jci.org/articles/view/91250> (accessed July 2017).

<sup>10</sup> National Jewish Health, May 2017, 'Trigger for autoimmune disease identified: Newly identified cells help explain why women suffer autoimmune disease more often', *ScienceDaily*, available at: [www.sciencedaily.com/releases/2017/05/170510174845.htm](http://www.sciencedaily.com/releases/2017/05/170510174845.htm) (accessed July 2017).

<sup>11</sup> AARDA, official webpage, 'Women & Autoimmunity', available at: <https://www.aarda.org/who-we-help/patients/women-and-autoimmunity/> (accessed July 2017).

<sup>12</sup> Rubtsova K., et al., 2017, 'B cells expressing the transcription factor T-bet drive lupus-like autoimmunity', *Journal of Clinical Investigation*, 127 (4), available at: <https://www.jci.org/articles/view/91250> (accessed July 2017).

<sup>13</sup> AARDA, 2011, 'New Report on Economic Burden of Autoimmune Disease', available at: <https://www.aarda.org/> (accessed July 2017).

contribute to the induction, development, and progression of autoimmune diseases'<sup>14</sup>. With regard to genetics, research has demonstrated that people who have a genetic predisposition to ADs, have a two to five-times higher risk of developing them compared to the general population<sup>15</sup>.

Despite the public health scale of the problem, the unknown aetiology of ADs, the difficulties involved in diagnosing them, the heavy costs to society and the unavailability of cures, scientific research has concentrated on only a few of the more than 100 known ADs<sup>16</sup>. Moreover, ADs are studied and treated differently depending on the organ affected due to the considerable variation in their causes and health effects. This situation also negatively impacts the funding allocated to research on autoimmunity. In fact, so long as ADs are not studied as a group, and are considered instead under a common umbrella category, funding will primarily be channelled to specific ADs while all-encompassing research efforts will be more limited<sup>17</sup>.

While the knowledge on autoimmune diseases is expanding rapidly, a better understanding of ADs, their causes, and the relationships between different types, has been deemed to be crucial in order to improve their diagnosis, prevention and management. There is, therefore, a need to encourage and finance crossover research in order to better understand the relationships between the different ADs and the different causes that may trigger them, which span from UVB radiation, dietary factors, stress, exposure to certain chemicals (e.g. quartz and solvents) and vitamin D deficiency<sup>18</sup>. Furthermore, scientific literature has pinpointed the importance of studying ADs under a common research umbrella and to increase research efforts to identify new treatments<sup>19</sup>. Finally, given the magnitude of the problems, together with the significant differences between Member States concerning how best to address and categorise these diseases, the EU can adopt an important coordination- and awareness-raising role and can prioritise the issue on the health policy agenda.

<sup>14</sup> WHO, 2006, 'Environmental health criteria on principles and methods for assessing autoimmunity associated with exposure to chemicals', *WHO Press*, Geneva, available at: <http://www.inchem.org/documents/ehc/ehc/ehc236.pdf> (accessed July 2017).

<sup>15</sup> Scanlin A., 2014, 'Autoimmune Diseases: The Growing Impact', *BioSupply Trends Quarterly*, available at: [http://www.bstquarterly.com/Assets/downloads/BSTQ/Articles/BSTQ\\_2014-04\\_AR\\_Autoimmune-Disease-The-Growing-Impact.pdf](http://www.bstquarterly.com/Assets/downloads/BSTQ/Articles/BSTQ_2014-04_AR_Autoimmune-Disease-The-Growing-Impact.pdf) (accessed July 2017).

<sup>16</sup> Scanlin A., 2014, 'Autoimmune Diseases: The Growing Impact', *BioSupply Trends Quarterly*, available at: [http://www.bstquarterly.com/Assets/downloads/BSTQ/Articles/BSTQ\\_2014-04\\_AR\\_Autoimmune-Disease-The-Growing-Impact.pdf](http://www.bstquarterly.com/Assets/downloads/BSTQ/Articles/BSTQ_2014-04_AR_Autoimmune-Disease-The-Growing-Impact.pdf) (accessed July 2017).

<sup>17</sup> Scanlin A., 2014, 'Autoimmune Diseases: The Growing Impact', *BioSupply Trends Quarterly*, available at: [http://www.bstquarterly.com/Assets/downloads/BSTQ/Articles/BSTQ\\_2014-04\\_AR\\_Autoimmune-Disease-The-Growing-Impact.pdf](http://www.bstquarterly.com/Assets/downloads/BSTQ/Articles/BSTQ_2014-04_AR_Autoimmune-Disease-The-Growing-Impact.pdf) (accessed July 2017).

<sup>18</sup> WHO, 2006, 'Environmental health criteria on principles and methods for assessing autoimmunity associated with exposure to chemicals', *WHO Press*, Geneva, available at: <http://www.inchem.org/documents/ehc/ehc/ehc236.pdf> (accessed July 2017).

<sup>19</sup> Cooper G., et al., 2009, 'Recent Insights in the Epidemiology of Autoimmune Diseases: Improved Prevalence Estimates and Understanding of Clustering of Diseases', *Journal of Autoimmunity*, 33(3-4), 197–207, available at: <http://doi.org/10.1016/j.jaut.2009.09.008> (accessed July 2017).

## PROCEEDINGS OF THE WORKSHOP

### 1.1. Introduction

#### 1.1.1. Welcome and opening

MEP Mr Alojz PETERLE, Co-Chair, ENVI Health Working Group

Mr Alojz PETERLE, MEP, opened the workshop by welcoming those in attendance. He stated that autoimmune diseases (ADs) are one of the most challenging types of diseases, which have increased significantly over the last decades. He noted that he was most pleased that the health working group in the ENVI committee was discussing the importance of autoimmune diseases.

Mr Peterle then gave some background on the situation of ADs over recent years, noting that although the exact cause is unknown, both environmental and genetic factors can trigger such diseases. With different symptoms which can change over time, these diseases are difficult to diagnose and are often subject to treatments aimed only at managing symptoms, rather than curing the disease. In addition, the range of symptoms means a range of specialists are needed to treat them, and thus there needs to be enhanced collaboration between these specialists. Mr Peterle noted that this workshop embodies that spirit, bringing together distinguished guests from various fields.

Mr Peterle then gave the floor to the first speaker.

### 1.2. Part I: The Current State of Play Of Autoimmune Diseases in Europe

#### 1.2.1. Autoimmune diseases: a public health perspective

Dr Luminita Silvia HAYES, Senior Advisor, World Health Organisation (WHO), Office at the European Union

Dr Luminita Silvia HAYES began her presentation by introducing the question: 'how can we make autoimmune diseases more visible to policy makers nationally and globally?'. Dr Hayes used non-communicable diseases (NCDs) to set the scene, noting that this group of diseases has attracted the attention of policy makers in the last decades. Prior to 2011, these diseases, cardiovascular disease, diabetes, cancer, and chronic respiratory diseases, had at least one strong civil society advocate, working largely independently from each other. Through significant resource and stakeholder mobilisation, the group representing diabetes managed to get a resolution passed at the United Nations General Assembly in 2007, establishing a World Diabetes Day. This, Dr Hayes said, was a worthwhile prize and is still a rallying cry for the field.

In 2011, the groups representing these four groups of diseases - cardiovascular disease, diabetes, cancer, and chronic respiratory diseases - came together to realise that their interest lay not only with getting commemorative days, but instead in reaching Heads of State and working towards a goal of health in all policies. This resulted in the United Nations Declaration on NCDs. Stakeholders behind this initiative are looking forward to the third high-level meeting in 2018. In addition, high level targets have been developed, as part of the Sustainable Development Goals, and in Europe, they represent one of the four pillars in the public health framework, Health 2020.

NCD mortality is generally on the decline in all European countries, although gender gaps exist, as do differences in health systems. The persistent inequity can in part be attributed to research not being undertaken to identify new public health interventions. Dr Hayes then introduced a score card that is part of the Global Monitoring Framework Scoreboard for Europe. It asks the question, in a business-as-usual scenario, how likely are the nine NCD-related targets of the global monitoring framework to be achieved by 2025? Dr Hayes pointed out that only two targets are on course to being reached with regard to overall mortality from cardiovascular diseases (and other NCDs) and to elevated blood-pressure. Three important targets scored poorly, related to tobacco and alcohol consumption, and obesity, and these three targets will almost certainly not reach their targets, despite their wide-scale nature and the large-scale coalitions working in their favour. This demonstrates, Dr Hayes concluded, that countries need to put more effort into actions supporting their policies.

Dr Hayes then switched the focus of her presentation back to ADs. Similar to the role diabetes played as a front-runner for NCDs, Dr Hayes named Psoriasis as the front-runner for ADs. This disease has been recognised by the World Health Assembly<sup>20</sup> as a public health problem of note. A resolution has directed that the WHO should produce a regulatory vote on the subject. This, Dr Hayes said, is a great achievement; however, it cannot be considered a sustainable model. Psoriasis is only one of many, many recognised ADs. It is inconceivable to imagine that more than a small fraction of them will be recognised in the same way. It thus makes more sense to determine the commonalities and the public health concerns related to all or most of these diseases. Attention and resources should focus on governance, surveillance, prevention, and health services, as was done in the case of the NCDs.

Dr Hayes noted that there some considerations for the public health issues, specific to ADs, which must be taken into account. They revolve around the current amount of data available, which is insufficient. They tend to focus on only a small number of ADs, and tend to be limited to industrialised countries. In addition, they are limited in the age, and timing of exposure, and more information is needed on the correlation between race and ethnicity to separate genetic from environmental causes.

From the public health perspective, the implications concern the expensive and life-long treatment often needed by those affected by ADs, gender equity (with many autoimmune diseases disproportionately affecting women), and environmental factors.

Dr Hayes then drew the lessons together to draw attention to three important areas where joint action could make a big difference: surveillance, health systems, and research. She then expanded on this further using musculoskeletal conditions as an example. Dr Hayes noted that this is an area of significance for two reasons: many ADs have musculoskeletal manifestations, and in this area, many developments have been made through joint action. Taken together, they account for a large number of DALYs lost annually (Disability-adjusted life year), with figures comparable to mental health or cancer, thus making it a serious problem.

Dr Hayes noted that one of the approaches to prevention of musculoskeletal conditions is to recognise the common risk factors, especially the behavioural risk factors, that are common to the NCDs. Population-based prevention on these risk factors helps both the NCDs and musculoskeletal conditions. In the case of ADs, such risks need to be identified and managed.

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<sup>20</sup> [http://apps.who.int/gb/ebwha/pdf\\_files/WHA67/A67\\_R9-en.pdf](http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R9-en.pdf)



Dr Hayes noted that population preventive methods also have an economic dimension. For example, for musculoskeletal conditions, it is known that physical activity can lead to improved mobility. She referenced the Health Economic Assessment Tools (HEAT) used by countries to assess the cost-effectiveness of environmental policies to promote walking and cycling<sup>21</sup>, and the Strategy and Action Plan for Healthy Ageing in Europe 2012-2020<sup>22</sup>, noting that such tools will be used by policy makers. She also spoke about People-Centred Health Systems, a framework adopted by WHO Europe. The main aspects include: empowering and engaging people, strengthening governance and accountability, reorienting the model of care, and coordination services within and across sectors.

Dr Hayes presented an example of a unified public health approach to musculoskeletal health, developed by Arthritis Research UK<sup>23</sup>. A model for advocates and scientists hoping to raise policy awareness for autoimmune disease, especially since the overlaps between musculoskeletal conditions and ADs mean that much of the framework is already provided. She also referred the audience to a 2007 paper by Shiffman and Smith on the setting of global health priorities<sup>24</sup>. The paper lists factors likely to foster policy attention and investment. Dr Haye wondered how this list could relate to autoimmune diseases – is there already policy cohesion? Are there visionary leaders and guiding institutions? Are there key messages? What are the policy windows? This last point, Dr Haye suggested, should be the start of further discussions.

#### 1.2.2. An overview of possible causes triggering autoimmune diseases

Prof. Aaron LERNER, senior Scientist, B. Rappaport School of Medicine, Technion-Israel Institute of Technology and Aesku-KIPP Institute, Wendelsheim, Germany

Prof LERNER, who is a trained gastroenterologist and nutritionist, spoke about the possible causes of ADs. He focused the presentation on this field. Prof Lerner began by noting that instances of ADs have increased tremendously, up to 9% per year for some diseases<sup>25</sup>. He then went on to give an overview of the dysbiotic effects contributing to such diseases – ranging from systemic effects, to effects on the skin, heart, liver, etc. – which are seen in many autoimmune diseases. Prof. Lerner noted that the microbiome (the genomes of the bacteria, fungi, archaea, and viruses that live inside us, in this case, the intestines) produces various molecules, which can have both adverse and advantageous consequences. He presented several examples of advantageous consequences, including those that provide energy or fight pathogens, but also examples of those that produce toxins or promote cancer. Prof. Lerner also explained how a normal protein can be changed in such a way that the body's immune system no longer recognises it, and treats it instead as foreign protein – which may be a first step towards an AD.

Prof. Lerner elaborated on this further, using the tight junction. This is a complex mechanism between two cells whose membranes join, stopping toxins from entering the body. Prof Lerner highlighted several environmental factors from pathogens to nutrients to lifestyle factors which can either breach the tight junction integrity, or increase intestinal permeability. He noted that there is a large body of research on this, including research on

<sup>21</sup> <http://www.euro.who.int/en/publications/abstracts/health-economic-assessment-tools-heat-for-walking-and-for-cycling.-methodology-and-user-guide.-economic-assessment-of-transport-infrastructure-and-policies.-2014-update>

<sup>22</sup> [http://www.euro.who.int/\\_data/assets/pdf\\_file/0008/175544/RC62wd10Rev1-Eng.pdf](http://www.euro.who.int/_data/assets/pdf_file/0008/175544/RC62wd10Rev1-Eng.pdf)

<sup>23</sup> <http://www.arthritisresearchuk.org/~media/Files/Policy%20files/2014/public-health-guide.ashx>

<sup>24</sup> Shiffman, J., & Smith, S. (2007). Generation of political priority for global health initiatives: a framework and case study of maternal mortality. *The Lancet*, 370(9595), 1370-1379.

<sup>25</sup> Lerner, A., Jeremias, P., & Matthias, T. (2015). The world incidence and prevalence of autoimmune diseases is increasing. *International Journal of Celiac Disease*, 3(4), 151-155.

progress<sup>26</sup>. In this study, it found that a lot of nutrients can impact the tight junction integrity, leading to things like 'leaky gut'<sup>27</sup>, either adversely or advantageously. If the adverse effects outweigh the advantageous ones, this could be a step towards the development of an AD.

Prof. Lerner then turned to the possible environmental factors leading to the development of an AD, noting that the microbiome can be affected by many different factors. He listed several factors, from diet and food additives to mode of delivery (C-section vs natural delivery) to hygiene to age, all affecting intestinal permeability. He also referred the audience to a publication<sup>28</sup> looking at seven food additives responsible for increasing numbers of ADs, noting that, for example, nanotechnology can result in a significant increase in such diseases.

Prof. Lerner then expanded further on gluten. He presented an overview of how gluten affects gut events, and the microbiome. He noted that there were a lot of immune effects, including stimulation of well-known pathways for autoimmunity. He singled out an enzyme which is heavily consumed, which can drive autoimmunity, especially with regard to Celiac disease. Prof. Lerner outlined a study<sup>29</sup> which looked at how a celiac patient reacts to this enzyme, found very often as a food additive. He noted that wheat eaten in previous times, was only 10% of gliadin proteins, compared to the gluten consumed today which is 80%, making it much more immunogenic.

Prof. Lerner spoke about bacteria, and horizontal gene transfer. For humans, genetic transfer is vertical, but for bacteria, genes can be transferred horizontally. If bacteria survive in a difficult situation and produce certain proteins, this genetic material can be transferred to other bacteria, resulting in large populations creating these proteins. This becomes an issue given the extensive use of probiotics used by the food industry. This means there are virulent genes, such as antibiotic resistance, in the probiotics, which are transferred to our microbiome. He noted that this has only been happening for the last 20-40 years, but there are various ways this can happen, from genetically manipulated bacteria/viruses to synthetic biology/'living pills', and the result is chronic modern human diseases.

Prof. Lerner finished by summarising the different gut events, and showing how various diseases are all impacted by these gut events, including celiac disease, psoriasis, depression, asthma, cirrhosis.

### 1.2.3. Questions & Answers

After the conclusion of Prof. Lerner's presentation, Mr Peterle commented on how important it is for legislators to understand the technical side to such problems. He then opened the floor for questions.

Dr Madan THANGAVELU (European Ayurveda Association) took the floor to comment that specialists, who have spent three to four decades in the field, find the sheer volume of new data difficult to comprehend. He noted that the biome itself is vast and ever-changing, and referred back to the ancient science for guidance, especially with regard to gluten. Dr

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<sup>26</sup> Environmental factors that breach TJ integrity and increase intestinal permeability. Submitted, Microorganisms, 2017

<sup>27</sup> Leaky gut, also known as intestinal permeability, causes undigested food particles, toxic waste products and bacteria to leak into the blood stream.

<sup>28</sup> Lerner, A., & Matthias, T. (2015). Changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of autoimmune disease. *Autoimmunity reviews*, 14(6), 479-489.

<sup>29</sup> Matthias, T., Jeremias, P., Neidhöfer, S., & Lerner, A. (2016). The industrial food additive, microbial transglutaminase, mimics tissue transglutaminase and is immunogenic in celiac disease patients. *Autoimmunity reviews*, 15(12), 1111-1119.

Thangavelu noted that it specifically states in text that grain should be kept for at least one season before being consumed. More current research in India shows that for many celiac sufferers, when put on a diet of aged grain (of older varieties), the disease disappears. He finished by asking whether legislators should stop to consider such issues.

Prof. Lerner took the floor to respond, noting that in India changes in consumption have increased incidences of celiac disease. However, Prof Lerner noted that there are a lot of new strategies to combat the disease, including manipulating the genes of the wheat, or taking ancient grain for re-cultivation. In the case of the latter, this proved very expensive, and in the former, Prof. Lerner noted that there are 22,000 types of wheat.

Prof. BACH also echoed the issue of asking legislators to consider such vast quantities of research some of which is contradictory. The legislator thus has to form an opinion on the major issues of public health. One way to do so is to ask major bodies (academies, societies) to provide a report about the opinion on a given topic, and, in Prof. Bach's experience, this will be a fair representation of the current debate on the topic.

Dr Hayes raised the issue of how to bring together the scientific community, with its vast amount of data and the policy-makers. She noted that, a Ministry of Health, for example will not read the data, and instead want to know if the issue is a problem for their country, how much does it cost (and also the cost of inaction), and what should be done. It is up to the scientific community to make the data digestible – and one way to do this is to look for commonalities. For example, many autoimmune diseases can be grouped together, because they are so similar.

Ms Kirsten LERSTRØM added to this by noting that often the perspective of those living with such diseases is missing.

### **1.3. Part II: Treatment and prevention of autoimmune diseases**

#### **1.3.1. Tackling autoimmune diseases: a US perspective**

Prof. Jean-Francois BACH, Permanent Honorary Secretary, Académie des sciences, France

Prof. BACH started his presentation by stressing that it is important to distinguish between autoimmunity, which is a physiological situation where the immune system responds to certain antigens of the host, from AD, which is a pathological situation where diseases are caused or significantly promoted by the autoimmune systems.

In his next slide Prof. Bach showed that ADs are very common in the United States, currently affecting 14.7 to 23.5 million people. Moreover, he highlighted that ADs are among the leading causes of mortality among women under 65 years old. He also underlined that when patients do not die, they suffer throughout their life as a result of the diseases in question, facing major handicaps and being subjected to life-long treatments.

Prof. Bach then described that main problem of ADs is that they are difficult to be diagnosed as they are not specifically symptomatic. In fact, he continued, the immune system can affect almost any organs of the human body, thus triggering a wide range of ADs, each of them encompassing various symptoms that are therefore difficult to be diagnosed by general practitioners.

Next, Prof Bach commented on a slide outlining the top-10 ADs in the United States and the percentages of people affected. Among the most common ADs there are: graves' diseases, rheumatoid arthritis and hashimoto's thyroiditis. In the slide in question Prof. Bach also highlighted that the ADs affect more women than men. In this latter regard, he

stressed that for certain diseases, e.g. lupus, for every ten people affected, only 1 is a man. Nevertheless, Prof. Bach also emphasised that ADs do not affect only women, although their prevalence is higher. And in order to prove his affirmation he gave the example of diabetes mellitus which affects mostly men.

Prof. Bach then briefly explained why women tend to suffer more than men from ADs. In particular, he observed that male hormones, androgens, have the capacity to slow down autoimmune reactions. Consequently, women are more prone to develop ADs due to the lack of androgens. He also explained that in this respect diabetes is an exception, because it starts very early in life and during childhood there is no acute difference in sex hormones between boys and girls.

Prof. Bach then showed statistics indicating that ADs' incidence is doubling every 20 years globally and explained the possible causes of the diseases in question. According to him, ADs are triggered by both environmental and genetic factors. With regard to the genetic aspect, he mentioned that ADs can be inherited, a factor that increases the risks for family members. Furthermore, he stated that in the case of Graves' disease there is an increased risk also for spouses.

Prof. Bach also spoke about the existence of certain genes which predispose to autoimmunity. He mentioned a study which demonstrated that some of the genes in question are shared by several ADs. This data, he remarked, is of utmost importance as it suggests that different ADs share similar mechanisms (to some extent), and, as such, can be treated with similar therapies<sup>30</sup>.

As for the environmental factors, Prof. Bach mentioned one study published in 2002 demonstrating that the decline of infectious diseases caused or contributed to the rise of ADs<sup>31</sup>. From the point of distribution of ADs and infectious diseases in the world, he noted that multiple sclerosis and diabetes – two of the most prototypic ADs – are far more present in the north part of the globe, e.g. the US and northern Europe; whereas tuberculosis and hepatitis A – two of the most prototypic infectious diseases – are more present in the southern part of the world, e.g. Africa. In this respect, Prof. Bach stated that ADs are more common in developed countries. He also mentioned a theory according to which the level of hygiene and sanitary conditions (e.g. drinking water, food, housing conditions, etc.) in a given country might have an impact on the development of ADs.

Prof. Bach concluded his talk by explaining the possible therapies for ADs. In the 1970s, he noted, the main treatment was immunosuppression which, however, could cause the death of the patients. Nowadays, however, the majority of ADs are treated with monoclonal antibody therapies. Yet, these therapies are particularly expensive and thus not affordable by the majority of patients. The challenge for policymakers, he emphasised, is to make these therapies available for all. Finally, Prof. Bach stressed that recent research suggests that autoantigen might be an effective way to treat ADs.

### 1.3.2. Prevention and treatment of autoimmune diseases: the case of Lupus

Ms Kirsten LERSTRØM, Chair of LUPUS EUROPE

Ms Kirsten LERSTRØM started her speech by presenting LUPUS EUROPE: a patient led umbrella organisation of national lupus patients' groups established in 1989. She added

<sup>30</sup> Fortune MD, et al., 2015, 'Statistical colocalization of genetic risk variants for related autoimmune diseases in the context of common controls', *Nat. Genet.*, 47, available at: <https://www.ncbi.nlm.nih.gov/pubmed/26053495?dopt=Abstract&holding=npg> (accessed October 2017).

<sup>31</sup> Bach, JF, 2002, 'The effect of infections on susceptibility to autoimmune and allergic diseases', *N Engl J Med*, available at: <http://www.nejm.org/doi/full/10.1056/NEJMra020100> (accessed October 2017).

that LUPUS EUROPE encompasses 26 national lupus groups, each one of those including between 10 to 6,000 members. Ms Lerstrøm stressed that LUPUS EUROPE is a charity registered in the UK which operates on funds from various sources, such as membership fees, donations, project partnerships, pharmaceutical sponsorships and others, e.g. support for general operations and specific projects. Moreover, she emphasised that the LUPUS EUROPE Board of Trustees is elected to office and serve on a voluntary basis and without personal honorarium.

Ms Lerstrøm stated that the European League Against Rheumatism (EULAR) estimated that in Europe there are approximately 500,000 people diagnosed with Lupus<sup>32</sup>.

Ms Lerstrøm then gave an outline of lupus, a complex disease which attacks the connective tissues. As such, almost any organs and body systems can be affected by this disease. Furthermore, Ms Lerstrøm observed that out of 10 people suffering from lupus, 9 are women. She also emphasised that the time to diagnose Lupus is on average 7 years, while the average diagnosed age is 37 years old. According to Ms Lerstrøm, these data show that people are diagnosed only after having suffered for a long period from the disease.

Ms Lerstrøm also explained that lupus is chronic, lifelong and usually emerges during childhood. As for the consequences, she noted that some people may experience one flare, whereas others cannot be exposed to sunlight. Many, as a consequence, also experience mental issues.

Ms Lerstrøm explained that the causes which can trigger the lupus disease might be genetic or environmental. As for the genetic factors, there are some people who have certain genes which might predispose them to having lupus. However, sometimes these genes are not triggered and thus the person in question never develops lupus. With regard to the environmental factors, Ms Lerstrøm mentioned that smoking, exercise and diet have indeed a strong impact on the possible development of the disease.

As far as the therapies are concerned, Ms Lerstrøm specified that there are some treatments available, but they do not cover all the symptoms' spectrum of the disease. She stated that stopping smoking, following a healthy diet, exercise, and following treatment plans may help the patients. Among the available treatment options for lupus she mentioned prednisolone and anti-malarials (hydroxychloroquine). However, she stressed that these medications also have some disadvantages. For instance, prednisolone creates dependency and is not available in all countries. Ms Lerstrøm also stated that if these treatments are not efficient, further immunosuppressives can be used, spanning from methotrexate (mild chemo) to azathioprine, from cyclosporine to mycophenolate mofetil. However, these treatments are expensive and therefore not affordable for the majority of the population.

With regard to the biologics used for lupus treatments, Ms Lerstrøm mentioned that rituximab, infliximab, etanercept, adalimumab and belimumab have been used, but with scarce success. In addition, the compounds approved for lupus treatments – anti-malarials, prednisolone and belimumab – do not work for all patients. Nowadays, she emphasised, there are more than 100 clinical studies ongoing, but so far only belimumab has passed phase II<sup>33</sup>.

Ms Lerstrøm stressed the importance of finding an effective treatment for Lupus, as almost half of the employees leave their jobs within a few years after being diagnosed<sup>34</sup>. For those

<sup>32</sup> EULAR, official webpage, available at: <https://www.eular.org/> (accessed October 2017).

<sup>33</sup> ClinicalTrials.gov, official webpage, available at: <https://clinicaltrials.gov/> (accessed October 2017).

<sup>34</sup> Gordon C et al, 2013, 'The substantial burden of systemic lupus erythematosus on the productivity and careers of patients: a European patient-driven online survey', *Rheumatology (Oxford)*, available at: <https://www.ncbi.nlm.nih.gov/pubmed/24049101> (accessed October 2017).

who remained employed, she observed, they only work at a reduced level. Given the above, Ms Lerstrøm recalled the importance to do better to treat lupus. Among the things that LUPUS EUROPE can do is to support those who have been diagnosed, give them the appropriate information on how to deal with the disease, as well as establish a dialogue with both researchers and policymakers.

Ms Lerstrøm also explained the actions which are urgently needed. In particular, changing the procedures to admit compounds, as well as creating partnership with the European Reference Network ReCONNET: a newly established network of specialist centres in Europe of nationally endorsed experts in rheumatic complex and rare connective tissue diseases.

### 1.3.3. Questions & Answers

Mr Peterle opened the floor for discussion.

Mr Madan THANGAVELU (European Ayurveda Association) remarked the importance of looking at the issue as a part of one health agenda. He also asked how to start an ongoing dialogue on ADs involving all the relevant actors, such as policymakers, patients, patient groups, international organisations, etc. He also underlined the importance for the WHO to collect better quality data.

Ms Lerstrøm reacted to Mr Thangavelu's comment stressing that ADs usually involve several organs. As such, it is difficult for specialist doctors to diagnose and treat them due to their cross-cutting nature. Consequently, she commented on the importance of establishing a holistic dialogue on this matter.

Mr Thangavelu replied to Ms Lerstrøm by emphasising the importance of making connections between the pure disease aspect and the mental issues that the disease might bring. In this regard, he observed that there is currently no policy discussion on the benefits of meditation to treat the mental disorders linked to chronic diseases. He also stressed the importance to see 'health in all policies'<sup>35</sup>.

Dr Hayes reacted to the last comment of Mr Thangavelu by underlining that 'health in all policies' is indeed one of the most important EU health initiatives. According to Dr Hayes it is in fact impossible to address ADs without tackling cross-cutting factors related to other policy areas, such as drinking water, pollution, housing conditions, which might be responsible causes for triggering ADs. In this regard, she stressed the importance for policymakers to take cross-sectoral decisions in line with the 'health in all policies' programme.

### 1.3.4. Closing remarks by the Chair

Mr Peterle thanked the speakers for their contributions and for sharing their knowledge on the topic. He remarked that on this matter is particularly important to establish a constant dialogue involving all the relevant players – as nobody alone can make progress on ADs. He also stressed that a certain degree of 'institutional osmosis' is necessary in order to tackle ADs effectively. The process should involve the European Parliament, the European Council, the European Commission, the WHO and all the relevant NGOs. Mr Peterle also underlined that certain soft measures can help in making progress on the matter, for instance sharing best practices and research results between Member States, developing health projects, as well as issuing non-binding recommendations, guidelines and code of conducts. Finally, Mr Peterle emphasised the importance of the role of patient's organisations in the prevention of ADs. He concluded by stating that the workshop itself was an expression of one unique health agenda.

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<sup>35</sup> European Commission, Directorate General for Health and Food Safety, official website, 'Health in all policies', available at: [https://ec.europa.eu/health/health\\_policies/policy\\_en](https://ec.europa.eu/health/health_policies/policy_en) (accessed October 201).



## ANNEX 1: PROGRAMME

# Autoimmune Diseases – Modern Diseases

Monday 25 September 2017 from 16.00 to 18.00  
European Parliament, Room A3G-2 in Altiero Spinelli, Brussels

### AGENDA

**Chair: Mr Alojz PETERLE (MEP)**

**16:00 – 16:10      Opening and welcome by the chair Mr Alojz PETERLE (MEP)**

#### **Part 1 – The current state of play of autoimmune diseases in Europe**

**16:10 - 16:25      Autoimmune diseases: a public health perspective**  
Dr Luminita Silvia HAYES, Senior Advisor, World Health Organisation (WHO), Office at the European Union

**16:25 - 16:40      An overview of possible causes triggering autoimmune diseases**  
Prof Aaron LERNER, Senior Scientist, B. Rappaport School of Medicine, Technion-Israel Institute of Technology and Aesku-KIPP Institute, Wendelsheim, Germany

**16:40 - 17:00      Questions & Answers**

#### **Part 2 – Treatment and prevention of autoimmune diseases**

**17:00 – 17:15      Tackling autoimmune diseases: a US perspective**  
Prof Jean-Francois BACH, Permanent Honorary Secretary, Académie des sciences, France

**17:15 – 17:30      Prevention and treatment of autoimmune diseases: the case of lupus**  
Ms Kirsten LERSTRØM, Chair of LUPUS EUROPE

**17:30 – 17:50      Questions & Answers**

**17:50 – 18:00      Closing remarks by the co-chair Mr Alojz PETERLE (MEP)**

## ANNEX 2: SHORT BIOGRAPHIES OF EXPERTS

**Dr Luminita Silvia HAYES**, Senior Advisor, World Health Organisation (WHO), Office at the European Union

Dr Luminita Hayes is a Senior Advisor in the World Health Organization (WHO) Office to the European Union, based in Brussels, working directly as part of the WHO Regional Office for Europe but also with a global mandate. She is a Medical Doctor specialised in public health, with 20+ years' experience. Dr Hayes holds a Master degree in Management of Social and Health Services. Previously, she worked for the Government of Romania - Ministry of Health and Ministry of Integration to EU – among others, representing the country to international organisations, including to the WHO and the European Commission. For the last 10 years she worked as a Medical Officer in the WHO headquarters in Geneva, within the department responsible for global prevention of non-communicable diseases and mental health.

**Prof Aaron Lerner**, Senior Scientist, B. Rappaport School of Medicine, Technion-Israel Institute of Technology and Aesku-KIPP Institute, Wendelsheim, Germany

After receiving his MD from the Sakler school of medicine, Tel-Aviv University (1976), Professor Lerner specialised in Paediatrics (1982), Paediatric Gastroenterology and Nutrition (1984) and Adult Gastroenterology (1987). He took several senior positions as head of Department of paediatrics (1995-2005) and head of Paediatric Gastroenterology and Nutrition unit, at the Carmel Medical Center, Haifa, Israel. After finishing his Medical Management degree M.H.A. in 1999, he spent research sabbaticals in Hahnemann University, Philadelphia, PA, USA (1991), State University of North Carolina, Chapel Hill, N.C, U.S.A (2005) and currently, involved in scientific projects in Aesku.Kipp Institute, Wendelsheim, Germany (2014-17).

His main research areas are: pathogenesis, diagnosis and treatment of systemic ADs in particular gastrointestinal conditions, environmental inducers of ADs, micro/dysbiosis and the place of post-translational modification of protein in ADs induction, new serological marker of celiac disease (anti-microbial and anti neo microbial transglutaminase in 2014-7), Industrial food processing additive that breach tight-junction integrity, the multi gut-remote organs' axes in systemic autoimmunity, non-celiac side effects of gluten, Horizontal gene transfer in human gut and gut-brain axis. Prof. Lerner presented in numerous international congresses, mainly of paediatrics, nutrition and autoimmunity, published 270 manuscripts in peer reviewed journals and is on the editorial board of 20 international journals.

**Prof Jean-Francois BACH**, Permanent Honorary Secretary, Académie des sciences

The scientific career of Prof. Bach encompassed different areas. One main focus has been autoimmune disorders, investigated from the three different perspectives of mechanisms, treatment and public health. His mechanistic studies have focused on:

- insulin-dependent diabetes, an auto-immune disease associated with the destruction by T-cells of the insulin-producing  $\beta$ -cells of the islets of Langerhans. Using an animal model which spontaneously develops this disease, the non-obese diabetic (NOD) mouse, the group has shown, as early as 1987, the direct role of the two T-cell subpopulations, CD4 and CD8, in the pathogenesis of the disease (J Exp Med. 1987;166:823-32). They were also the first to show, in 1989, the importance of regulatory T-cells in controlling the occurrence of the disease (J Exp Med. 1989;169:1669-1680).



- systemic lupus erythematosus. Using a murine model of this disease, they produced one of the first monoclonal anti-DNA autoantibody and studied its idiotypes. They have shown the existence of a premature insufficiency in thymic function and a very early production of autoantibodies directed against the nucleosome (histone and DNA complex) preceding the production of anti-DNA antibodies. In the human disease, they were the first to provide an analytical description of its renal manifestations. They found the anti-nucleosome antibodies that they had previously described in the mouse and were the first to show the effect of anti- $\beta_2$  GP1 antibodies on coagulation, a fact that explains the thromboses observed in patients suffering from lupus and antiphospholipid syndrome (Am J Med. 1992;93(2):181-186).

- human myasthenia. They demonstrated in 1994 the existence of a polymorphism for the acetylcholine receptor gene (the target of the autoimmune reaction causing the disease) which was significantly associated with the disease (Proc Natl Acad Sci U S A. 1994;91(11):4668-72). They have shown the particular role in pathogenesis of autoantibodies raised against the embryonic form of the acetylcholine receptor in causing neonatal myasthenia that results from placental transfer of maternal autoantibodies to the foetus.

Prof. Bach has developed new immunotherapeutic approaches for insulin-dependent diabetes and obtained pioneering results in the mid-80s, using cyclosporine (Lancet, 1986, 328 (8499): 119-124) and in the beginning of this decade, using a monoclonal anti-CD3 antibody (N Engl J Med. 2005;352(25):2598-608). This latter strategy is currently being developed pharmaceutically. In the public health area, he has successfully led a programme of eradication of Rheumatic Fever in the French Caribbean Islands (Lancet. 1996;347(9002):644-8).

During recent years, Prof. Bach has also developed a major interest in the Hygiene hypothesis in allergic and autoimmune diseases both in the clinic and in experimental models. His original contribution to the field in 2002 was to propose for the first time, combining personal observations and a comparative analysis of published data, that it was possible to extend the hypothesis from the field of allergy, where it was first formulated, to that of autoimmunity. The paper in question (N Engl J Med. 2002;347(12):911-20) elicited a major interest, illustrated well by the number of citations (476).

For 20 years, Prof. Bach has been the director of a Unité de recherche, supported by the two main French research organisations, INSERM (National institute for health and medical research) and CNRS (National centre for scientific research), and the university Paris Descartes (former René Descartes-Paris V).

### **Ms Kirsten LERSTRØM, Chair of LUPUS EUROPE**

Kirsten Lerstrøm was elected Chair of the patient organisation LUPUS EUROPE in 2012, after three years as Vice-Chair and a board member since 2008. During this time, Ms Lerstrøm has been behind the organisations' development of network and scientific advancements. Ms Lerstrøm was diagnosed with lupus (SCLE) in 1989 and since developed several other autoimmune conditions. She has been receiving a disability pension since 2003.

Ms Lerstrøm graduated in 1987 MSc Econ, Copenhagen Business School, specialising in international affairs and entrepreneurship. 1987-1995 The Danish Design Centre, Area Manager of Industry relations and Education. Author and editor several books and educational material on industrial design, product development and design management. 1995 – 2000 Own consultancy firm on Strategic Planning and use of IT. 2000 – 2002 Context A/S, Sales manager IT-Solutions in particular e-learning programmes and health tools.



## ANNEX 3: PRESENTATIONS

Presentation by Luminita Hayes

# Autoimmune diseases

## Towards a public health approach

**Luminita Hayes**, Senior Adviser, WHO Office at the EU  
**Gauden Galea**, Director, NCDs and Life-course,  
WHO/Europe  
**European Parliament**, 25<sup>th</sup> September 2017



World Health Organization  
REGIONAL OFFICE FOR Europe



Organisation mondiale de la Santé  
BUREAU REGIONAL DE L'Europe



Weltgesundheitsorganisation  
REGIONALBÜRO FÜR Europa



Всемирная организация здравоохранения  
Европейское региональное бюро



## Outline

1. Lessons learned from NCDs
2. Specific issues for autoimmune disorders
3. Example of developing a public health approach:
  - The case of musculo-skeletal manifestations

## Lessons from NCDs



### Practical DIABETES

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Leader

#### United Nations Resolution on Diabetes

Professor Martin Slink AM, MD, FRACP

First published: 7 September 2006 [Full publication history](#)

DOI: 10.1002/pdi.978 [View/Save citation](#)

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View Issue TOC  
Volume 23, Issue 7  
September 2006  
Page 278

The beginnings of the campaign for a United Nations Resolution on Diabetes took place three years ago when Clare Rosenfeld, then 16 years, approached me during the 2003 World Diabetes Congress in Paris. Clare had lived with type 1 diabetes since the age of seven years and asked: 'Don't you think there should be a United Resolution on Diabetes?' Over the next two years in my travels I cautiously explored this question with diabetes associations in over 40 countries and the answer from each was a resounding 'yes'. This led to a meeting of potential key stakeholders in Washington DC in December 2005 and final approval of a Strategic Plan for the campaign by the International Diabetes Federation Board of Management in February 2006.

The case for global attention to diabetes is overwhelming. For too long has diabetes lived in the shadows and for too long have governments ignored this epidemic which now afflicts over 230 million adults worldwide and which is increasing at the rate of seven million per year. Diabetes affects over 5.7% of the world's adult population and indirectly affects at least two- to three-fold more. It is more than simply a risk factor for cardiovascular disease. It needs to be better recognised as a disease in itself. It is responsible for an amputation every 30 seconds, is the major cause of renal failure and adult-onset blindness, and causes as many deaths as HIV/AIDS (3.5 million per year). Rather than being a disease of affluence in developed countries, the greatest burden is being felt in the developing

## Going it alone...

## A UN Resolution on Diabetes

<http://onlinelibrary.wiley.com/doi/10.1002/pdi.978/full>



### United Nations high-level meeting on noncommunicable disease prevention and control

#### NCD summit to shape the international agenda

Date: 19-20 September 2011  
Place: New York, USA

Noncommunicable diseases - or NCDs - like heart attacks and strokes, cancers, diabetes and chronic respiratory disease account for over 63% of deaths in the world today. Every year, NCDs kill 9 million people under 60. The socio-economic impact is staggering. Global leaders will meet at the United Nations in New York from 19-20 September 2011 to set a new international agenda on NCDs.

This is only the second time in the history of the UN that the General Assembly meets on a health issue (the last issue was AIDS). The aim is for countries to adopt a concise, action-oriented outcome document that will shape the global agendas for generations to come.

#### Meeting outcomes

- ↓ Political declaration adopted at the UN General Assembly  
pdf, 97kb
- ↓ Summary report of the discussions at the round tables  
pdf, 335kb

## ...Joining Forces

## The UN Declaration on NCDs and the SDG Process

[http://www.who.int/nmh/events/un\\_ncd\\_summit2011/en/](http://www.who.int/nmh/events/un_ncd_summit2011/en/)



World Health Organization  
REGIONAL OFFICE FOR Europe



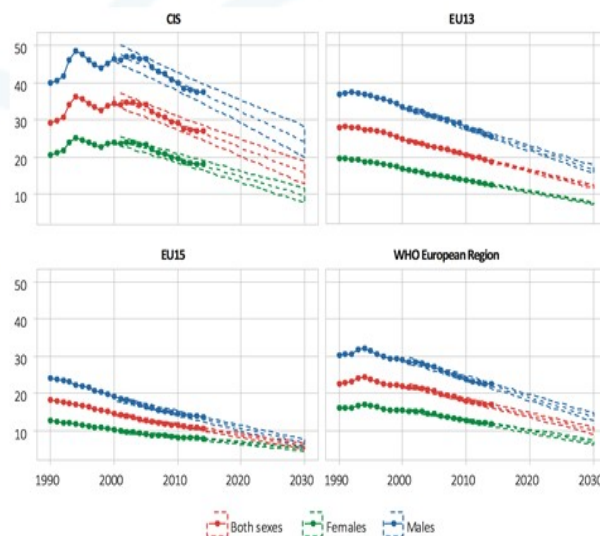
World Health Organization  
REGIONAL OFFICE FOR Europe





## Risk of dying from NCDs: Decreasing trends but gender gaps persist

Unconditional  
Probability of  
Dying (%)



## Global Monitoring Framework Scoreboard for Europe





## Autoimmune conditions



 World Health Organization  
REGIONAL OFFICE FOR Europe

 Organisation mondiale de la Santé  
BUREAU REGIONAL DE L'Europe

 Weltgesundheitsorganisation  
REGIONALBÜRO FÜR Europa

 Всемирная организация здравоохранения  
Европейское региональное бюро



## Going it alone...

### WHA Resolution WHA67/A67\_R9

HOME ABOUT OUR CAUSE OUR ACTIONS GET INVOLVED NEWS

**A historic milestone**

One of our proudest advocacy successes is the approval of Resolution WHA67.9 by the World Health Organization (WHO).

This Resolution is the only international resolution focusing solely on psoriasis. It is particularly significant because it confirms that psoriasis:

- Is a chronic, painful, debilitating and disabling non-communicable disease, without a cure;
- Has physical as well as psycho-social and socio-economic consequences;
- Is connected to psoriasis arthritis and increases the risk of various co-morbid diseases;
- Can lead to immense, needless suffering due to insufficient access to healthcare.

Because of this, the Resolution is a historic milestone for the global psoriasis community.

You can read the [entire Resolution here](#).

**The road to resolution WHA 67.9**

A decade ago psoriasis was absent from the international agenda. Very few policy-makers had ever heard about the disease. The WHO website provided almost no info on it. Few took psoriasis seriously.

So we set ourselves an ambitious target: to get the WHO to approve an official Resolution on psoriasis. This would be a powerful signal to states around the world to take action on psoriasis.

We put together a dedicated advocacy team. We gained the support of IAPSO (the International Alliance of Patient Organizations) and Panama, Argentina, Qatar and Ecuador as champion states. Policy papers were written and submitted. In statements at WHO meetings, we argued for delegates to take a closer look at psoriasis. At the 66th and 67th World

[Link to IFA-PSO website](#)

SIXTY-SEVENTH WORLD HEALTH ASSEMBLY WHA67.9  
Agenda item 13.5 24 May 2014

### Psoriasis

The Sixty-seventh World Health Assembly,  
Having considered the report on psoriasis,<sup>1</sup>

Recalling all relevant resolutions and decisions adopted by the World Health Assembly on the prevention and control of noncommunicable diseases, and underlining the importance for Member States to continue addressing key risk factors for noncommunicable diseases through the implementation of the WHO global action plan for the prevention and control of noncommunicable diseases 2013–2020;<sup>2</sup>

Recognizing the urgent need to pursue multilateral efforts to promote and improve human health, providing access to treatment and health care education;

Recognizing also that psoriasis is a chronic, noncommunicable, painful, disfiguring, and disabling disease for which there is no cure;

[Link to WHA67/A67\\_R9](#)



## ...or Joining Forces

Addison's disease | Agammaglobulinemia | Alopecia areata | Amyloidosis | Ankylosing spondylitis | Anti-GBM/Anti-TBM nephritis | Antiphospholipid syndrome | Autoimmune angioedema | Autoimmune dysautonomia | Autoimmune encephalomyelitis | Autoimmune hepatitis | Autoimmune inner ear disease (AIED) | Autoimmune myocarditis | Autoimmune pancreatitis | Autoimmune retinopathy | Autoimmune urticaria | Axonal & neuronal neuropathy (AMAN) | Bald disease | Behcet's disease | Benign mucosal pemphigoid | Bullous pemphigoid | Castleman disease (CD) | Celiac disease | Chagas disease | Chronic inflammatory demyelinating polyneuropathy (CIDP) | Chronic recurrent multifocal osteomyelitis (CRMO) | Chung-Strauss | Cicatricial pemphigoid | Cogan's syndrome | Cold agglutinin disease | Congenital heart block | Coxsackie myocarditis | CREST syndrome | Crohn's disease | Dermatitis herpetiformis | Dermatofibrosis | Devic's disease (neuromyelitis optica) | Discoid lupus | Dressler's syndrome | Endometriosis | Eosinophilic esophagitis (EoE) | Eosinophilic fasciitis | Erythema nodosum | Essential mixed cryoglobulinemia | Evans syndrome | Fibromyalgia | Fibrosing alveolitis | Giant cell arteritis (temporal arteritis) | Giant cell myocarditis | Glomerulonephritis | Goodpasture's syndrome | Granulomatosis with polyangiitis | Graves' disease | Guillain-Barre syndrome | Hashimoto's thyroiditis | Hemolytic anemia | Henoch-Schönlein purpura (HSP) | Herpes gestationis or pemphigoid gestationis (PG) | Hygromyoglossitis | IgA Nephropathy | IgG4-related sclerosing disease | Immune thrombocytopenic purpura (ITP) | Inclusion body myositis (IBM) | Interstitial cystitis (IC) | Juvenile arthritis | Juvenile diabetes (Type 1 diabetes) | Juvenile myositis (JM) | Kawasaki disease | Lambert-Eaton syndrome | Leukocytoclastic vasculitis | Lichen planus | Lichen sclerosus | Lignous conjunctivitis | Linear IgA disease (LAD) | Lupus | Lyme disease chronic | Meniere's disease | Microscopic polyangiitis (MPA) | Mixed connective tissue disease (MCTD) | Mooren's ulcer | Mucosa-Habermann disease | Multiple sclerosis | Myasthenia gravis | Myositis | Narcolepsy | Neuromyelitis optica | Neutropenia | Ocular cicatricial pemphigoid | Optic neuritis | Palindromic rheumatism (PR) | PANDAS | Paraneoplastic cerebellar degeneration (PCD) | Paroxysmal nocturnal hemoglobinuria (PNH) | Parry-Romberg syndrome | Pars planitis (peripheral uveitis) | Parsonage-Turner syndrome | Pemphigus | Peripheral neuropathy | Perivascular encephalomyelitis | Pernicious anemia (PA) | POEMS syndrome | Polyarteritis nodosa | Polyglandular syndromes type I, II, III | Polymyalgia rheumatica | Polymyositis | Postmyocardial infarction syndrome | Postpericardiotomy syndrome | Primary biliary cirrhosis | Primary sclerosing cholangitis | Progesterone dermatitis |

**Psoriasis | Psoriatic arthritis** | Pure red cell aplasia (PRCA) | Pseudotumor gangrenosum | Reiter's phenomenon | Reactive Arthritis | Reflex sympathetic dystrophy | Relapsing polychondritis | Restless legs syndrome (RLS) | Retroperitoneal fibrosis | Rheumatic fever | Rheumatoid arthritis | Sarcoidosis | Schmidt's syndrome | Scleritis | Scleroderma | Sjögren's syndrome | Sperm & testicular autoimmunity | Stiff person syndrome (SPS) | Subacute bacterial endocarditis (SBE) | Susac's syndrome | Sympathetic ophthalmia (SO) | Takayasu's arteritis | Temporal arteritis/Giant cell arteritis | Thrombocytopenic purpura (TTP) | Tolosa-Hunt syndrome (THS) | Transverse myelitis | Type 1 diabetes | Ulcerative colitis (UC) | Unfractionated heparin-induced thrombocytopenia (UHIT) | Uveitis | Vasculitis | Wegener's granulomatosis (or Granulomatosis with polyangiitis (GPA))

Source: <https://www.eardis.org/diseases-list/>

Governance

Surveillance

Prevention

Health Systems







## Specific Considerations

- Insufficient data
  - Data only about a small number of all the conditions
  - Data limited to industrialised countries
  - Correlations with age and timing of exposures: eg early childhood exposure to certain infections may be associated with auto-immune disease many years later
  - Correlations with race and ethnicity: need more research to tease genetic from environmental causes
- Public health policy implications
  - A number of auto-immune diseases exert disproportionate burden in women or men: a gender equity issue
  - Lifelong treatment: high cost to society
  - More than half associated with external causes: drugs, heavy metals, occupational exposure, infections
  - Timing of exposure important: life course implications

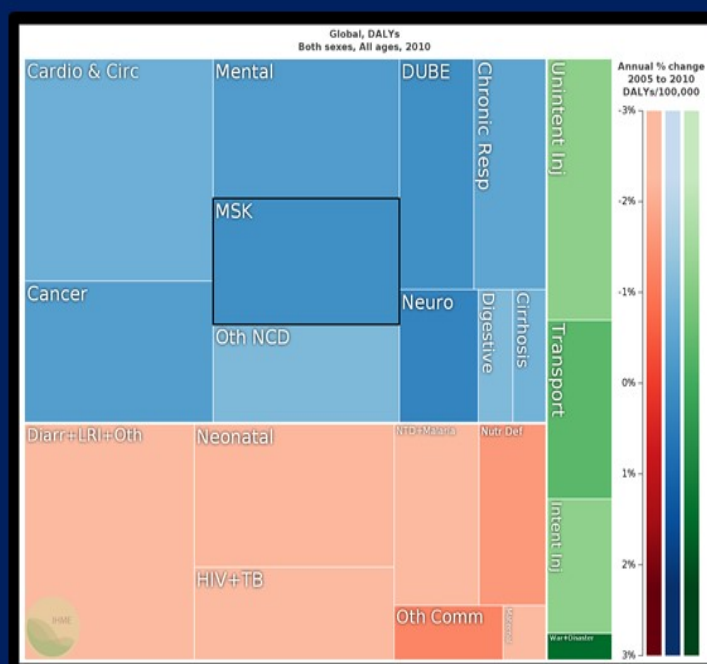


## General considerations

- **Surveillance:** better instruments and data about incidence, prevalence, and outcomes internationally
- **Health systems:** better understanding of total cost to society and to households, with person-centred systems of treatment and care and health care financing
- **Research:** into environmental causes and life course effects (epigenetics, early childhood) for applications to prevention

# Musculo-skeletal Diseases

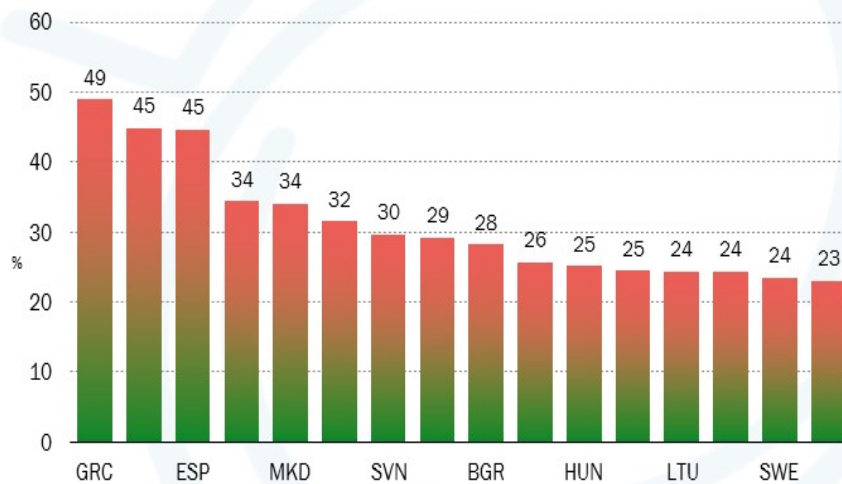
## Public Health Considerations



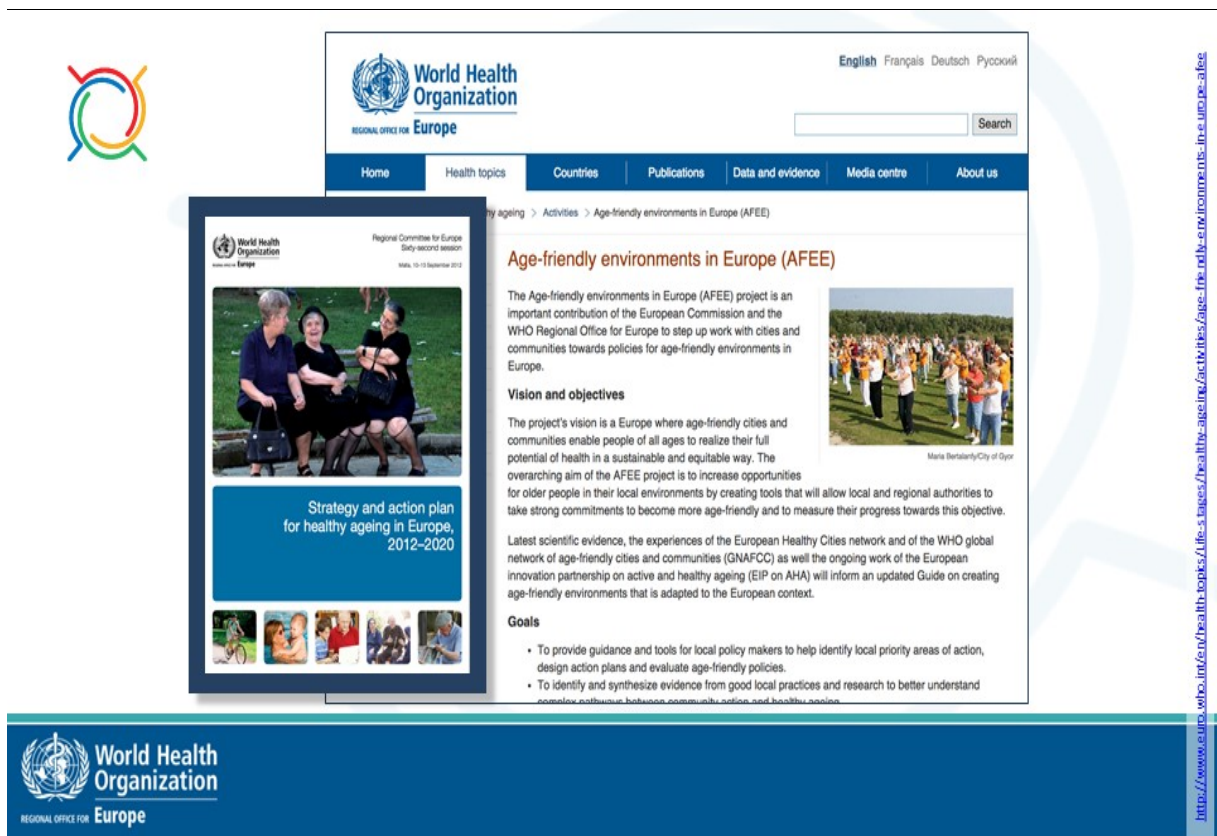


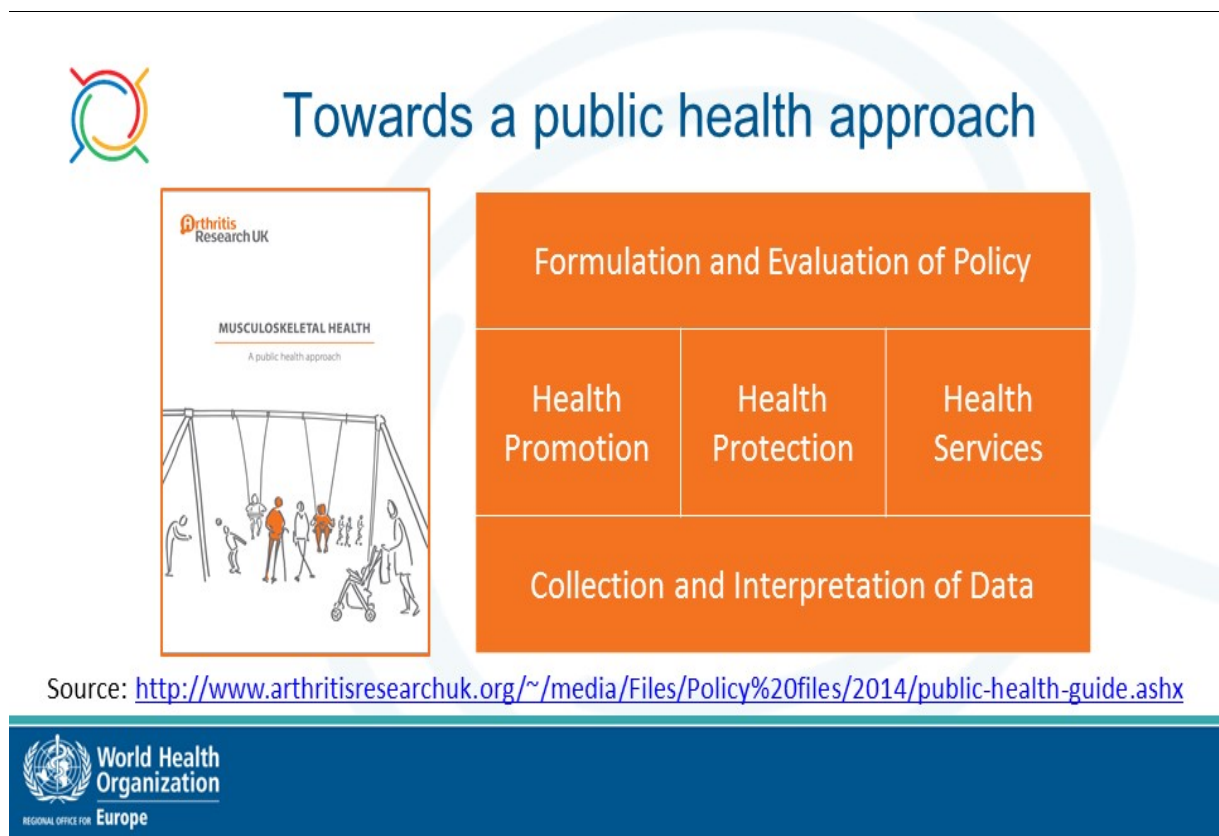
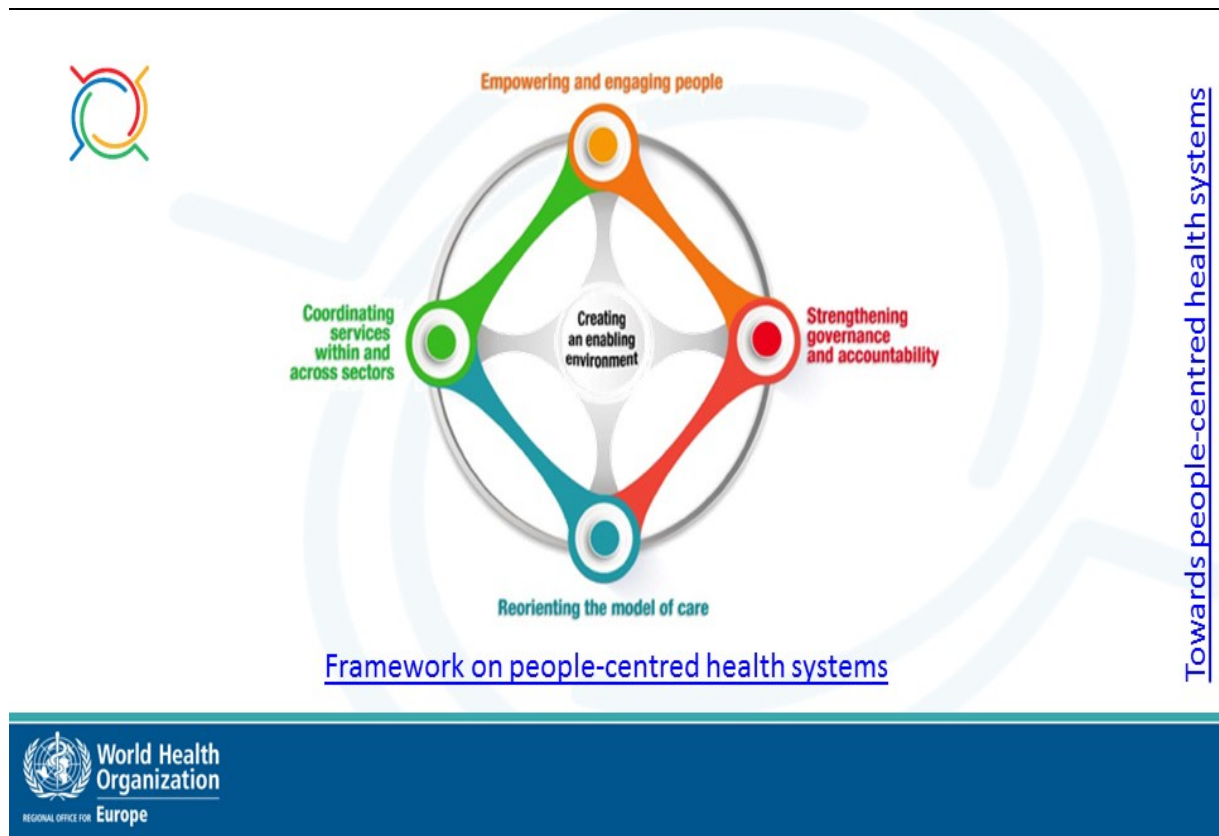
### WHO European Childhood Obesity Surveillance Initiative

Prevalence of overweight among 7-year-old boys 2009/2010, by country

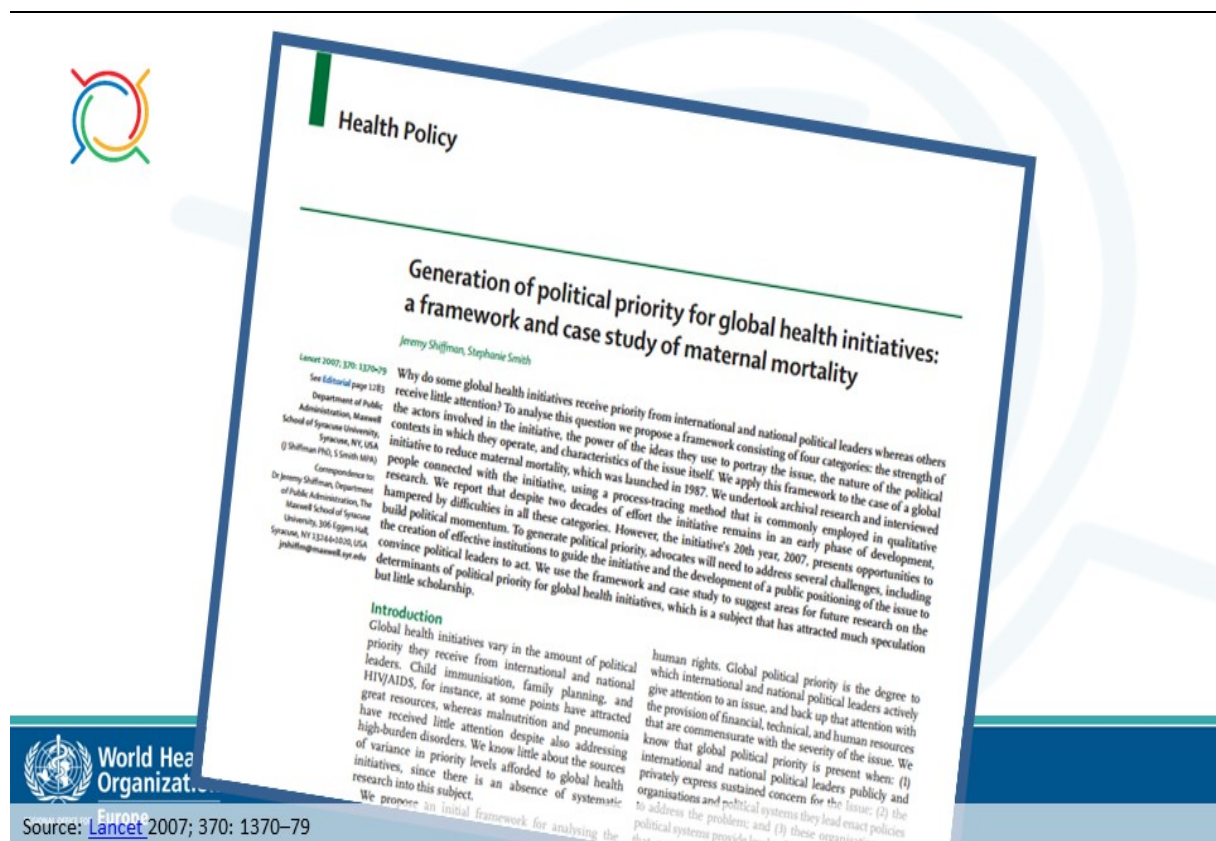












# Thank You







## Presentation by Aaron Lerner




**AESKU.KIPP INSTITUTE**  
RESEARCH FOR HUMAN HEALTH  
RESEARCH FOR HUMAN HEALTH

### Potential causes triggering autoimmune disease

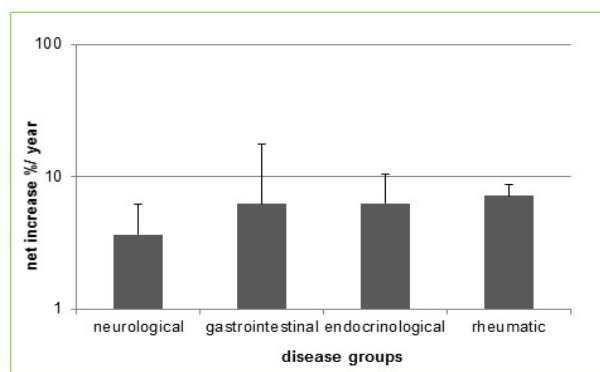
Prof. Aaron Lerner<sup>1,2</sup>

**25 Sept, 2017**

**Committee on Environment, Public health& food Safety (ENVI) workshop  
Autoimmune diseases-Modern Diseases**

1. B. Rappaport School of Medicine, Technion-Israel institute of Technology, Haifa, Israel. aaronlerner1948@gmail.com
2. Aesku.Kipp Institute, Wendelsheim, Germany. info@aesku.com


### Net increase %/year of different disease groups



Disease kind	Statistical significance (p)	Countries	Diseases
neurological	p<0,0001	Finland, Denmark, Norway, Italy, Spain	MS, Myasthenia Gravis
gastrointestinal	p<0,0001	Denmark, Canada, Sweden, USA, Finland, Israel, Netherlands, UK, Czech, Scotland, Spain, Estonia, New Zealand	Autoimmune Hepatitis, IBD, Chron's, Celiac Disease
endocrinological	0.02	Brazil, Canada, Israel, Serbia, Europe	Autoimmune thyroiditis, IDDM
rheumatic	0.02	Canada, UK	SARD, RA, SLE

Lerner A, Jeremias P, Matthias T. The world incidence and prevalence of autoimmune diseases is increasing: A review. *Internat J Celiac Disease*. 2015;3:151-155.

## The dysbiotic effects contributions to human diseases

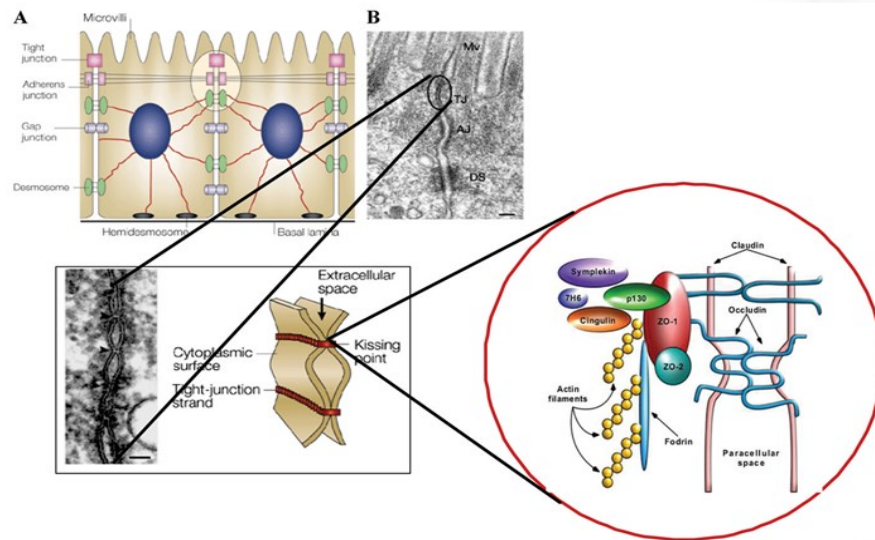


Domain/organ	Dysbiotic effects
Systemic	↗autoimmunity, allergy, cancerogenesis.
Metabolic	↗adiposity, ↘nutrient accessibility, ↘SCFA.
Behavior	↗anxiety, stress, depression, pain, ↗hunger/satiety. ↘mood, cognition, memory, learning, sleep.
Skin	↗inflammation, immune stimulation.
Bone	↗absorption, inflammation, osteopenia/osteoporosis. ↘bone mass
Joint	↗inflammation, PTMPs, immune stimulation.
Thyroid	↗inflammation, ↘iodine uptake. ↗gut hormones
Lung	↗inflammation, infections, immune stimulation.
Heart	↗toxic metabolites, inflammation, atherosclerosis.
Liver	↗inflammation, immune activation, gut bacterial overload, oxidative stress, fibrosis, endotoxemia.
Gut	↗permeability, inflammation, malabsorption.
Endocrine pancreas	↗insulinitis, insulin resistance.
Kidney	↗inflammation, toxic metabolites, endotoxemia.

## The effects of the intestinal microbiota metabolites or transformed molecules

Beneficial microbial metabolites or constituents	Advantages	Harmful microbial metabolites	disadvantages
SCFAs	Nutrient, energy providing	Lipopolysaccharide supply	Obesity, metabolic syndrome, leaky gut
Propionate production	Gluconeogenesis, cholesterol lowering	Toxins production	Cancer promotion
Butyrate production	Cancer prevention, colonocyte energy	Tissue invasion	Infections, leaky gut
Vitamin productions: B:1,2,5,6,7,8,9,11,12. Vitamin K	Various metabolic cellular effects	Leaky gut	Autoimmune disease, IBD, immune disorders
Anti-inflammatory signals	Normal gut immune function	Microbial enzyme's PTMP	Autoimmune and allergic disease
Antimicrobial production	Pathogens fighting	Pro-inflammatory signals <sup>3</sup>	IBD, immune disorders
Non-digestible carbohydrates-bulk effect	Improved intestinal motility	Acetate production	Hypercholesterolemia, cardiovascular diseases
Bile acids	Improved fat/vitamin absorption, gut barrier, regulate serum lipids and glucose	Secondary bile acids	Colon cancer <sup>1</sup>
Microbial proteases	Protective of intestinal permeability	Microbial proteases	Harmful for intestinal permeability
		Red meat rich L-carnitine metabolism	atherosclerosis
		Organic acids	Hypertension, obesity, colonic cancer, autism
		Metabolic imbalance	IBS, metabolic syndrome
		Amino acids: tyrosine to phenols	Colonic cancer, autism
		Trimethylamine production	coronary vascular disease

### Macroscopic arrangement (A) and microscopic composition (B) of intercellular tight junctions.



The structural components of intercellular tight junctions can be classified as integral membrane proteins (occludin, claudins, and JAM), junctional complex proteins (ZO-1, ZO-2, p130 or ZO-3, 7H6, Symplekin, and cingulin), and cell cytoskeleton structures (microtubules, intermediate filaments and microfilaments).

Fasano A. Leaky gut and autoimmune diseases. *Cline Rev Allergy Immunol.* 2012;42:71-8.  
Tight Junctions, Intestinal Permeability, and Autoimmunity Celiac Disease and Type 1 Diabetes Paradigms.  
Jeroen Visser et al. *N Y Ann Med* 2010



### Environmental factors breaching TJ integrity/increasing intestinal permeability

Categories	names	Categories	names
Pathogens	H. Pylori	drugs	Proton pump inhibitors
	Enteropathogenic E. coli		Non-steroidal anti-inflammatory drugs
	Enterohemorrhagic E. coli		Selected bile salts
	V. parahemo-lyticus	toxins	Clostridium toxin
	Salmonella enterica/typhimurium		Ochratoxin A
	Clostridium difficile		marine toxins
	Clostridium perfringens		EDTA
	Bacteroides fragilis	Lifestyle factors	Western diet
	Vibrio cholera		obesity
	Shigella flexneri		Hypoperfusion
	Campylobacter jejuni	Gut perfusion	Proteases
	Reovirus	Microbial enzymes	Peanut, soybean, wheat, milk proteins, nuts, sesame
	Rotavirus	Allergens	Arsenic, phenols, mercury, azoxymethane.
	High fat diet	Carcinogens	Stress related psychiatric disorders
nutrients	High carbohydrate diet	Stress	high-intensity exercise
	Vitamin A deprivation		
	Vitamin D deprivation		
	fructose		
	gluten		
	Processed food additives: sugar, salt, organic acids, microbial transglutaminase, emulsifiers, nanoparticles		
	Medium chain fatty acids		
	Acyl carnitines		

Environmental factors that breach TJ integrity and increase intestinal permeability. Submitted, *Microorganisms*, 2017



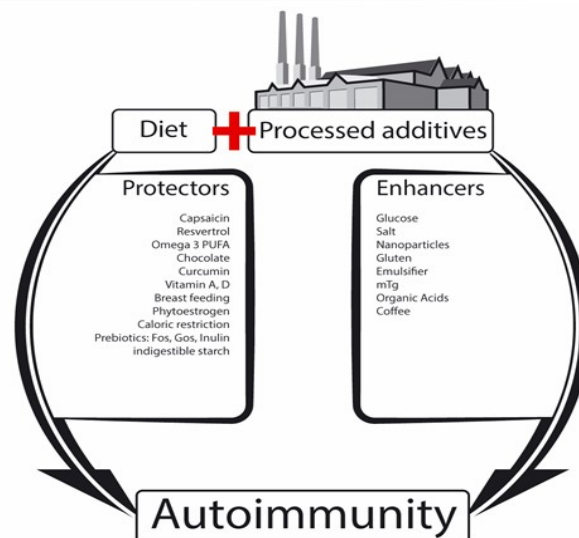
### Environmental factors enhancing TJ integrity/regulating intestinal permeability

Categories	names
Prebiotic Nutrients	galactooligosaccharides
	fructooligosaccharides
Short chain fatty acids	butyrate
Polyunsaturated fatty acids	PUFA
Nutrients	Glutamine
	Zinc
Plant-derived flavonoids	Quercetin and its metabolite DHBA
	Propolis
	green tea, coffee, berries, grapes, and other fruits/vegetables
vitamins	A, D
Probiotics	E. coli nissle 1917
VSL#3	Lactobacillus plantarum MB452
VSL#3	Bifidobacterium infantis Y1
	Lactobacillus salivarius UCC118
	Lactobacillus salivarius CCUG38008
	Lactobacillus rhamnosus GG
	Lactobacillus casei DN-114 001
	Lactobacillus casei Shirota
Microbial enzymes	Proteases
Chemical compounds	Gelatin tannate

Environmental factors that enhance TJ integrity and regulate intestinal permeability. Submitted, Microorganisms, 2017



### The leaky gut might initiate the autoimmune cascade

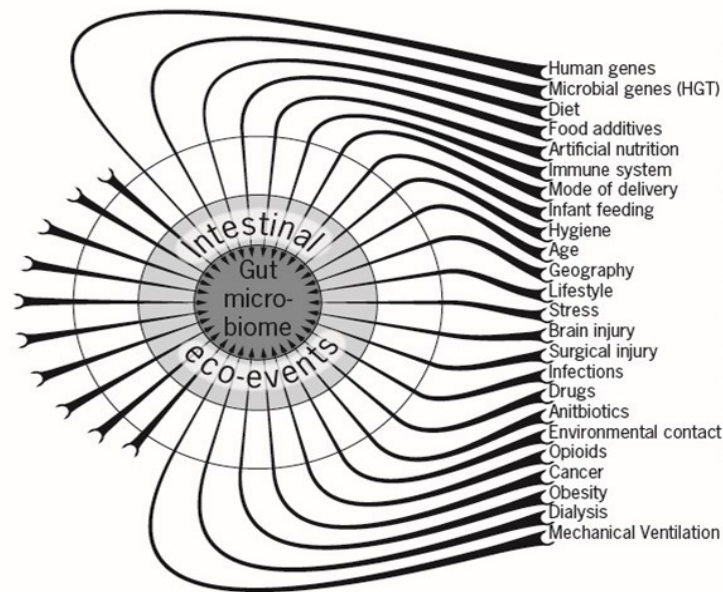


Schematic illustration of the factors that are associated with increasing (enhancers) or decreasing (protectors) of intestinal permeability at the TJ level.

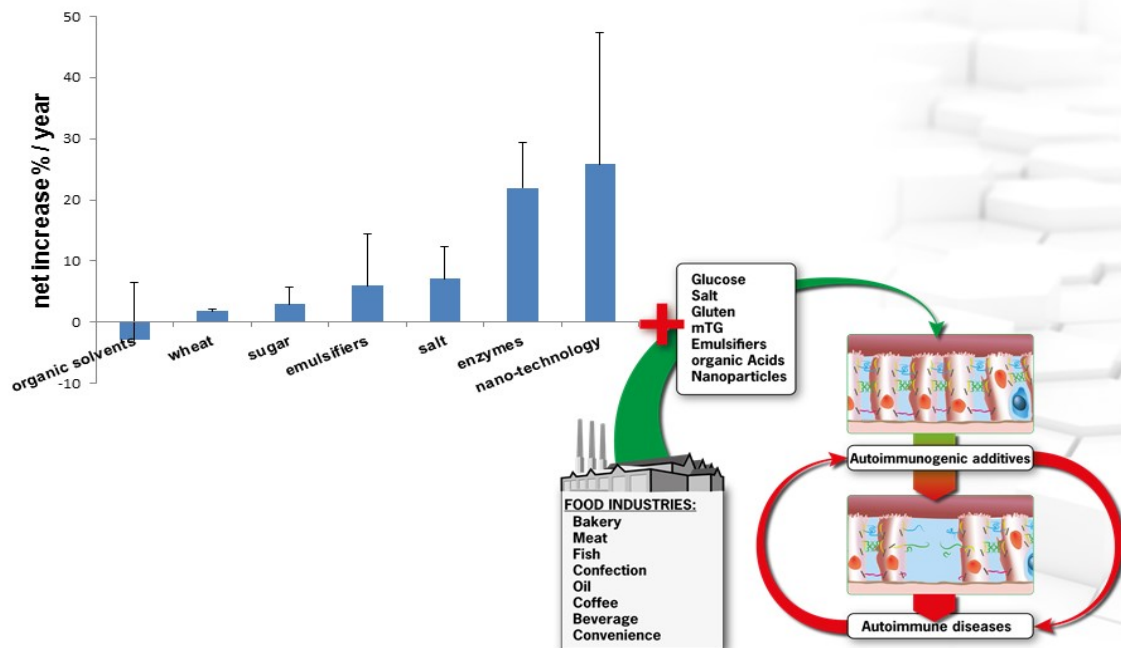




### The microbiome affects and is affected by everything



### Change in nutrition responsible for the increasing numbers of ADs?



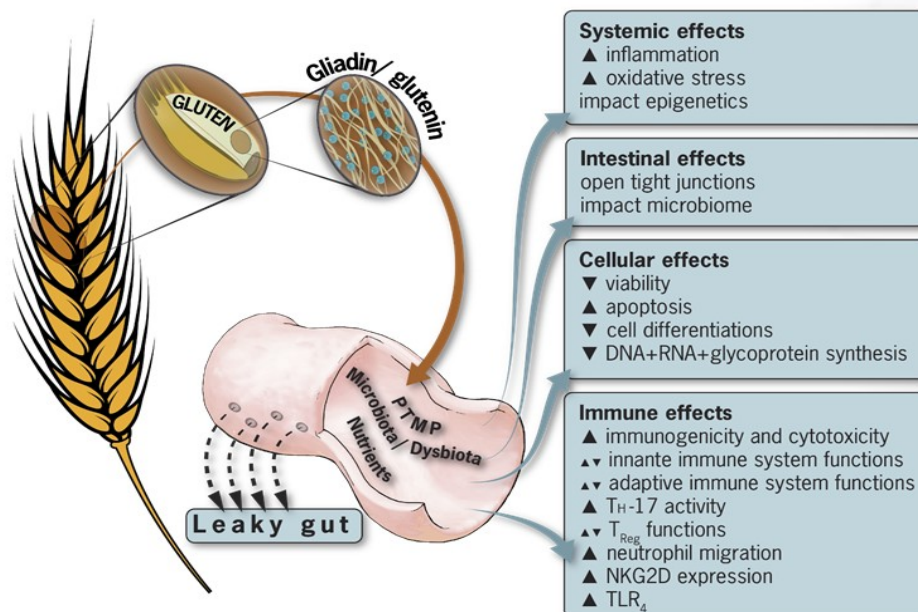
## Mechanism of TJ integrity breaching

Food additives	Net % increase/year	Mechanism of TJ integrity breaching
<b>Glucose</b>	2.9±2.8	Change in distribution of ZO-1, claudin-1, E cadherin. Perijunctional cytoskeleton condensation.
<b>Salt</b>	7.1±5.3	Increased phosphorylation of myosin light chain, contraction of the perijunctional actomyosin ring, loss of function of claudin 2 and 15.
<b>Organic solvents</b>	-2.9±9.3	Alterations in TJ proteins, dissociates the PTP1B-E-cadherin-beta-catenin complex
<b>Emulsifiers</b>	6±8.4	P-glycoprotein inhibition, decrease the hydrophobicity of the mucus layer, actine disbandment and structural separation of TJ, change the distribution of ZO-1 and actine.
<b>Gluten</b>	1.8±0.4	Rearrangement of the cytoskeleton through the zonulin pathway, reduces F-actin content, interaction between occludin and Zo-1 is compromised, zonulin release is leading to PKC-mediated cytoskeleton reorganization, zonulin release by binding to the CXCR3 receptor in intestinal cells, in a MYD88-dependent pathway and subsequent transactivation of EGFR by PAR2.
<b>Microbial transglutaminase</b>	21.9±7.4	Increases luminal microbial load, Hypothesis: cross-linking TJ proteins, imitating emulsifiers and nanoparticles functions.
<b>Nanoparticles</b>	25.8±21.5	Redistribution of ZO-1 TJ proteins, clustering of integrin $\alpha(V)\beta(3)$ along the cell border, F-actin reorganization and claudin 4 down regulation, open epithelial TJ via C-Jun Nh2-terminal kinase-dependent pathway, TJ electrostatic interactions

Lerner A, Matthias T. Changes in intestinal tight junction permeability associated with industrial food additives explain the rising incidence of autoimmune disease. *Autoimmun Rev.* 2015;14:479-89



## Gluten detrimental to human health



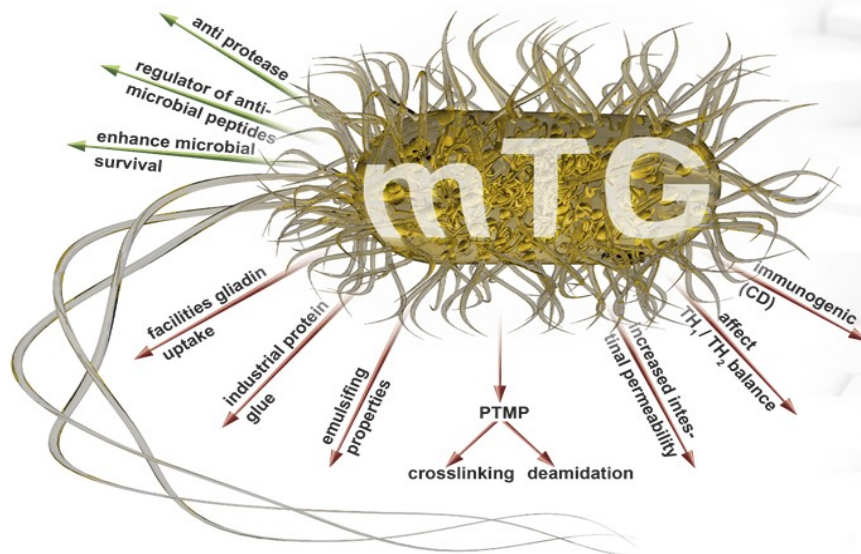
Lerner A, Shoenfeld Y, Matthias T. Gluten ingestion side effects and withdrawal advantages in non-celiac autoimmune diseases. *Nutr Rev.* 2017, In press.





## Effects of mTg that might drive autoimmunity

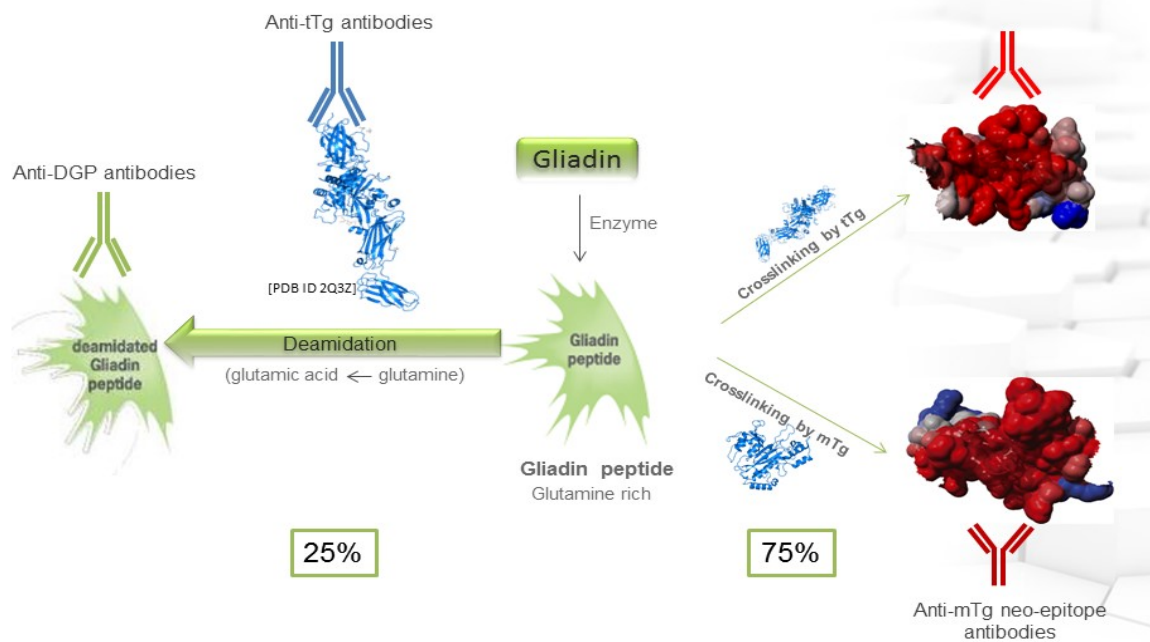
**Luminal (green) and systemic (red) effects of the mTg that might drive autoimmunity**



Aaron Lerner, Rustam Aminov, Torsten Matthias. Intestinal dysbiotic transglutaminases are potential environmental drivers of systemic autoimmunogenesis. *Frontiers in Microbiology*, 2016



## Antibodies in Celiac Disease

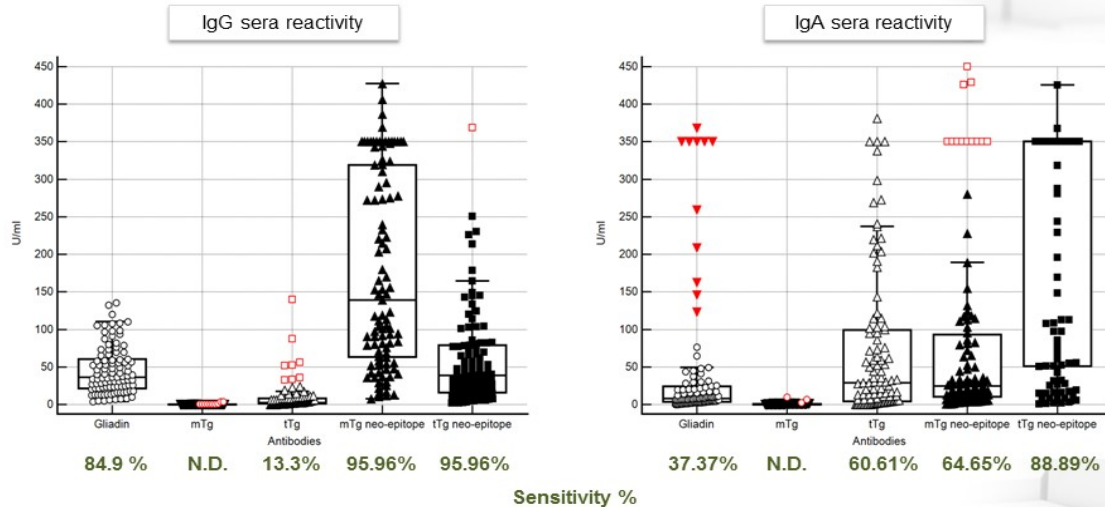


Courtesy of Dr. Christian Meesters, AESKU.KIPP Institut 2012



## Immunoreactivity of mTg and tTg neo-epitopes

n=109 pediatric celiac patients



High immunoreactivity of neo-epitopes compared to single antigens

Matthias T, Jeremias P, Neidhöfer S, Lerner A. The industrial food additive microbial transglutaminase, mimics the tissue transglutaminase and is immunogenic in celiac disease patients. *Autoimmun Rev*, 2016;15:1111-1119.



## Timeline of History\*

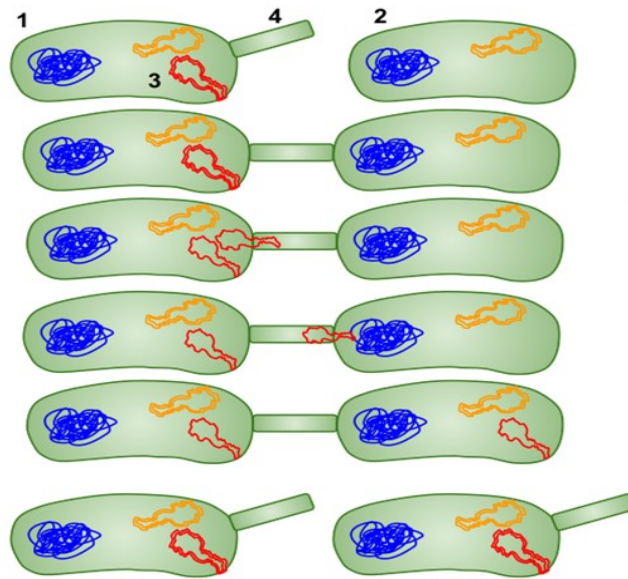
Years before the present:

4.5 billion	Formation of planet earth
3.8 billion	Emergence of organisms, beginning of biology
2.5 million	Evolution of the genus Homo in Africa
2 million	Human spread from Africa to Euroasia
500000	Neanderthals evolved in Europe and Middle East
200000	Homo sapiens evolved in East Africa
70000	Homo sapiens spread out of Africa
45000	Sapiens settled in Australia
30000	Extinction of Neanderthals
15-20000	Discovery of wheat in the fertile croissant
	Gluten-10% of wheat proteins
16000	Sapiens settled in America
12000	The Agricultural revolution
2400	Buddhism in India
2000	Christianity
1400	Islam
500	The scientific revolution
200	The industrial revolution. Massive extinction of plants and Animal
+2016....	65% of USA consume processed food
+2017....	Gluten- 80% of wheat proteins
+2017....	Gluten intake sky high
+2017....	Gluten peptides are more toxic to celiacs.

\*Sapiens, A brief history of humankind, Yuval Noah Harari, 2011.



### Horizontal gene transfer



[https://simple.wikipedia.org/wiki/Horizontal\\_gene\\_transfer](https://simple.wikipedia.org/wiki/Horizontal_gene_transfer) (changed in 9 December 2014)

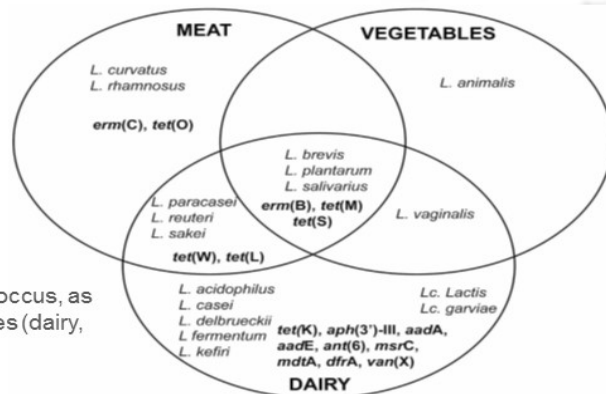


### Antibiotic resistance in foodborne Lactobacillus and Lactococcus species

As shown by molecular characterization of vancomycin resistant clinical isolates of *Staphylococcus aureus*, Transfer of AR genes from a commensal reservoir to opportunistic pathogens such as enterococci is the first step toward AR Transmission to pathogens (Levy and Marshall, 2004).

A recent metagenome-wide analysis, performed on a large cohort of human gut microbiota revealed predominance of tetracycline Resistance genes (Huetal., 2013), which appears to correlate with the prevalence of such AR determinants in food borne Lactic Acid Bacteria.

Genetic exchanges in bacteria are more prone to occur in crowded environments, such as the GI tract and fermented foods.



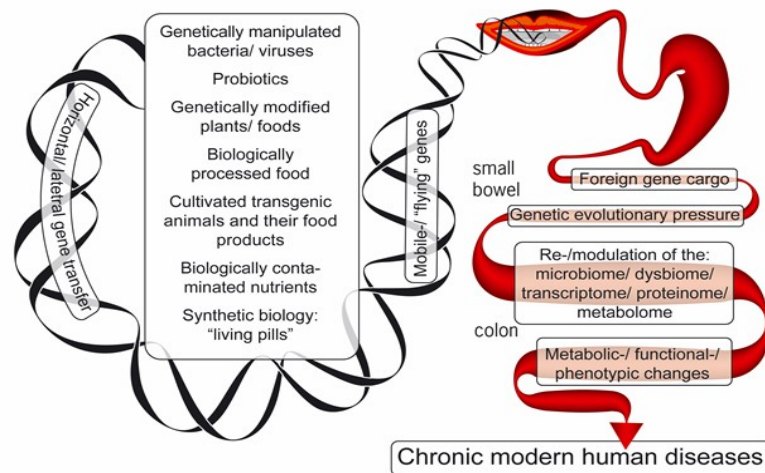
The distribution of AR Lactobacillus and AR Lactococcus, as well as of the AR genes, in the different food sources (dairy, meat, vegetable).  
AR genes are indicated in **bold**.

Devirgiliis et al. Update on antibiotic resistance in foodborne Lactobacillus and Lactococcus species. Front Microbiol. 2013





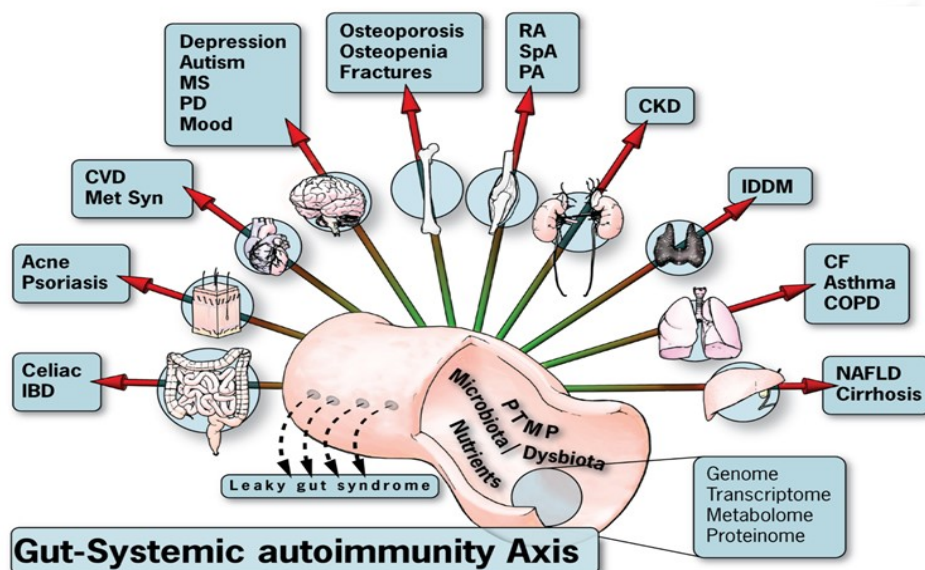
## Horizontal gene transfer in the gut



Lerner A, Aminov R, Matthias T. Horizontal gene transfer in the gut. *Frontiers in Immunology*, Submitted, 2017.



## GUT - the Trojan horse in remote organs' autoimmunity



Lerner A, Matthias T. GUT-the Trojan horse in remote organs' autoimmunity. *Journal of Clinical & Cellular Immunology*, 2016;7:401.



Presentation by Jean-Francois Bach

## *Autoimmune Disease: Definitions*

- Autoimmunity- immune response to normal antigens of the host
- Autoimmune disease- disease caused or significantly promoted by autoimmunity

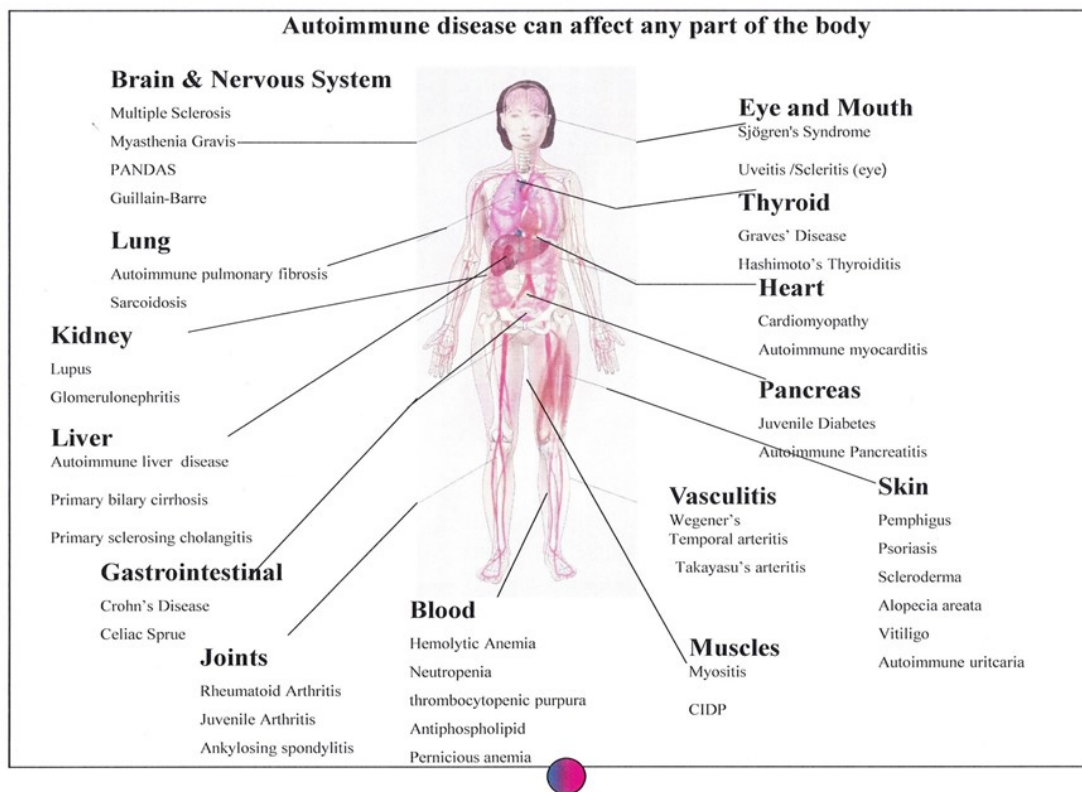
## *Autoimmune Disease: Prevalence*

- At least 100 diseases affecting every organ system
- In the USA: 14.7 to 23.5 million people (5% to 8%)
- Most require life-long treatment
- Among the 10 leading causes of mortality among women under 65

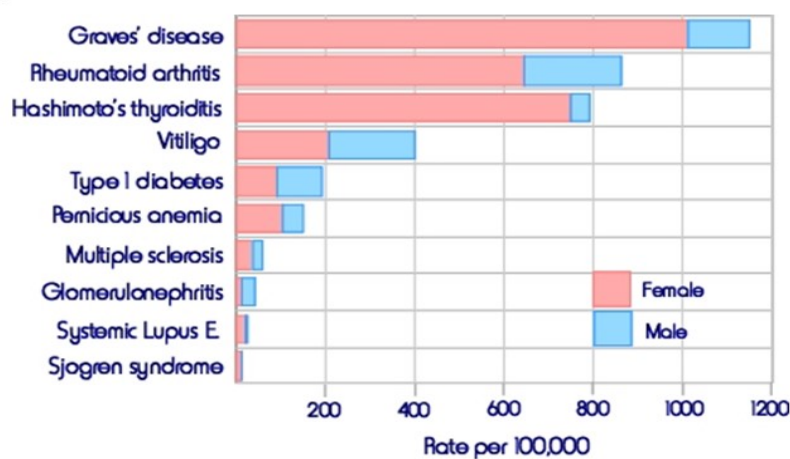
### ***For comparison:***

- Heart disease (22 million)
- Cancer (9 million)

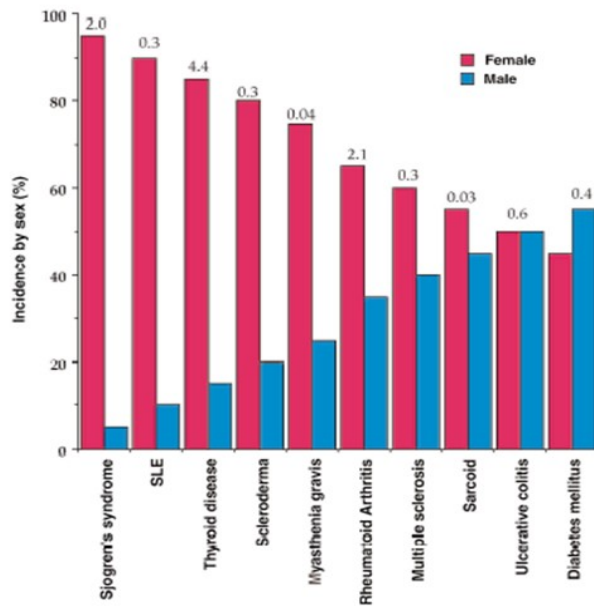




## Prevalence of the top-10 autoimmune diseases in US

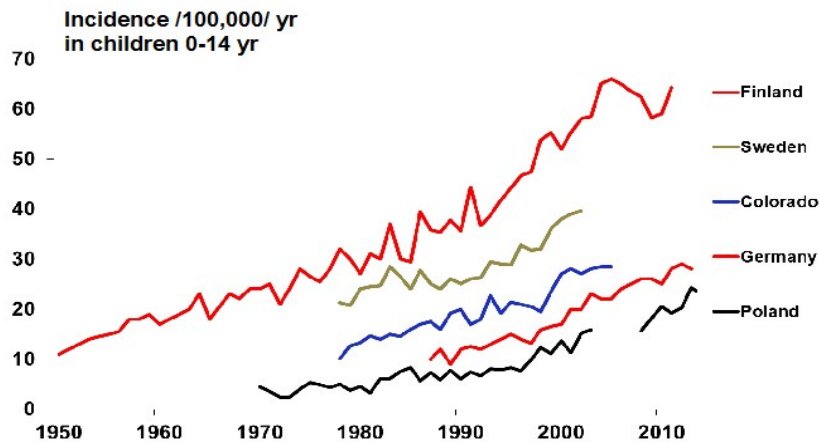


## Sex distribution of the major autoimmune diseases in the USA



## T1D incidence is doubling every 20 years

What environmental factors are responsible?



Rewers M. Ann NY Acad Sci 2008; 1150:1-13, updated

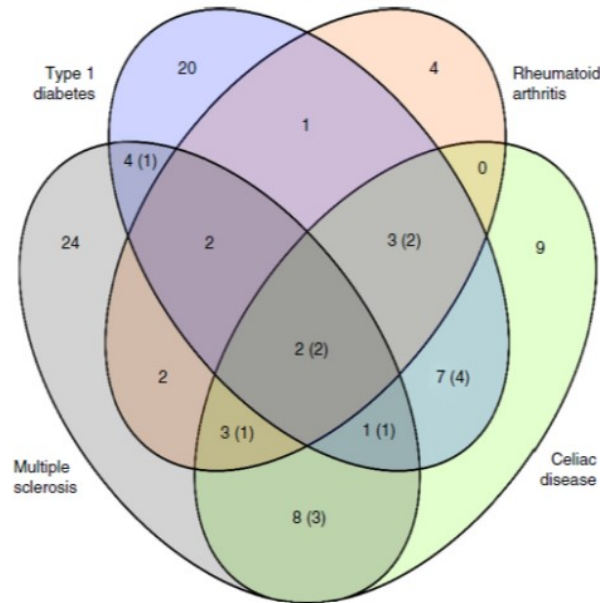
## Autoimmune Disease- Causes

### Familial Risks for Graves' Disease

	<u>Risk</u>
One Parent	6.22
One Sibling	5.04
Twins	16.45
Spouses	2.75

**Li et al 2009**

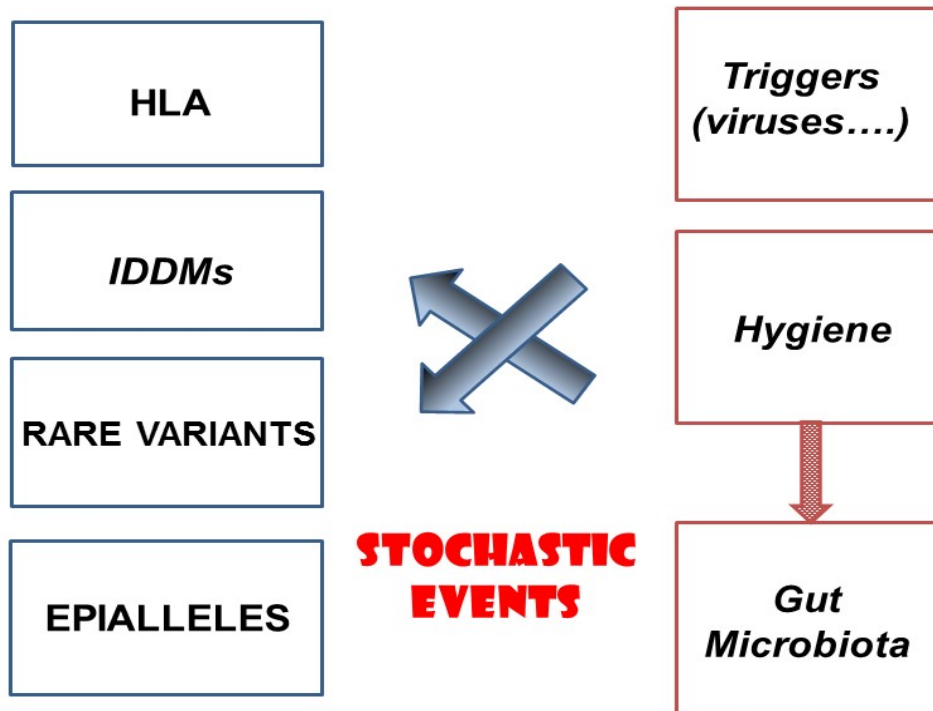
**Venn diagram showing a summary of the disease assignments for 90 regions that showed association with at least one disease**



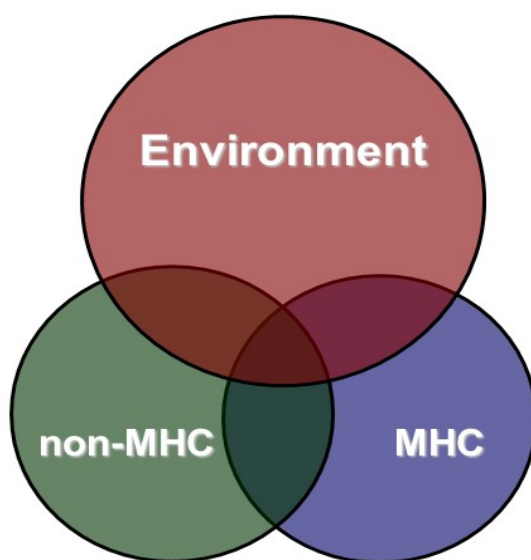
*Fortune MD et al. Nature Genetics 2015;47: 839-844*

## THE CASE OF MISSING HERITABILITY

- 1) SNPs may be distinct from rare meaningful variants
- 2) Medium or low penetrance variants
- 3) Architecture of the genome : Rare Copy Number Variations or deletions
- 4) Epistasis
- 5) Epigenetics
- 6) Disease heterogeneity
- 7) Rare or infrequent variants that segregate within individual families (even within monozygotic twins)

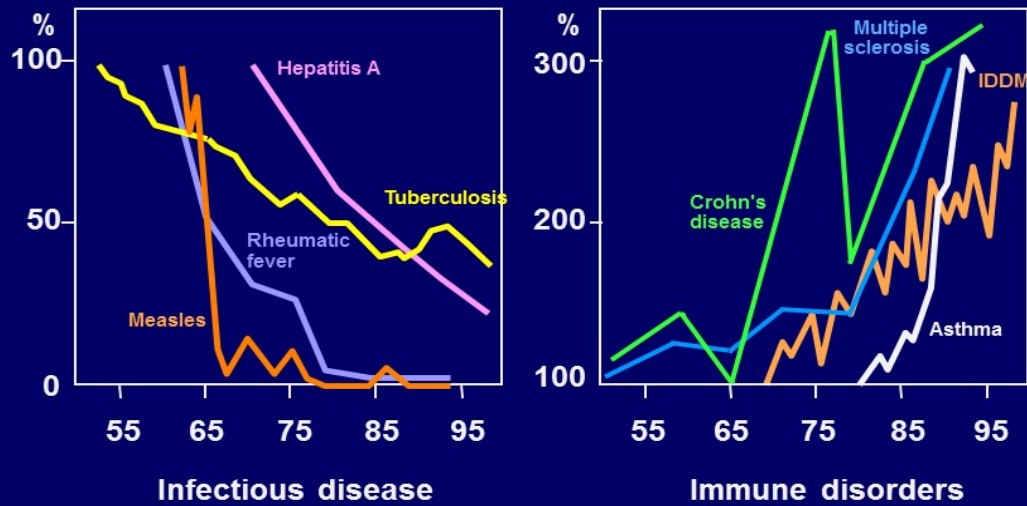


**Environment is more than half the risk.**

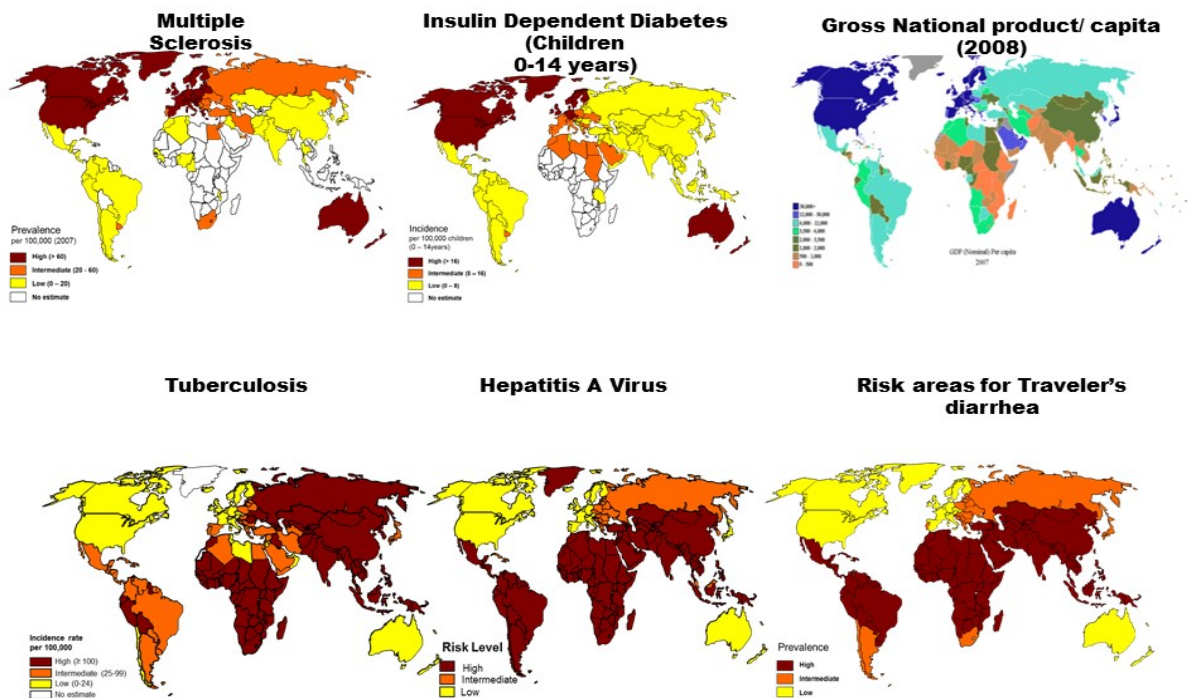




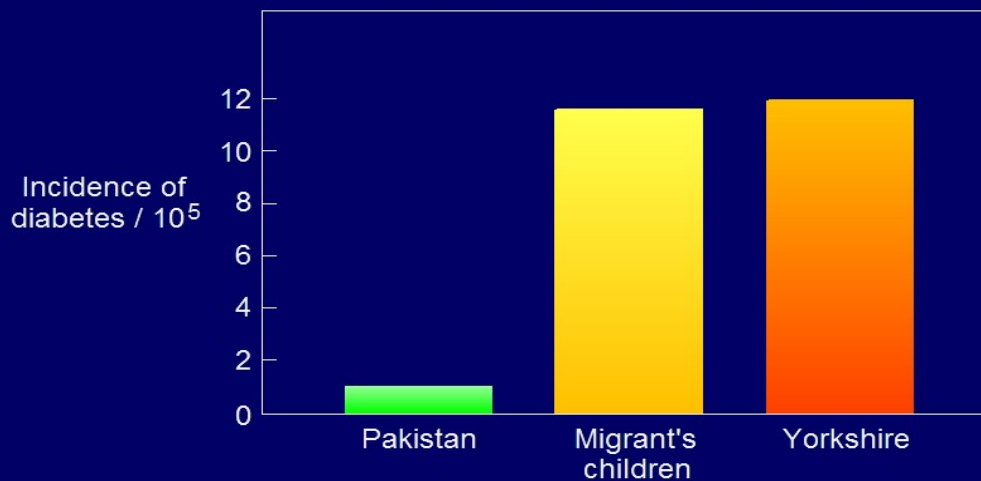
## INCIDENCE OF PROTOTYPE INFECTIOUS DISEASE AND IMMUNE DISORDERS OVER 4 DECADES



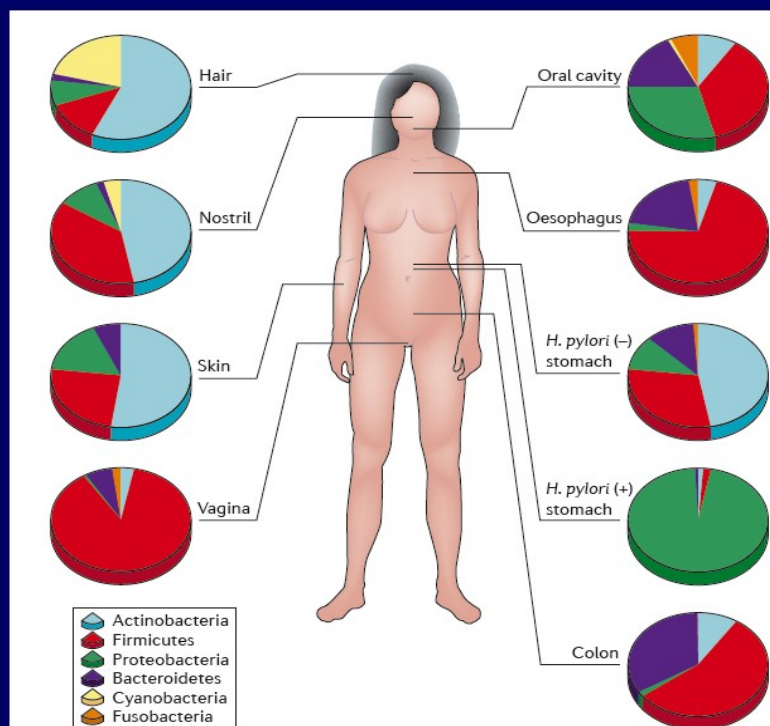
JF Bach N Engl J Med 2002, 347: 911- 920



## IDDM incidence in children of migrants from Pakistan to Yorkshire

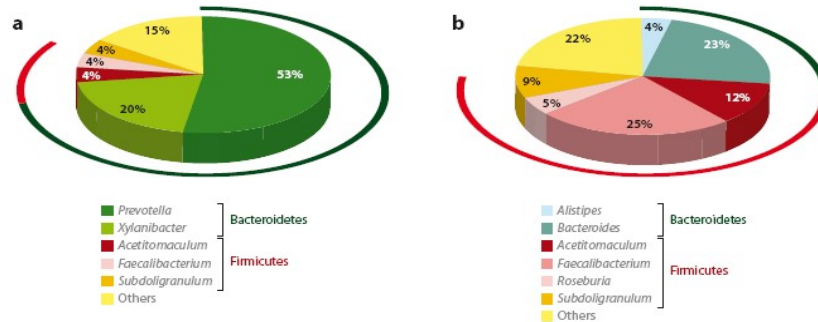


*Staines A. (1997) and Bodansky H.J. (1992)*



*Cho and Blaser Nat Rev Genetics 2012, 13:260*

## IMPACT OF DIET IN SHAPING GUT MICROBIOTA REVEALED BY A COMPARATIVE STUDY IN CHILDREN FROM EUROPE AND RURAL AFRICA



**Figure 1**

Bacterial taxa of the intestinal microbiota differ depending on diet. Taxa identified using 16S ribosomal RNA sequencing of DNA from fecal samples of children from (a) Burkina Faso and (b) Italy. The colors indicate differential distribution of classes of bacteria, including Firmicutes (red) and Bacteroidetes (green). Figure reproduced from Reference 14.

C De Filippo et al. 2010 *Proc. Natl. Acad. Sci. USA* 107:14691–96

## FACTORS CONTRIBUTING TO THE APPEARANCE OF INFECTIONS

### Sources of pathogenic agents

- drinking water
- food (cold storage)
- climate
- housing conditions

### Anti-infectious defense

- genetic factors
- nutrition
- antibiotics
- vaccination

## **THERAPY OF AUTOIMMUNE DISEASES**

---

- **Immunosuppression**
- **Monoclonal antibodies (targets T cells, B cells...)**
- **Autoantigen?**

## Presentation by Kirsten Lerstrom



UNITING PEOPLE WITH LUPUS  
THROUGHOUT EUROPE



1

### Disclaimer



LUPUS EUROPE is a patient led umbrella organization of national lupus patient groups.

LUPUS EUROPE is a UK Charity No 803768

LUPUS EUROPE operates on funds from membership fees, donations, project partnerships, pharmaceutical sponsorships and other such support for general operations and specific projects.

Industry sponsors for operations and initiatives are GSK, UCB, Merck, Lilly and other smaller grants for annual convention.

LUPUS EUROPE Board of Trustees is elected to office and serve on a voluntary basis and do so without personal honorarium.



## LUPUS EUROPE



Established in 1989

26 national lupus groups:

Between 10- 6,000 members each

Total membership of +30,000

Approx 500,000 diagnosed with lupus in Europe\*

Orphanet 2016 –not rare

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## Complex and complicated: Autoimmune, connective tissue +



Multifaceted, multidimensional

Almost any organ and body system can be affected

Anchored in Rheumatology, but also other specialties could be involved

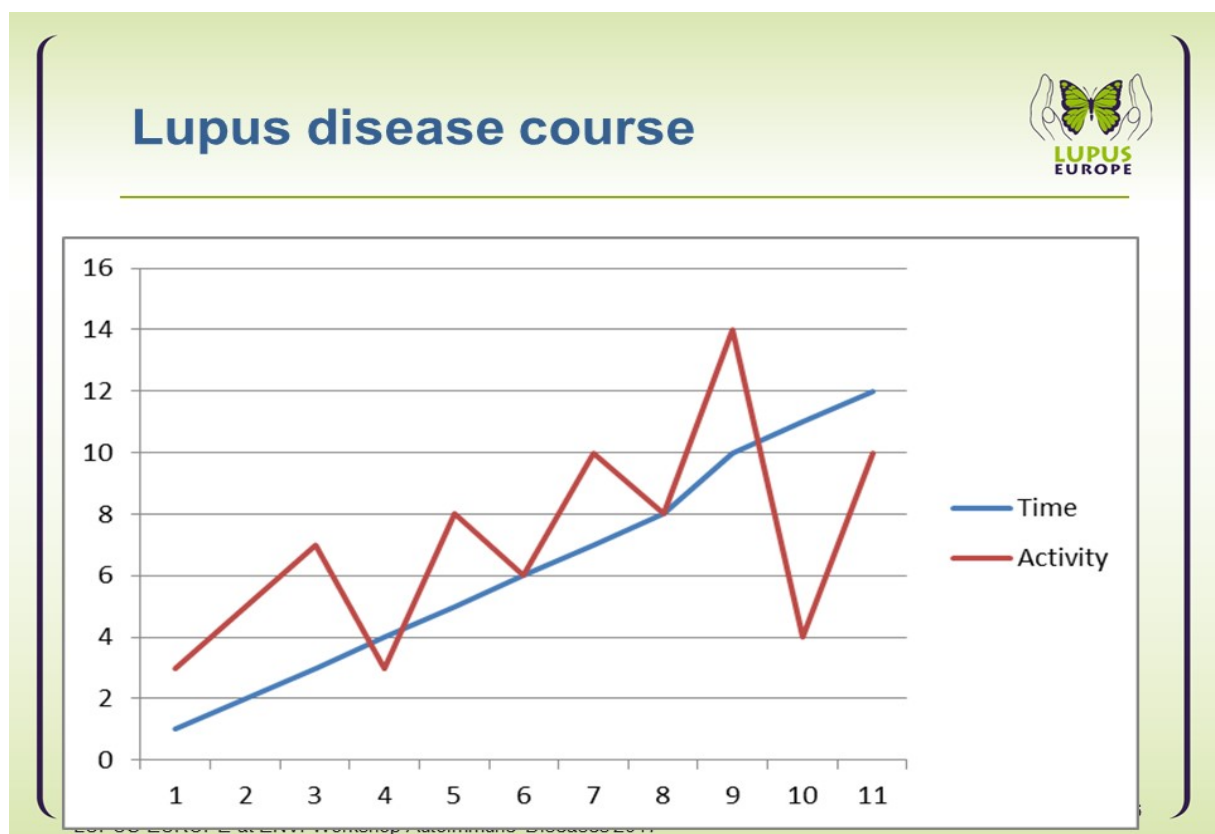
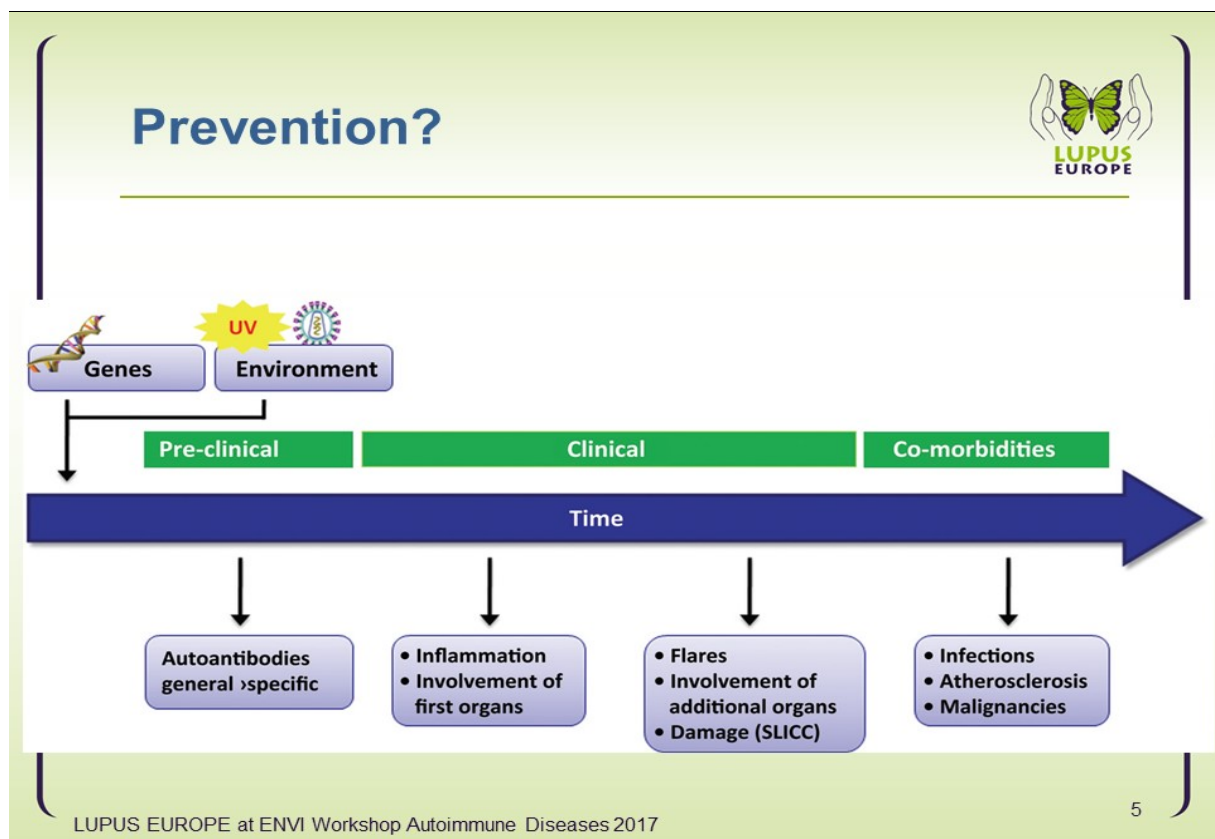
Average diagnosis age: 37 years  
Time to diagnosis: 7 years\*

9 out of 10 is female\*

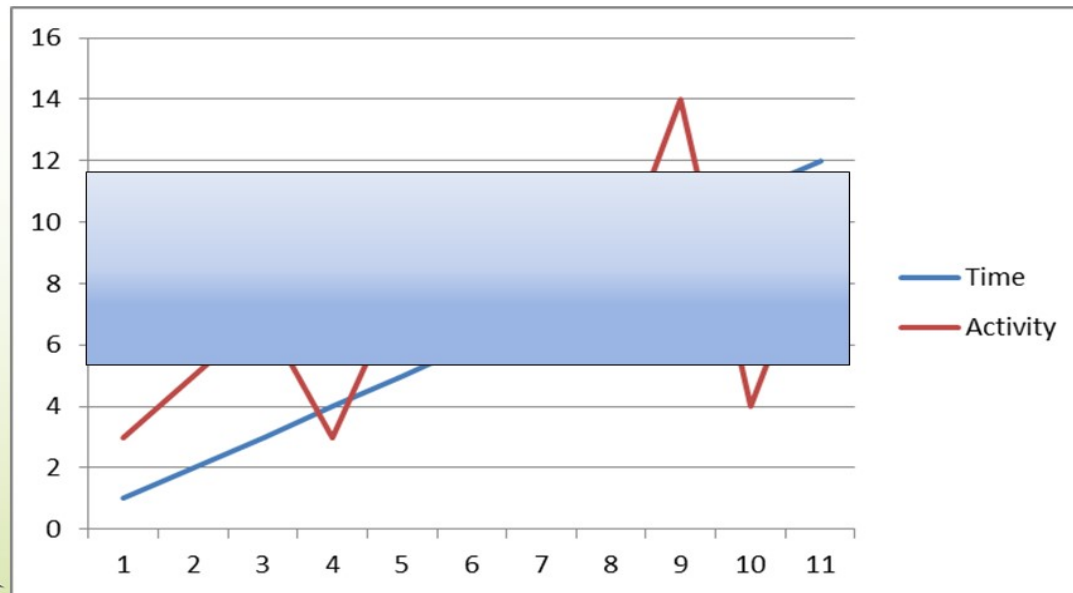
- at the time of creating career and establishing family!

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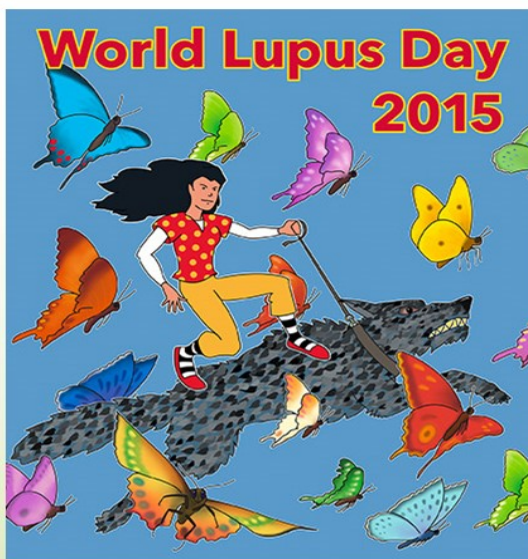
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## Lupus disease – aim of control



## Tame your wolf – tame your lupus



It is the firm belief of LUPUS EUROPE that:

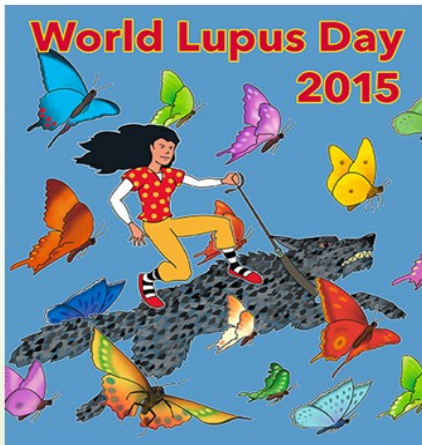
- Being involved in one's own disease
- Adherence to treatment
- Having the patient's voice heard in projects and trials

*- will help improve the situation for people living with lupus*

Tame your wolf – tame lupus was the theme for World Lupus Day 2015 campaign



## Treatment options



*Fast acting agent to quell unwanted disease activity:*

Prednisolone

*Long term and maintenance:*

Anti-malarials (Hydroxychloroquine)

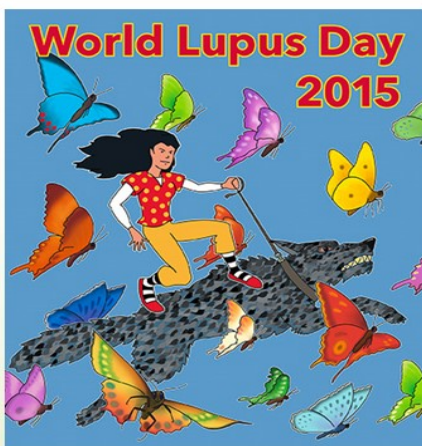
*If not enough then further immunosuppressives can be added:*

Methotrexate (milder chemo) to azathioprin, cyclosporine to mycophenolate mofetil

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## New biologics



*Biologics used:*

rituximab,  
infliximab,  
etanercept,  
adalimumab

and belimumab

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## Only one compound in 50+ years!



1955 Antimalarias approved for treatment of lupus  
1959 Prednisolone approved for lupus treatment  
2011-12 Belimumab approved by FDA and EMA\*

More than 100 open lupus trials on [clinicaltrials.gov](https://clinicaltrials.gov), but so far only belimumab has passed phase III

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## Treatment not good enough



Almost half out of employment within a few years of diagnosis\*

For the majority of those remaining in employment, it is on considerably reduced terms\*

**We** NEED to do better

\* C. Gordon et al, Rheumatology, 2013

The substantial burden of systemic lupus erythematosus on the productivity and careers of patients: a European patient-driven online survey

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## Kick Lupus! – PAG sustainability



### Recognition of the rôle of patient group.

In lupus we have recognized that we cannot make change alone – lifting this task requires close collaboration of all stakeholders!

LUPUS EUROPE has trained and will continue to enhance the capabilities of representatives as well as member groups maintaining the focus of patient values and engagement.

Our core operations and actors are living with lupus.

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## Kick Lupus! – action needed now



### Revision of research tools:

Clinical classification of SLE – ACR/EULAR cooperation

Genes and possible biomarkers – IMI PRECISEADS

EULAR Recommendations on Management of SLE – revision

Patient Reported Outcome measures in SLE – revision in Intl consortium

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## Kick Lupus! – action needed now



### European Reference Network ReCONNET:

Newly established network of specialist centres in Europe of nationally endorsed experts in rheumatic complex and rare connective tissue diseases.

Patient advocacy group representatives from the 13 disease areas are part of the network and involved in development of the framework required to support such a network – databases, communication and exchange platforms, experience building activities nationally and internationally to be used in the vast communication task of the network.

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## Conclusion – the case of lupus



1. Complex and complicated – difficult to live with as well as manage in typical health system setting
2. Living with lupus – diagnosed in average at the age of 37 after in average 7 years of disease symptoms
3. Within a few years of diagnosis only about half maintain employment, and if so for the majority on reduced terms
4. Treatment options – keeping us out of hospital, not own bed
5. Understanding disease, capturing symptoms and mapping manifestations are still in development
6. Complex and difficult to prove efficacy and efficiency
7. Sustainability and recognition of PAG needed

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