

Precision medicine in Alzheimer – why sex matters

Several pathologies affect men and women differently, and neglecting sex differences can result in suboptimal diagnosis and treatment for both sexes. A recent review and perspective led by Dr. Maria Teresa Ferretti (University of Zurich, Switzerland) and Professor Harald Hampel (Sorbonne University, Paris, France) investigate sex differences in Alzheimer's and their key role for the future of precision medicine.

In the cardiovascular field, sex differences have been extensively discussed and studied over the past 20 years. In a significant shift towards precision medicine, the American Heart Association has recently issued guidelines for sex specific prevention of stroke (<http://stroke.ahajournals.org/content/early/2014/02/06/01.str.0000442009.06663.48>).

Could this be true also for neurological and psychiatric diseases, which are notoriously heterogeneous in biology, clinical presentation and disease progression? It seems possible that failing to recognize and appropriately consider sex and gender differences has compromised the development and validation of optimal diagnostic and therapeutic tools for diseases such as Alzheimer's, for which clinical trials consistently provide disappointing results. Unfortunately, we still know very little about this.

While evidence is mounting that male and female brains respond differently to diseases, largely due to hormonal and genetic differences (<https://www.ncbi.nlm.nih.gov/pubmed/29924994>), most laboratory and clinical studies are still neglecting this aspect. In fact, data derived from men and women populations are being analyzed and reported cumulatively, without further analysis of differences between groups. For Alzheimer's, women represent 2/3 of patients worldwide –but beyond this epidemiological data, research into sex differences in AD is astonishingly limited.

A group of international scientists, called '**Women's Brain Project**', has decided to campaign for awareness and for promoting sex and gender-sensitive precision medicine in the field of neurology and psychiatry. The group has teamed up with the "**Alzheimer's Disease Precision Medicine Initiative**" (APMI), the first international research working group dedicated to the implementation of breakthrough *precision medicine* for Alzheimer's disease.

Together, the WBP and APMI have reviewed the scientific literature to document whether and how Alzheimer's disease differentially affects men and women. The authors looked at sex- differences in symptoms, biomarkers, risk factors, and in response to medical intervention.

This extensive review, published today in the internationally leading journal *Nature Reviews Neurology*, clearly demonstrates that sex and gender differences are indeed of very high relevance for diagnosis and treatment of Alzheimer's disease, as supported by several independent studies. However, this

important issue has only begun to be addressed by the community, and more systematic and rigorously controlled work needs to be done.

*“We have found consistent sex differences in the progression of the disease and in risk factors reported in the literature”, says **Professor Harald Hampel**, senior author of the publication and Chair of the Alzheimer Precision Medicine Initiative (APMI) . **Professor Hampel** continues “for instance, women show faster cognitive decline and brain shrinkage than men, once first memory symptoms appear and the Alzheimer dementia stage is diagnosed. On the other hand, some metabolic risk factors such as obesity seem to be stronger represented in men. These differences have to be taken into consideration when designing personalized disease models for prevention, diagnosis and treatment. A one-size-fits all approach in Alzheimer’s has not worked – Alzheimer’s is highly heterogeneous and we have to take into consideration the specific needs of each patient. We believe that studying sex-differences will be crucial to ensure that men and women receive the best possible treatment in the framework of precision medicine for Alzheimer’s disease”*

The Authors believe *“that a lot more work should be done in this field, requiring a concerted effort from the scientific community”*.

*“What we found was that there were very few well-designed studies addressing the question of sex differences in AD” commented lead author **Dr. Maria Teresa Ferretti**. “Many studies failed to analyze sex differences at all. In papers reporting the results of recently completed phase 3 clinical trials for Alzheimer’s, there was no consideration to analyse sex differences. The neuroscience field just hasn’t got to grips with investigating relevant sex-differences in brain diseases”*.

The authors have identified 5 critical domains that need to be addressed for future studies, with specific recommendations for each:

- reporting of sex and gender specific data
- biomarkers
- risk factors
- clinical trials
- preclinical research

Recommendations include actively studying both male and female animals in pre-clinical research, explicitly reporting sex-differences in scientific reports (also if negative results are found) and examining the outcomes of clinical trials with respect to how men and women’s responses to drugs differ.

*“We hope this landmark publication will raise critical awareness amongst the scientific community and the public at large regarding the importance of studying sex-differences in brain health and disease, for both men and women” explains **Dr. Annemarie Schumacher Dimech**, President of the Women’s Brain Project. “This work runs alongside our campaign in generating social awareness around the importance of brain health and engaging policy makers, pharmaceutical companies and regulators to effect positive change”*.

Source:

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Sex differences in Alzheimer disease —the gateway to precision medicine

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About the Women’s Brain Project:

The Women’s Brain Project, established in 2016, is a non profit organization composed by scientists, patients and caregivers, that aims to stimulate a global discussion on gender and sex determinants of female vulnerability to brain and mental disease. To find out more, please visit

www.womensbrainproject.com

About the Alzheimer’s Disease Precision Medicine Initiative” (APMI):

The Alzheimer’s Disease Precision Medicine Initiative” (APMI), established in 2016, is an international consortium of scientists aimed to facilitate reforms in the conceptualization of Neurological diseases, such as Alzheimer’s, away from a traditional one-size fits all approach to drug development towards individualized biomarker-guided targeted therapy for the right patient at the right time.

Professor Harald Hampel, MD, PhD, MA, MSc

Professor Harald Hampel is Full Professor and AXA research fund and Sorbonne University Excellence Chair at Sorbonne University, Departments of Neurology and Neuroscience, Paris, France.

He is principal investigator and speaker of the Alzheimer Precision Medicine Initiative and of the Cholinergic Systems Working Group and Senior Associate Editor of the journal of the Alzheimer Association, "Alzheimer's & Dementia".

He published more than 600 peer-reviewed research papers and edited 8 books, won multiple awards for his research focusing on brain health & disease, biomarker and therapy discovery in Alzheimer's disease. He holds international research grants and is principal investigator of research consortia.

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