# Women, Menopause, Insulin Resistance and Alzheimer's: What is the link?

Filomena Trindade, MD, MPH, ABFM, ABOIM

February 27, 2019

GENOVA DIAGNOSTICS®

# Lahnor Powell, ND, MPH

**Medical Education Specialist for Genova Diagnostics**

GENOVA DIAGNOSTICS

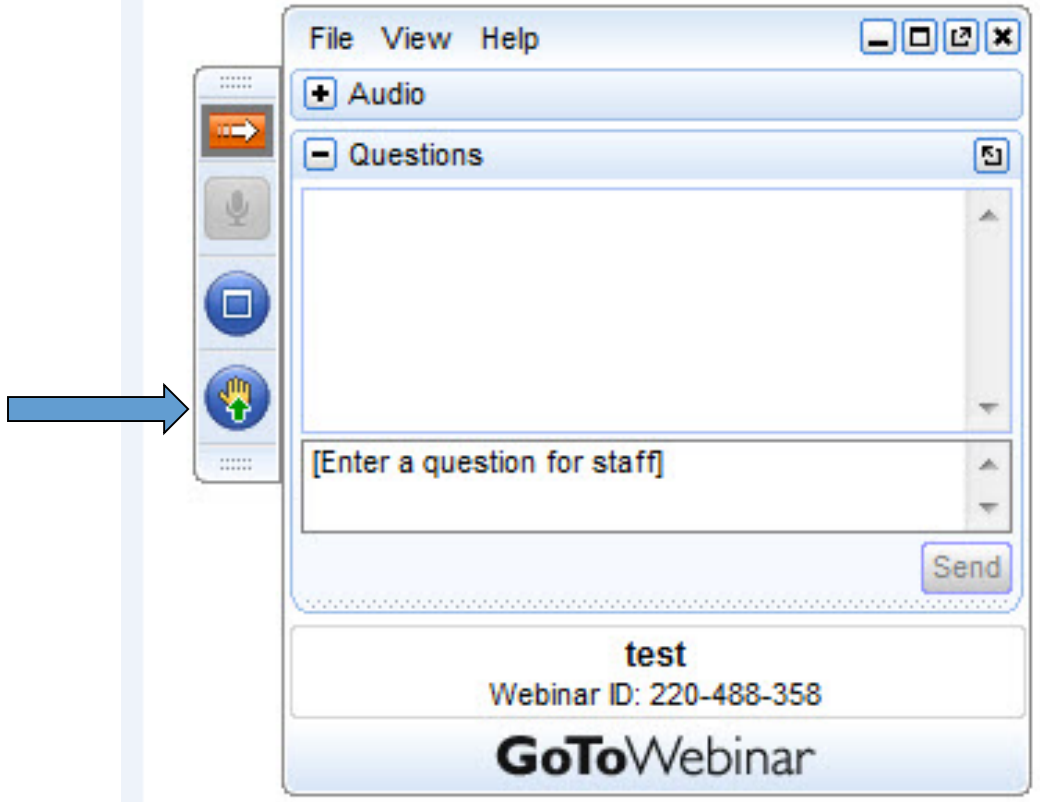
# Filomena Trindade MD, MPH, ABFM, ABOIM

**Presenter**

GENOVA DIAGNOSTICS

# Technical Issues & Clinical Questions

- Please type any technical issue or clinical question into either the “Chat” or “Questions” boxes, making sure to send them to “Organizer” at any time during the webinar.
- We will be compiling your clinical questions and answering as many as we can the final 15 minutes of the webinar.




DISCLAIMER: *Please note that any and all emails provided may be used for follow up correspondence and/or for further communication.*

GENOVA DIAGNOSTICS

# Need More Resources?

*Explore*

**WWW.GDX.NET**

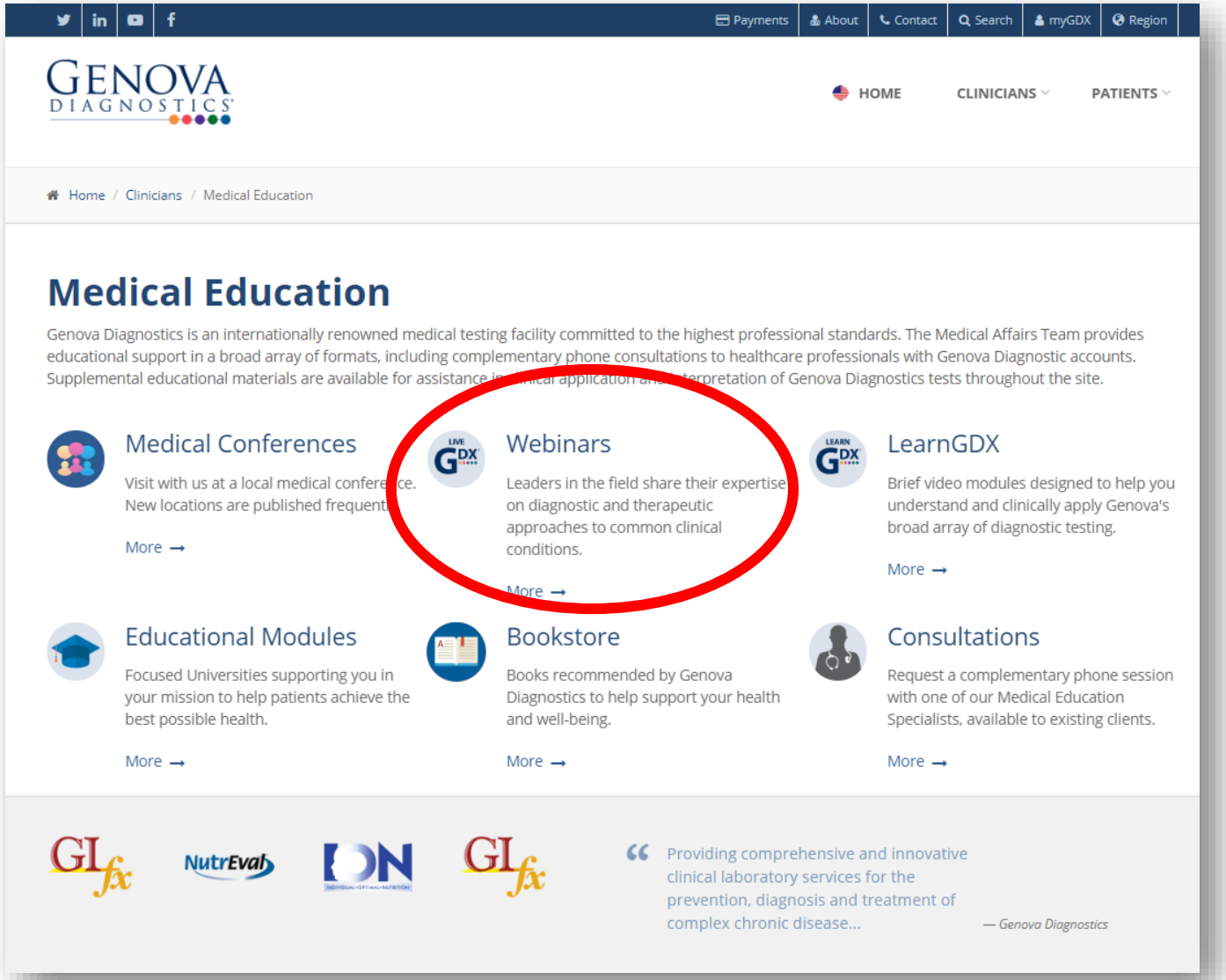
*for more information and educational resources, including…*

**LEARN GDX –** Brief video modules

**LIVE GDX –** Previous webinar recordings

**GI University –** Focused learning modules

**MY GDX –** Order materials and get results




GENOVA DIAGNOSTICS

# Women, Menopause, Insulin Resistance and Alzheimer's: What is the link?

Filomena Trindade, MD, MPH, ABFM, ABOIM

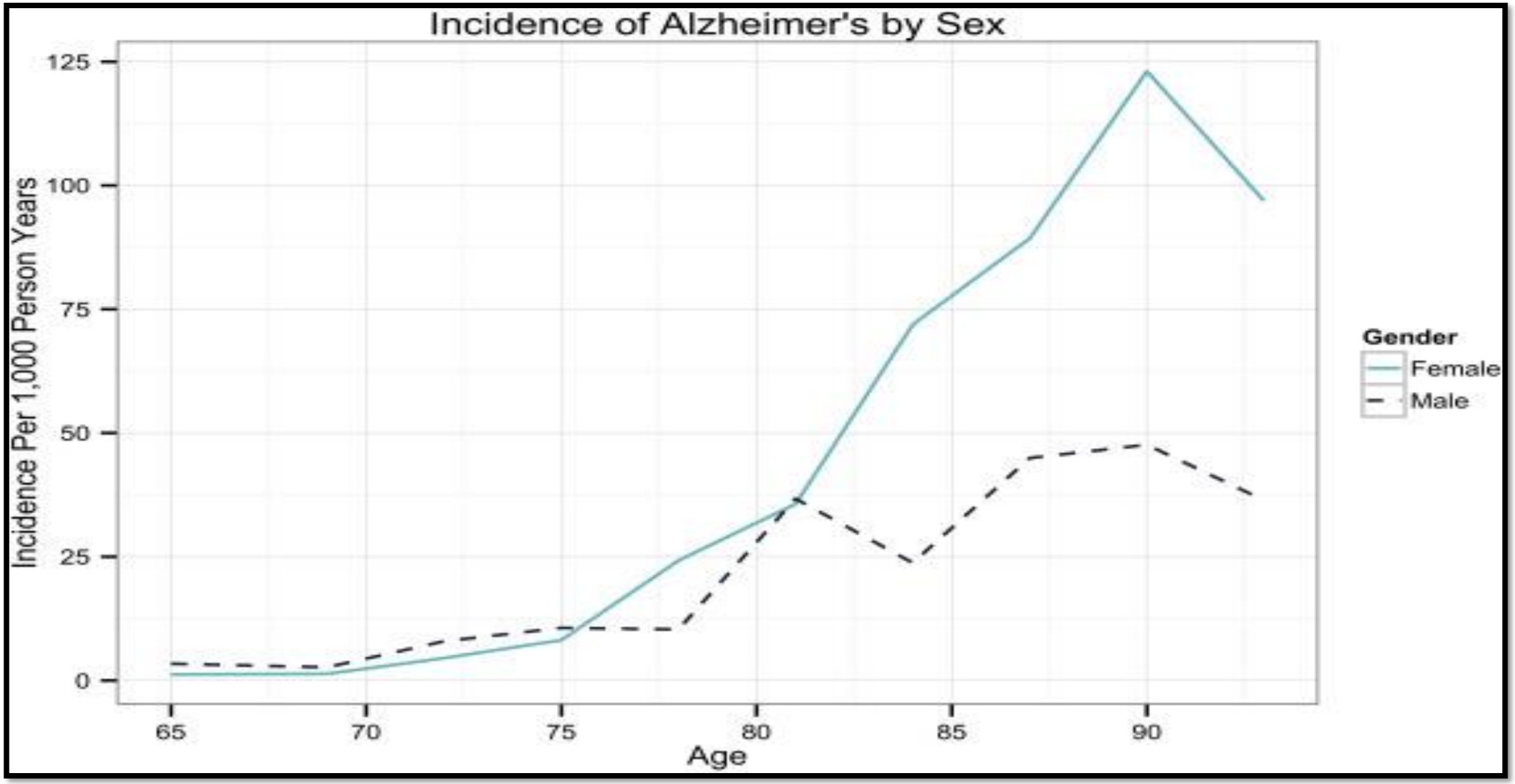
February 27, 2019

GENOVA DIAGNOSTICS®

# Objectives for This Presentation

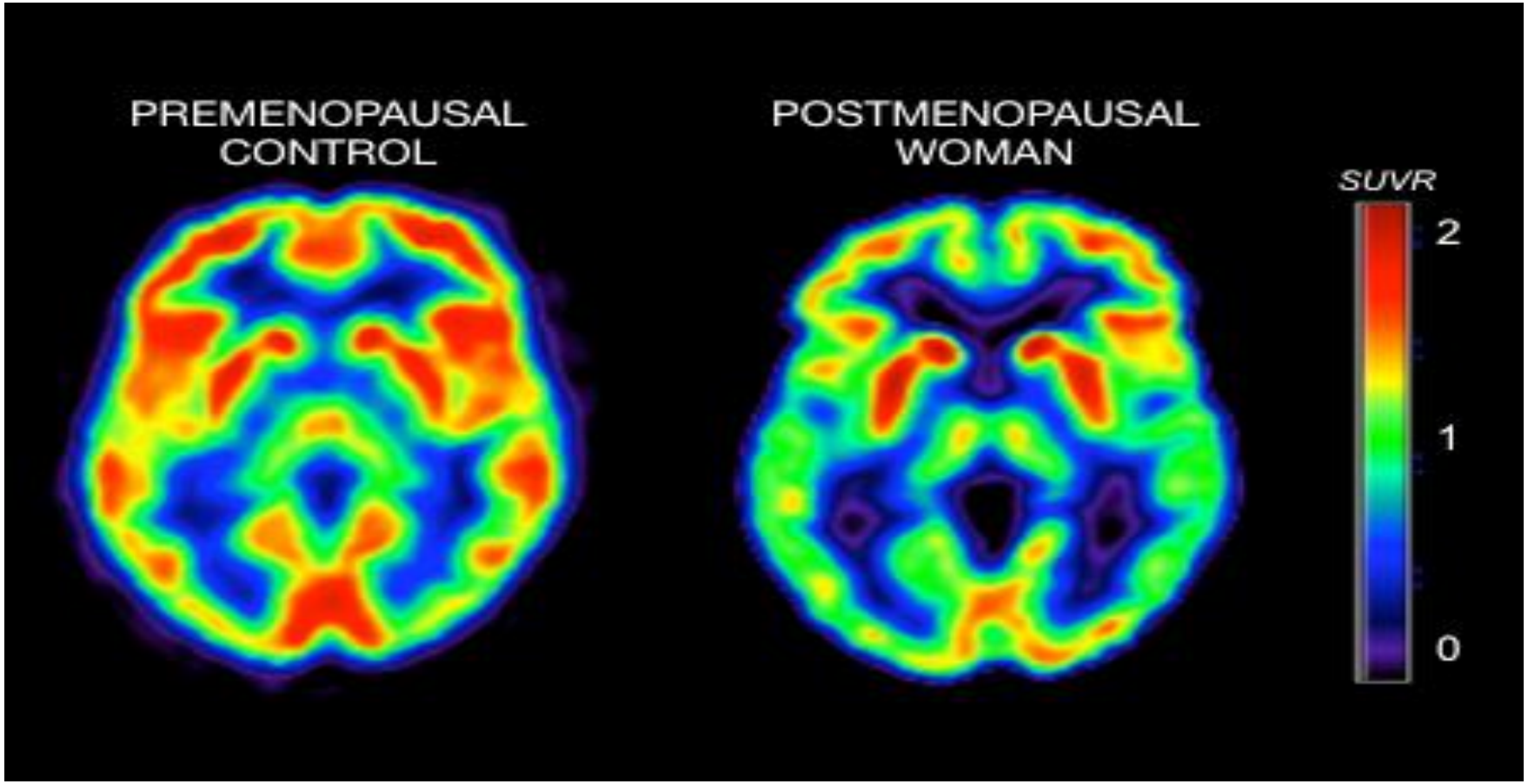
- Gain a basic understanding on the pathophysiology of mild cognitive decline and Alzheimer's and how it relates to insulin resistance and the menopausal transition in women
- Review the potential mechanisms of diabetes type 2 and how it contributes to Alzheimer's disease in women
- Identify the hallmarks of hormone replacement with respect to Alzheimer's disease in women


GENOVA DIAGNOSTICS




GENOVA DIAGNOSTICS

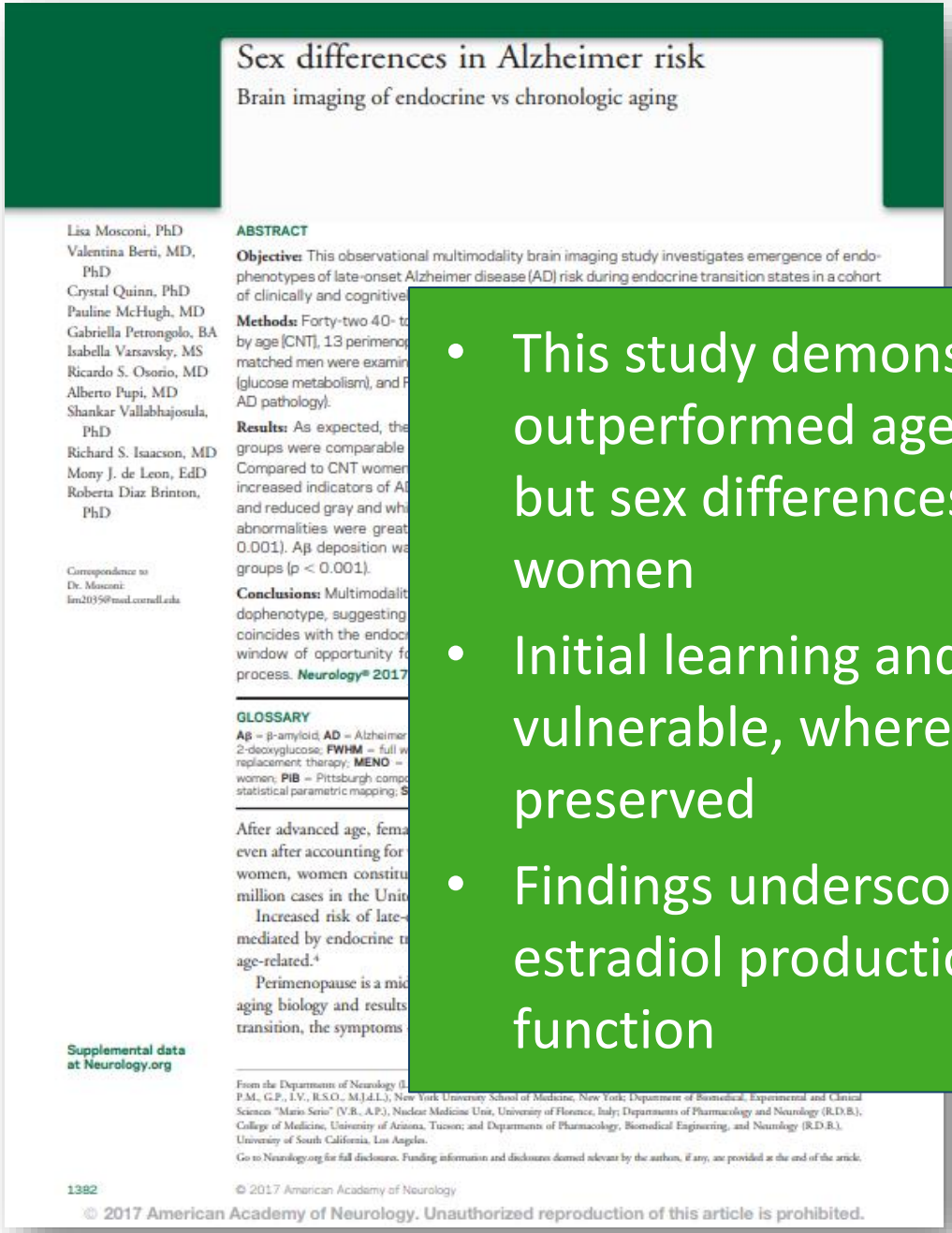
Brandalyn C, et al. *J Steroid Biochem Mol Biol*. 2016;160:134-47.




"The color scale reflects brain activity, with brighter colors indicating more activity, and darker colors indicating lower activity. The scan to the right (menopause) looks 'greener' and overall darker, which means that the woman's brain has substantially lower brain activity (more than 30 percent less) than the one to the left (no signs of menopause)."

GENOVA DIAGNOSTICS

Weill Cornell Medicine. https://news.weill.cornell.edu/news/2017/10/menopause-triggers-metabolic-changes-in-brain-that-may-promote-alzheimers. Accessed April 23, 2018.



# Sex differences in Alzheimer risk

## Brain imaging of endocrine vs chronologic aging

Lisa Mosconi, PhD
Valentina Berti, MD, PhD
Crystal Quinn, PhD
Pauline McHugh, MD
Gabriella Petrongolo, BA
Isabella Varsavsky, MS
Ricardo S. Osorio, MD
Alberto Pupi, MD
Shankar Vallabhajosula, PhD
Richard S. Isaacson, MD
Mony J. de Leon, EdD
Roberta Diaz Brinton, PhD

Correspondence to Dr. Mosconi: lm2035@med.cornell.edu

ABSTRACT

**Objective:** This observational multimodality brain imaging study investigates emergence of endo-phenotypes of late-onset Alzheimer disease (AD) risk during endocrine transition states in a cohort of clinically and cognitive

**Methods:** Forty-two 40- t by age [CNT], 13 perimeno matched men were examin (glucose metabolism), and AD pathology).

**Results:** As expected, the groups were comparable Compared to CNT women increased indicators of A and reduced gray and wh abnormalities were great 0.001). Aβ deposition w groups ($p < 0.001$).

**Conclusions:** Multimodalit dophenotype, suggesting coincides with the endoc window of opportunity f process. Neurology® 2017

GLOSSARY

Aβ = β-amyloid; AD = Alzheimer 2-deoxyglucose; FWHM = full w replacement therapy; MENO = women; PiB = Pittsburgh compo statistical parametric mapping; S

After advanced age, fema even after accounting for women, women constitu million cases in the Unit

Increased risk of late- mediated by endocrine t age-related.[4]

Perimenopause is a mi aging biology and results transition, the symptoms

Supplemental data at Neurology.org

From the Departments of Neurology (L P.M., G.P., I.V., R.S.O., M.J.d.L.); New York University School of Medicine, New York; Department of Biomedical, Experimental and Clinical Sciences "Mario Serio" (V.B., A.P.); Nuclear Medicine Unit, University of Florence, Italy; Departments of Pharmacology and Neurology (R.D.B.), College of Medicine, University of Arizona, Tucson; and Departments of Pharmacology, Biomedical Engineering, and Neurology (R.D.B.), University of South California, Los Angeles.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

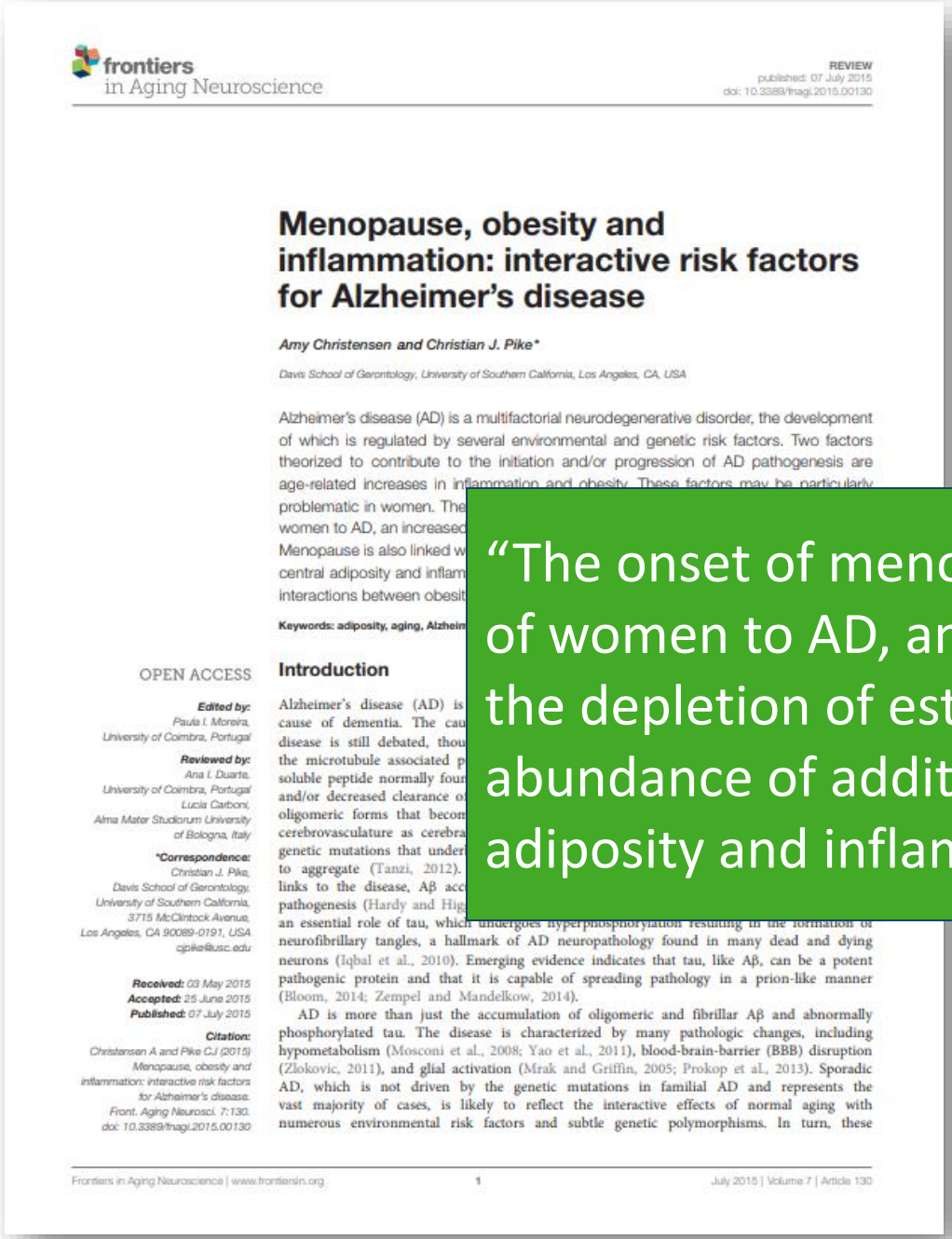




- This study demonstrated that, in early midlife, women outperformed age-matched men across all memory measures, but sex differences were attenuated for postmenopausal women
- Initial learning and memory retrieval were particularly vulnerable, whereas memory consolidation and storage were preserved
- Findings underscore the significance of the decline in ovarian estradiol production in midlife and its role in shaping memory function

GENOVA DIAGNOSTICS

Mosconi L, et al. *Neurology*. 2017;89(13):1382-90.



frontiers in Aging Neuroscience

REVIEW
published: 07 July 2015
doi: 10.3389/fnagi.2015.00130

# Menopause, obesity and inflammation: interactive risk factors for Alzheimer's disease

*Amy Christensen and Christian J. Pike**

*Davis School of Gerontology, University of Southern California, Los Angeles, CA, USA*

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder, the development of which is regulated by several environmental and genetic risk factors. Two factors theorized to contribute to the initiation and/or progression of AD pathogenesis are age-related increases in inflammation and obesity. These factors may be particularly problematic in women. The
women to AD, an increased
Menopause is also linked w
central adiposity and inflam
interactions between obesit

**Keywords: adiposity, aging, Alzhein**

OPEN ACCESS

***Edited by:***
*Paula I. Moreira,*
*University of Coimbra, Portugal*

***Reviewed by:***
*Ana I. Duarte,*
*University of Coimbra, Portugal*
*Lucia Carboni,*
*Alma Mater Studiorum University of Bologna, Italy*

****Correspondence:***
*Christian J. Pike,*
*Davis School of Gerontology, University of Southern California, 3715 McClintock Avenue, Los Angeles, CA 90089-0191, USA*
*cjpike@usc.edu*

***Received:*** *03 May 2015*
***Accepted:*** *25 June 2015*
***Published:*** *07 July 2015*

***Citation:***
*Christensen A and Pike CJ (2015) Menopause, obesity and inflammation: interactive risk factors for Alzheimer's disease. Front. Aging Neurosci. 7:130. doi: 10.3389/fnagi.2015.00130*

## Introduction

Alzheimer's disease (AD) is
cause of dementia. The cau
disease is still debated, thou
the microtubule associated p
soluble peptide normally four
and/or decreased clearance o
oligomeric forms that becom
cerebrovasculature as cerebra
genetic mutations that under
to aggregate (Tanzi, 2012).
links to the disease, Aβ acc
pathogenesis (Hardy and Hig
an essential role of tau, which undergoes hyperphosphorylation resulting in the formation of neurofibrillary tangles, a hallmark of AD neuropathology found in many dead and dying neurons (Iqbal et al., 2010). Emerging evidence indicates that tau, like Aβ, can be a potent pathogenic protein and that it is capable of spreading pathology in a prion-like manner (Bloom, 2014; Zempel and Mandelkow, 2014).

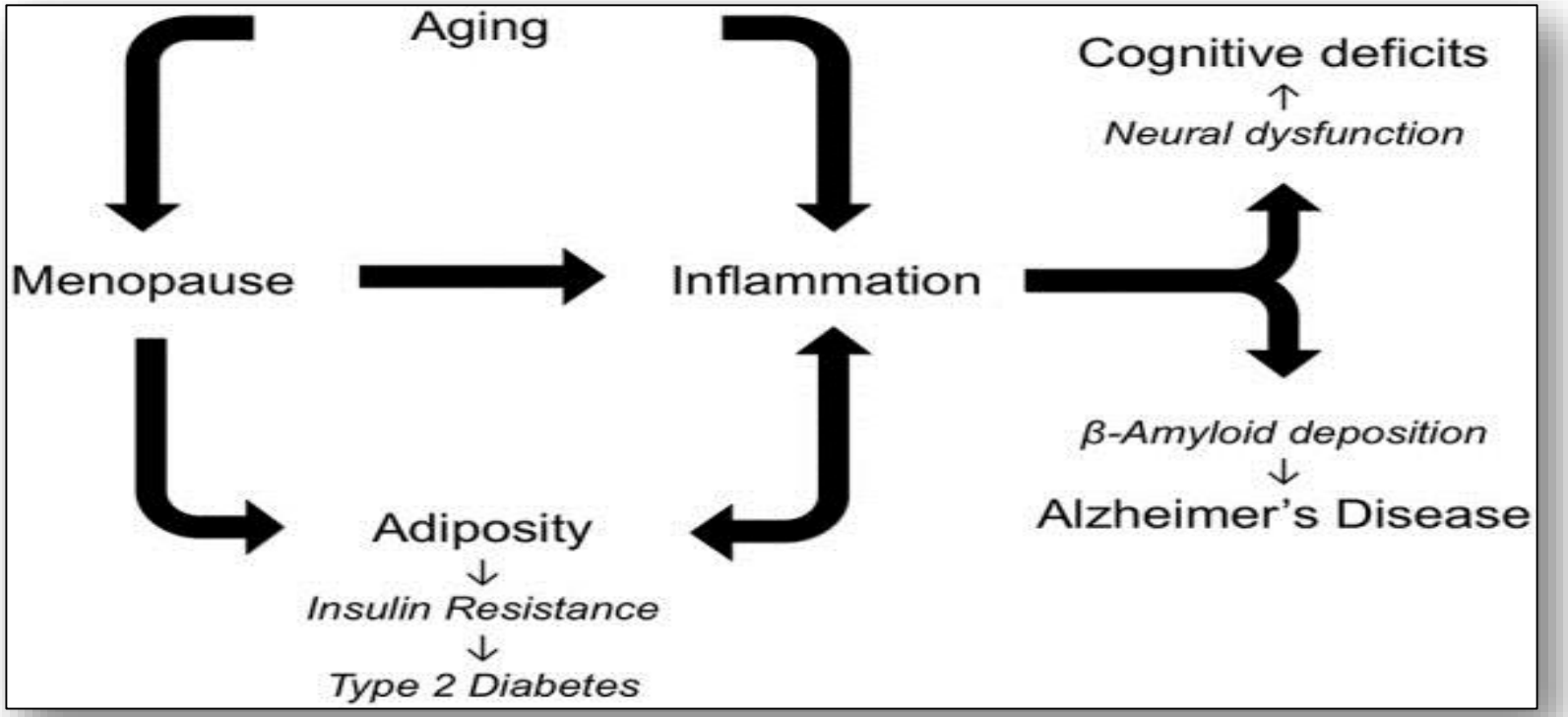
AD is more than just the accumulation of oligomeric and fibrillar Aβ and abnormally phosphorylated tau. The disease is characterized by many pathologic changes, including hypometabolism (Mosconi et al., 2008; Yao et al., 2011), blood-brain-barrier (BBB) disruption (Zlokovic, 2011), and glial activation (Mrak and Griffin, 2005; Prokop et al., 2013). Sporadic AD, which is not driven by the genetic mutations in familial AD and represents the vast majority of cases, is likely to reflect the interactive effects of normal aging with numerous environmental risk factors and subtle genetic polymorphisms. In turn, these



"The onset of menopause in mid-life elevates the vulnerability of women to AD, an increased risk that is likely associated with the depletion of estrogens. Menopause is also linked with an abundance of additional changes, including increased central adiposity and inflammation."

GENOVA DIAGNOSTICS

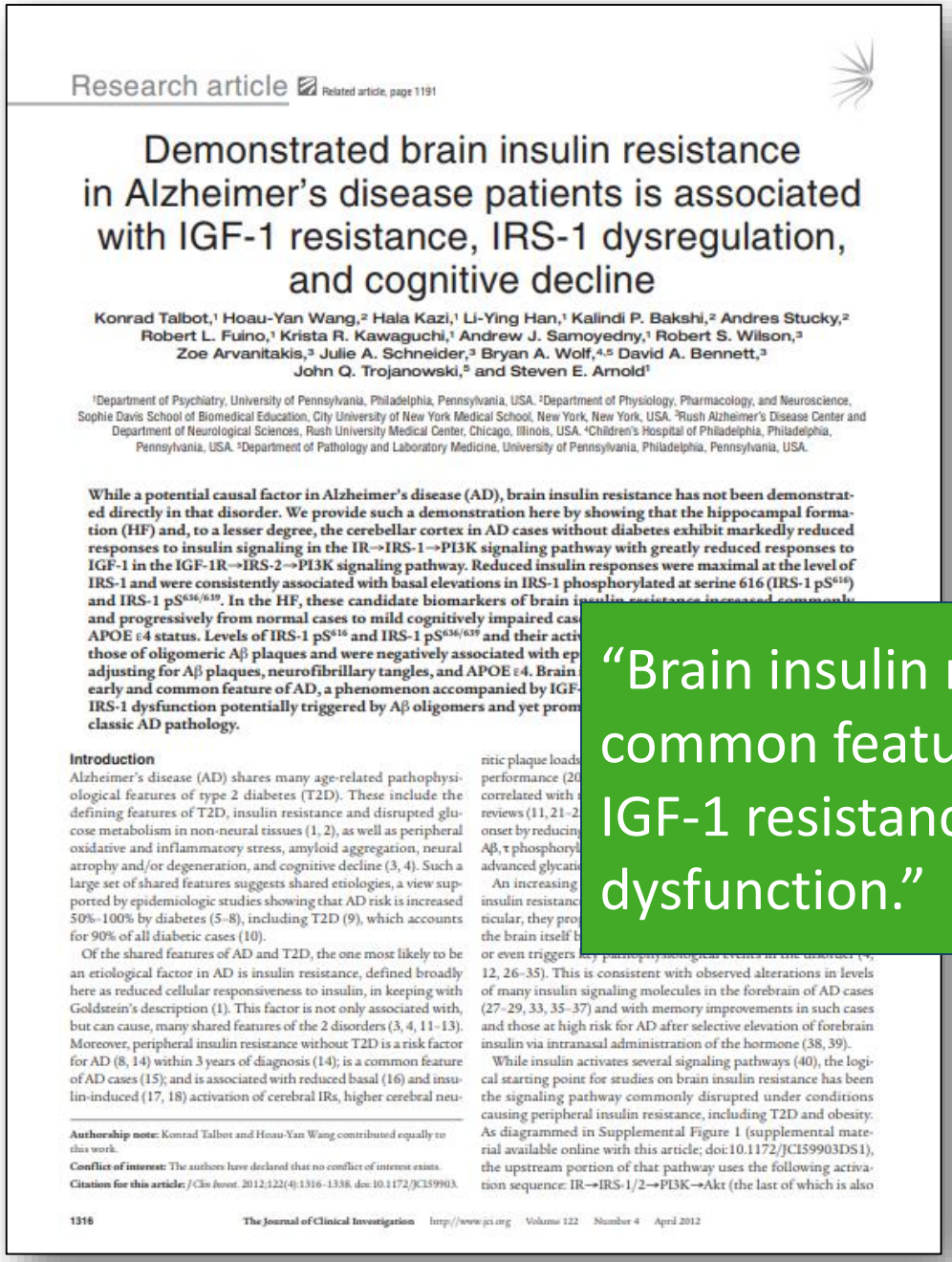
Christensen A, et al. *Front Aging Neurosci*. 2015;7:130.




**"Alzheimer's disease (AD) is a multifactorial disorder in which multiple risk factors are theorized to interact in regulating pathogenesis.** As depicted in the diagram an essential factor in AD is increasing age, which is also associated with elevated inflammation and, in women, menopause. The loss of estrogens at menopause increases central adiposity, which in turn increases inflammation and predisposes women to metabolic syndrome, insulin resistance, and AD. Individually and cooperatively, aging, menopause, adiposity, and inflammation lead to cognitive deficits and AD."

GENOVA DIAGNOSTICS

Christensen A, et al. *Front Aging Neurosci*. 2015;7:130.



Research article Related article, page 1191

# Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline

Konrad Talbot,[1] Hoau-Yan Wang,[2] Hala Kazi,[1] Li-Ying Han,[1] Kalindi P. Bakshi,[2] Andres Stucky,[2] Robert L. Fuino,[1] Krista R. Kawaguchi,[1] Andrew J. Samoyedny,[1] Robert S. Wilson,[3] Zoe Arvanitakis,[3] Julie A. Schneider,[3] Bryan A. Wolf,[4,5] David A. Bennett,[3] John Q. Trojanowski,[5] and Steven E. Arnold[1]

[1]Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania, USA. [2]Department of Physiology, Pharmacology, and Neuroscience, Sophie Davis School of Biomedical Education, City University of New York Medical School, New York, New York, USA. [3]Rush Alzheimer's Disease Center and Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA. [4]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA. [5]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

**While a potential causal factor in Alzheimer's disease (AD), brain insulin resistance has not been demonstrated directly in that disorder. We provide such a demonstration here by showing that the hippocampal formation (HF) and, to a lesser degree, the cerebellar cortex in AD cases without diabetes exhibit markedly reduced responses to insulin signaling in the IR→IRS-1→PI3K signaling pathway with greatly reduced responses to IGF-1 in the IGF-1R→IRS-2→PI3K signaling pathway. Reduced insulin responses were maximal at the level of IRS-1 and were consistently associated with basal elevations in IRS-1 phosphorylated at serine 616 (IRS-1 pS$^{616}$) and IRS-1 pS$^{636/639}$. In the HF, these candidate biomarkers of brain insulin resistance increased commonly and progressively from normal cases to mild cognitively impaired cas… APOE ε4 status. Levels of IRS-1 pS$^{616}$ and IRS-1 pS$^{636/639}$ and their acti… those of oligomeric Aβ plaques and were negatively associated with ep… adjusting for Aβ plaques, neurofibrillary tangles, and APOE ε4. Brain … early and common feature of AD, a phenomenon accompanied by IGF-… IRS-1 dysfunction potentially triggered by Aβ oligomers and yet prom… classic AD pathology.**

## Introduction

Alzheimer's disease (AD) shares many age-related pathophysiological features of type 2 diabetes (T2D). These include the defining features of T2D, insulin resistance and disrupted glucose metabolism in non-neural tissues (1, 2), as well as peripheral oxidative and inflammatory stress, amyloid aggregation, neural atrophy and/or degeneration, and cognitive decline (3, 4). Such a large set of shared features suggests shared etiologies, a view supported by epidemiologic studies showing that AD risk is increased 50%–100% by diabetes (5–8), including T2D (9), which accounts for 90% of all diabetic cases (10).

Of the shared features of AD and T2D, the one most likely to be an etiological factor in AD is insulin resistance, defined broadly here as reduced cellular responsiveness to insulin, in keeping with Goldstein's description (1). This factor is not only associated with, but can cause, many shared features of the 2 disorders (3, 4, 11–13). Moreover, peripheral insulin resistance without T2D is a risk factor for AD (8, 14) within 3 years of diagnosis (14); is a common feature of AD cases (15); and is associated with reduced basal (16) and insulin-induced (17, 18) activation of cerebral IRs, higher cerebral neu…

…ritic plaque loads… performance (20… correlated with … reviews (11, 21–2… onset by reducin… Aβ, τ phosphoryl… advanced glycati…

An increasing … insulin resistanc… ticular, they pro… the brain itself b… or even triggers …

12, 26–35). This is consistent with observed alterations in levels of many insulin signaling molecules in the forebrain of AD cases (27–29, 33, 35–37) and with memory improvements in such cases and those at high risk for AD after selective elevation of forebrain insulin via intranasal administration of the hormone (38, 39).

While insulin activates several signaling pathways (40), the logical starting point for studies on brain insulin resistance has been the signaling pathway commonly disrupted under conditions causing peripheral insulin resistance, including T2D and obesity. As diagrammed in Supplemental Figure 1 (supplemental material available online with this article; doi:10.1172/JCI59903DS1), the upstream portion of that pathway uses the following activation sequence: IR→IRS-1/2→PI3K→Akt (the last of which is also

**Authorship note:** Konrad Talbot and Hoau-Yan Wang contributed equally to this work.

**Conflict of interest:** The authors have declared that no conflict of interest exists.

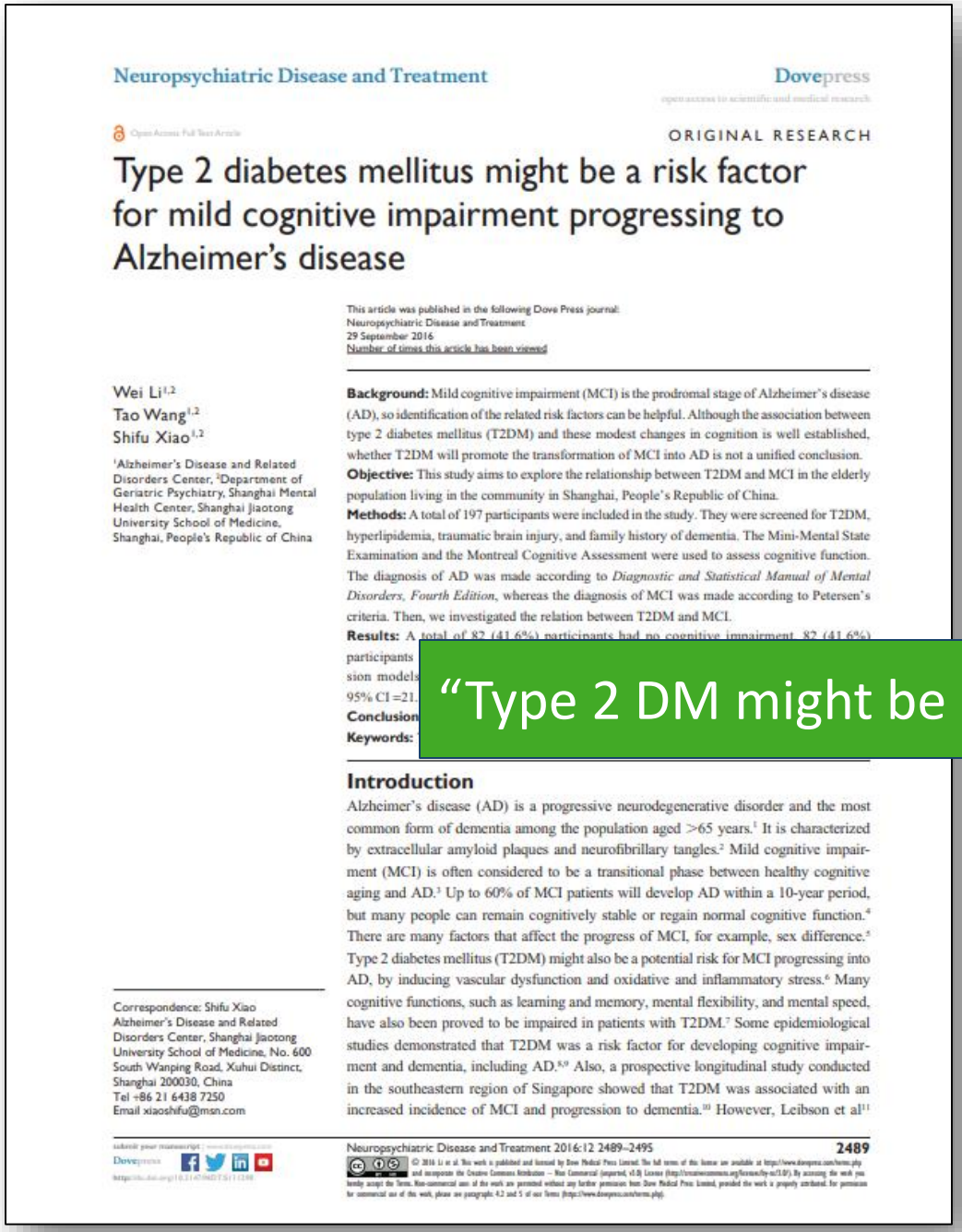
**Citation for this article:** *J Clin Invest.* 2012;122(4):1316–1338. doi:10.1172/JCI59903.



"Brain insulin resistance thus appears to be an early and common feature of AD, a phenomenon accompanied by IGF-1 resistance and closely associated with IRS-1 dysfunction."

GENOVA DIAGNOSTICS

Talbot K, et al. *J Clin Invest*. 2012;122(4):1316-38.



Neuropsychiatric Disease and Treatment

Dovepress

ORIGINAL RESEARCH

# Type 2 diabetes mellitus might be a risk factor for mild cognitive impairment progressing to Alzheimer's disease

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
29 September 2016
Number of times this article has been viewed

Wei Li[1,2]
Tao Wang[1,2]
Shifu Xiao[1,2]

[1]Alzheimer's Disease and Related Disorders Center, [2]Department of Geriatric Psychiatry, Shanghai Mental Health Center, Shanghai Jiaotong University School of Medicine, Shanghai, People's Republic of China

**Background:** Mild cognitive impairment (MCI) is the prodromal stage of Alzheimer's disease (AD), so identification of the related risk factors can be helpful. Although the association between type 2 diabetes mellitus (T2DM) and these modest changes in cognition is well established, whether T2DM will promote the transformation of MCI into AD is not a unified conclusion.

**Objective:** This study aims to explore the relationship between T2DM and MCI in the elderly population living in the community in Shanghai, People's Republic of China.

**Methods:** A total of 197 participants were included in the study. They were screened for T2DM, hyperlipidemia, traumatic brain injury, and family history of dementia. The Mini-Mental State Examination and the Montreal Cognitive Assessment were used to assess cognitive function. The diagnosis of AD was made according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, whereas the diagnosis of MCI was made according to Petersen's criteria. Then, we investigated the relation between T2DM and MCI.

**Results:** A total of 82 (41.6%) participants had no cognitive impairment, 82 (41.6%) participants

sion models

95% CI =21.

**Conclusion**

**Keywords:**

## Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia among the population aged >65 years.[1] It is characterized by extracellular amyloid plaques and neurofibrillary tangles.[2] Mild cognitive impairment (MCI) is often considered to be a transitional phase between healthy cognitive aging and AD.[3] Up to 60% of MCI patients will develop AD within a 10-year period, but many people can remain cognitively stable or regain normal cognitive function.[4] There are many factors that affect the progress of MCI, for example, sex difference.[5] Type 2 diabetes mellitus (T2DM) might also be a potential risk for MCI progressing into AD, by inducing vascular dysfunction and oxidative and inflammatory stress.[6] Many cognitive functions, such as learning and memory, mental flexibility, and mental speed, have also been proved to be impaired in patients with T2DM.[7] Some epidemiological studies demonstrated that T2DM was a risk factor for developing cognitive impairment and dementia, including AD.[8,9] Also, a prospective longitudinal study conducted in the southeastern region of Singapore showed that T2DM was associated with an increased incidence of MCI and progression to dementia.[10] However, Leibson et al[11]

Correspondence: Shifu Xiao
Alzheimer's Disease and Related Disorders Center, Shanghai Jiaotong University School of Medicine, No. 600 South Wanping Road, Xuhui Distinct, Shanghai 200030, China
Tel +86 21 6438 7250
Email xiaoshifu@msn.com

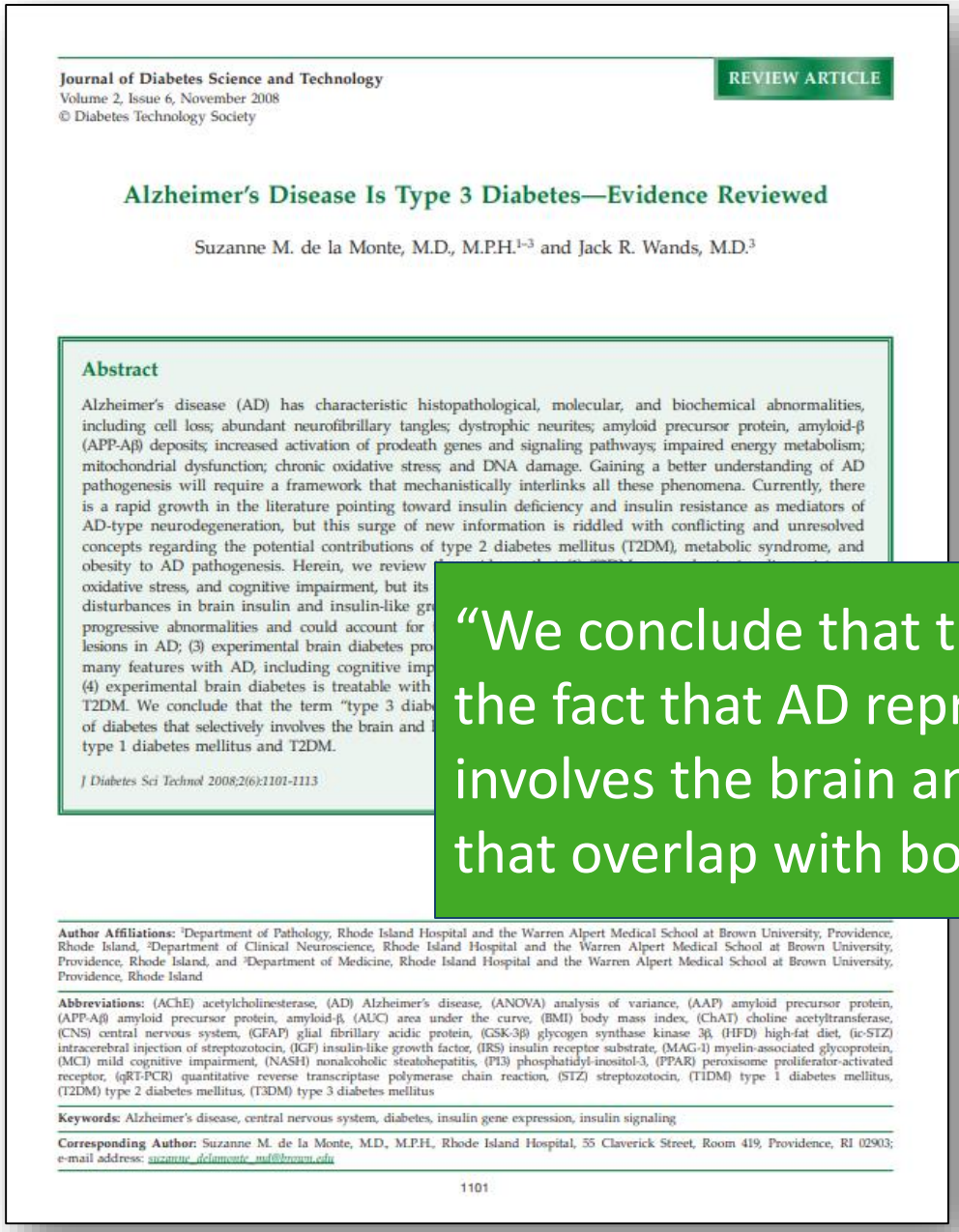




"Type 2 DM might be a risk factor for MCI progressing into AD."

GENOVA DIAGNOSTICS

Li W, et al. *Neuropsychiatr Dis Treat*. 2016;12:2489-95.



Journal of Diabetes Science and Technology
Volume 2, Issue 6, November 2008


REVIEW ARTICLE

# Alzheimer's Disease Is Type 3 Diabetes—Evidence Reviewed

Suzanne M. de la Monte, M.D., M.P.H.[1–3] and Jack R. Wands, M.D.[3]

**Abstract**

Alzheimer's disease (AD) has characteristic histopathological, molecular, and biochemical abnormalities, including cell loss; abundant neurofibrillary tangles; dystrophic neurites; amyloid precursor protein, amyloid-β (APP-Aβ) deposits; increased activation of prodeath genes and signaling pathways; impaired energy metabolism; mitochondrial dysfunction; chronic oxidative stress; and DNA damage. Gaining a better understanding of AD pathogenesis will require a framework that mechanistically interlinks all these phenomena. Currently, there is a rapid growth in the literature pointing toward insulin deficiency and insulin resistance as mediators of AD-type neurodegeneration, but this surge of new information is riddled with conflicting and unresolved concepts regarding the potential contributions of type 2 diabetes mellitus (T2DM), metabolic syndrome, and obesity to AD pathogenesis. Herein, we review
oxidative stress, and cognitive impairment, but its
disturbances in brain insulin and insulin-like gr
progressive abnormalities and could account for
lesions in AD; (3) experimental brain diabetes pro
many features with AD, including cognitive imp
(4) experimental brain diabetes is treatable with
T2DM. We conclude that the term "type 3 diab
of diabetes that selectively involves the brain and
type 1 diabetes mellitus and T2DM.

*J Diabetes Sci Technol 2008;2(6):1101-1113*

**Author Affiliations:** [1]Department of Pathology, Rhode Island Hospital and the Warren Alpert Medical School at Brown University, Providence, Rhode Island, [2]Department of Clinical Neuroscience, Rhode Island Hospital and the Warren Alpert Medical School at Brown University, Providence, Rhode Island, and [3]Department of Medicine, Rhode Island Hospital and the Warren Alpert Medical School at Brown University, Providence, Rhode Island

**Abbreviations:** (AChE) acetylcholinesterase, (AD) Alzheimer's disease, (ANOVA) analysis of variance, (AAP) amyloid precursor protein, (APP-Aβ) amyloid precursor protein, amyloid-β, (AUC) area under the curve, (BMI) body mass index, (ChAT) choline acetyltransferase, (CNS) central nervous system, (GFAP) glial fibrillary acidic protein, (GSK-3β) glycogen synthase kinase 3β, (HFD) high-fat diet, (ic-STZ) intracerebral injection of streptozotocin, (IGF) insulin-like growth factor, (IRS) insulin receptor substrate, (MAG-1) myelin-associated glycoprotein, (MCI) mild cognitive impairment, (NASH) nonalcoholic steatohepatitis, (PI3) phosphatidyl-inositol-3, (PPAR) peroxisome proliferator-activated receptor, (qRT-PCR) quantitative reverse transcriptase polymerase chain reaction, (STZ) streptozotocin, (T1DM) type 1 diabetes mellitus, (T2DM) type 2 diabetes mellitus, (T3DM) type 3 diabetes mellitus

**Keywords:** Alzheimer's disease, central nervous system, diabetes, insulin gene expression, insulin signaling

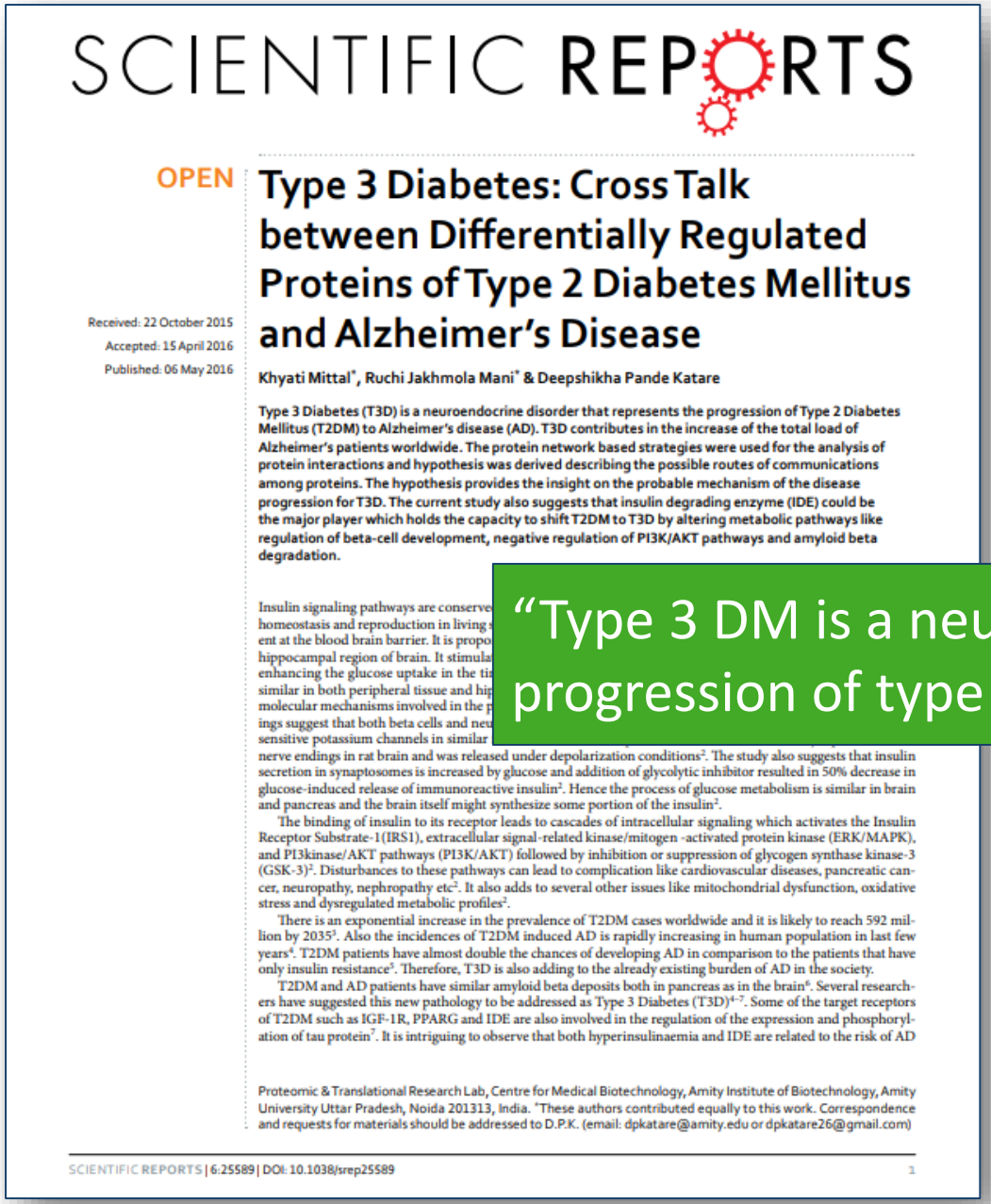
**Corresponding Author:** Suzanne M. de la Monte, M.D., M.P.H., Rhode Island Hospital, 55 Claverick Street, Room 419, Providence, RI 02903; e-mail address: suzanne_delamonte_md@brown.edu



"We conclude that the term type 3 diabetes accurately reflects the fact that AD represents a form of diabetes that selectively involves the brain and has molecular and biochemical features that overlap with both type1DM and T2DM."

GENOVA DIAGNOSTICS

de la Monte SM, et al. *J Diabetes Sci Technol*. 2008;2(6):1101-13.



SCIENTIFIC REPORTS

OPEN

# Type 3 Diabetes: Cross Talk between Differentially Regulated Proteins of Type 2 Diabetes Mellitus and Alzheimer's Disease

Received: 22 October 2015
Accepted: 15 April 2016
Published: 06 May 2016

Khyati Mittal*, Ruchi Jakhmola Mani* & Deepshikha Pande Katare

**Type 3 Diabetes (T3D) is a neuroendocrine disorder that represents the progression of Type 2 Diabetes Mellitus (T2DM) to Alzheimer's disease (AD). T3D contributes in the increase of the total load of Alzheimer's patients worldwide. The protein network based strategies were used for the analysis of protein interactions and hypothesis was derived describing the possible routes of communications among proteins. The hypothesis provides the insight on the probable mechanism of the disease progression for T3D. The current study also suggests that insulin degrading enzyme (IDE) could be the major player which holds the capacity to shift T2DM to T3D by altering metabolic pathways like regulation of beta-cell development, negative regulation of PI3K/AKT pathways and amyloid beta degradation.**

Insulin signaling pathways are conserve
homeostasis and reproduction in living
ent at the blood brain barrier. It is propo
hippocampal region of brain. It stimula
enhancing the glucose uptake in the ti
similar in both peripheral tissue and hi
molecular mechanisms involved in the p
ings suggest that both beta cells and neu
sensitive potassium channels in similar
nerve endings in rat brain and was released under depolarization conditions[2]. The study also suggests that insulin secretion in synaptosomes is increased by glucose and addition of glycolytic inhibitor resulted in 50% decrease in glucose-induced release of immunoreactive insulin[2]. Hence the process of glucose metabolism is similar in brain and pancreas and the brain itself might synthesize some portion of the insulin[2].

The binding of insulin to its receptor leads to cascades of intracellular signaling which activates the Insulin Receptor Substrate-1(IRS1), extracellular signal-related kinase/mitogen -activated protein kinase (ERK/MAPK), and PI3kinase/AKT pathways (PI3K/AKT) followed by inhibition or suppression of glycogen synthase kinase-3 (GSK-3)[2]. Disturbances to these pathways can lead to complication like cardiovascular diseases, pancreatic cancer, neuropathy, nephropathy etc[2]. It also adds to several other issues like mitochondrial dysfunction, oxidative stress and dysregulated metabolic profiles[2].

There is an exponential increase in the prevalence of T2DM cases worldwide and it is likely to reach 592 million by 2035[3]. Also the incidences of T2DM induced AD is rapidly increasing in human population in last few years[4]. T2DM patients have almost double the chances of developing AD in comparison to the patients that have only insulin resistance[5]. Therefore, T3D is also adding to the already existing burden of AD in the society.

T2DM and AD patients have similar amyloid beta deposits both in pancreas as in the brain[6]. Several researchers have suggested this new pathology to be addressed as Type 3 Diabetes (T3D)[4–7]. Some of the target receptors of T2DM such as IGF-1R, PPARG and IDE are also involved in the regulation of the expression and phosphorylation of tau protein[7]. It is intriguing to observe that both hyperinsulinaemia and IDE are related to the risk of AD

Proteomic & Translational Research Lab, Centre for Medical Biotechnology, Amity Institute of Biotechnology, Amity University Uttar Pradesh, Noida 201313, India. *These authors contributed equally to this work. Correspondence and requests for materials should be addressed to D.P.K. (email: dpkatare@amity.edu or dpkatare26@gmail.com)



"Type 3 DM is a neuroendocrine disorder that represents the progression of type 2 DM to AD."

GENOVA DIAGNOSTICS

Mittal K, et al. *Sci Rep*. 2016;6:25589.

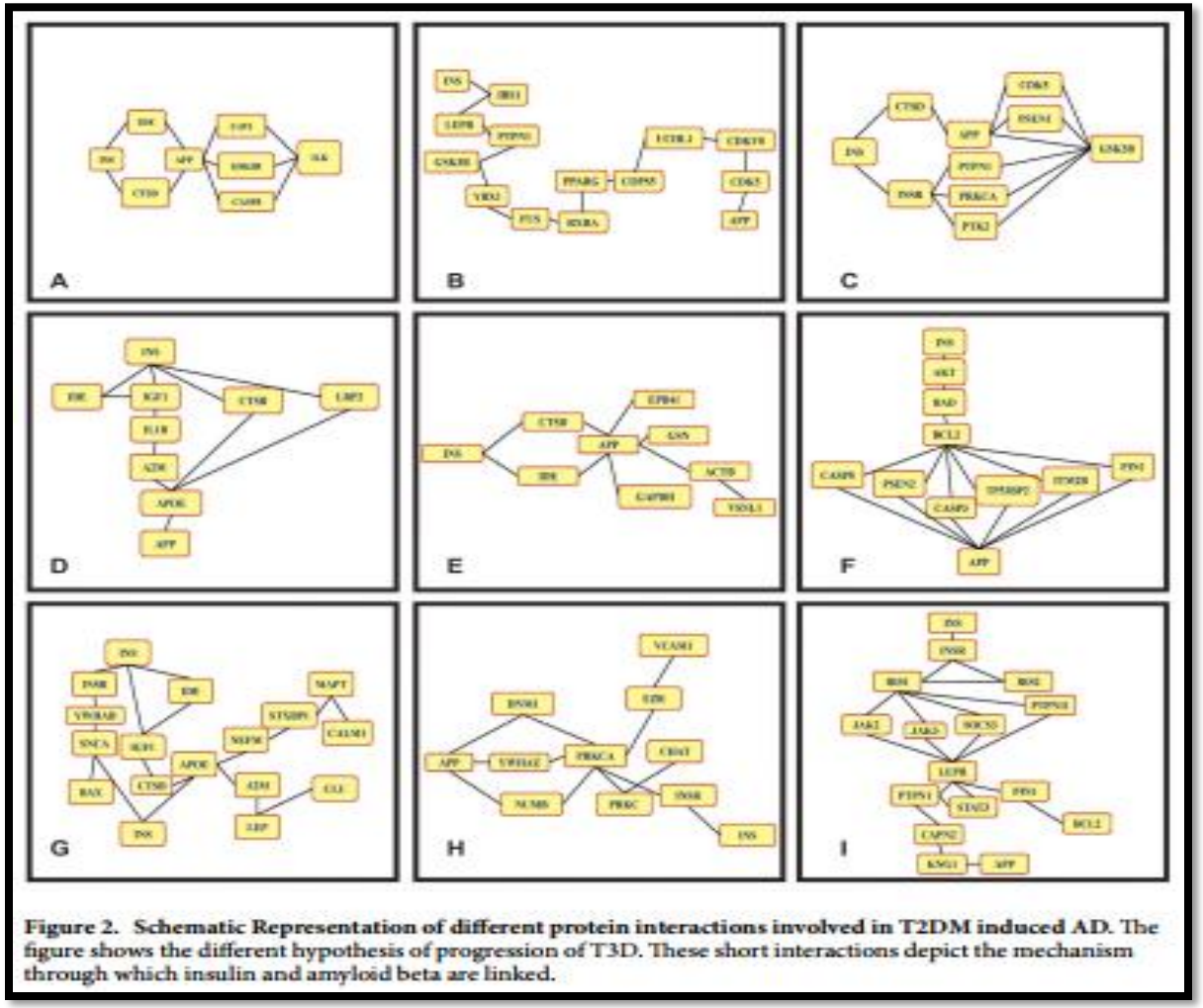



**Figure 2. Schematic Representation of different protein interactions involved in T2DM induced AD.** The figure shows the different hypothesis of progression of T3D. These short interactions depict the mechanism through which insulin and amyloid beta are linked.

Mechanism through which insulin and amyloid beta are linked.

GENOVA DIAGNOSTICS

Mittal K, et al. *Sci Rep*. 2016;6:25589.

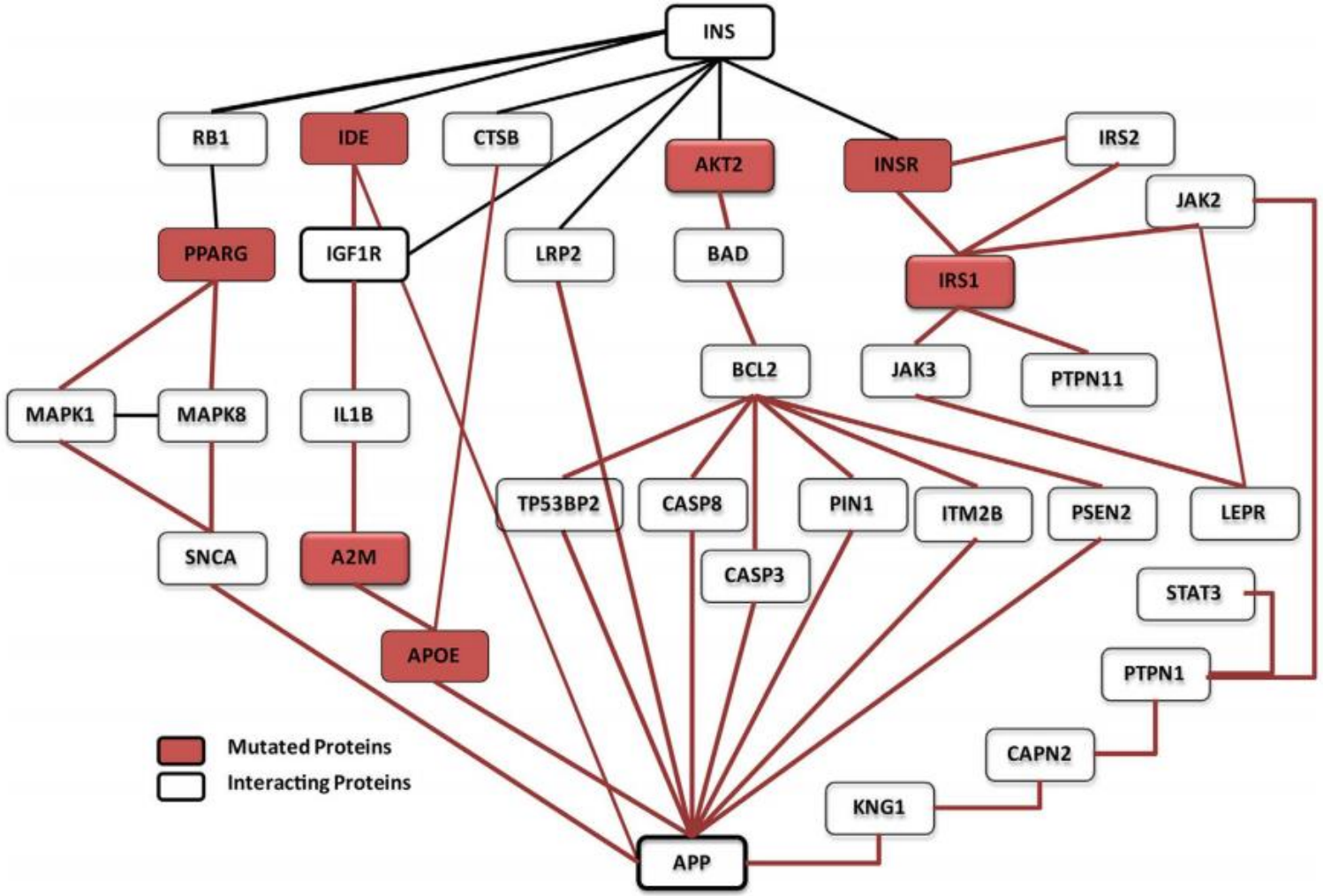



**Figure 3. Interaction of selected proteins from the network supposedly followed in T3D (mutated proteins are highlighted in red).** Final protein- interaction network was framed which includes mutated and differentially expressed proteins which link Type 2 Diabetes and Alzheimer's disease.

GENOVA DIAGNOSTICS

Mittal K, et al. *Sci Rep*. 2016;6:25589.

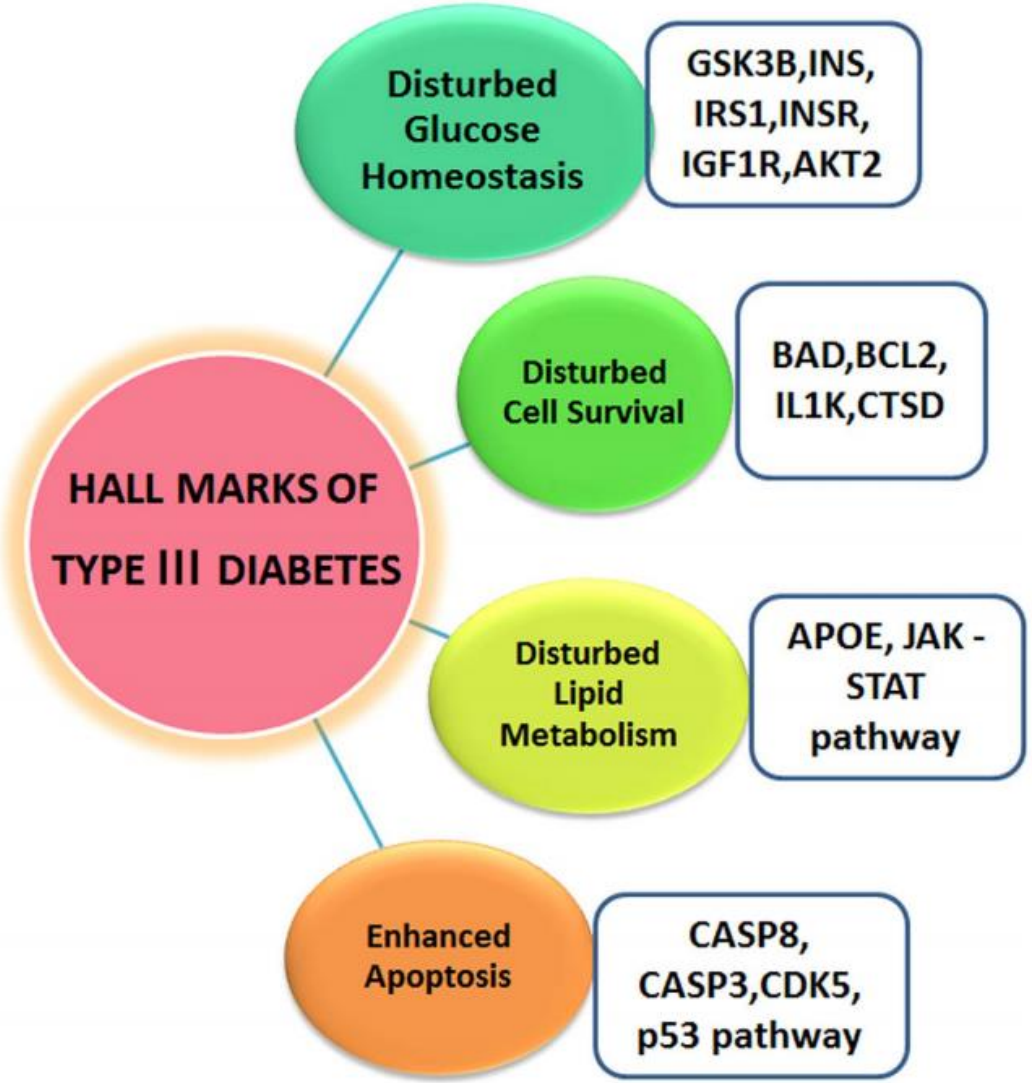
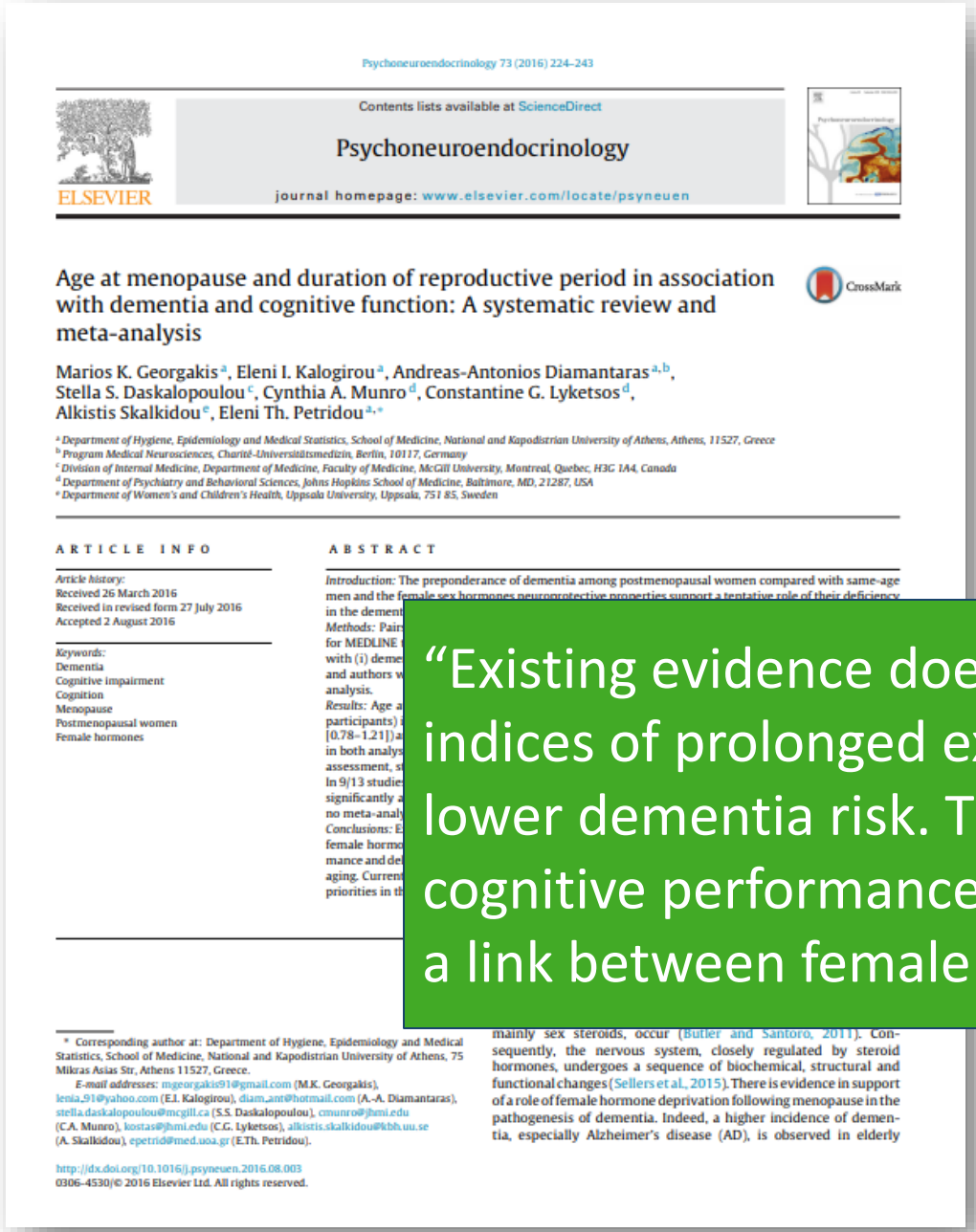



**Figure 4. Hallmarks of Type 3 Diabetes.** Attributes of Type 3 Diabetes represents the disturbed metabolic processes and pathways in Type 3 diabetes.

GENOVA DIAGNOSTICS

Mittal K, et al. *Sci Rep*. 2016;6:25589.



Psychoneuroendocrinology 73 (2016) 224–243

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

# Age at menopause and duration of reproductive period in association with dementia and cognitive function: A systematic review and meta-analysis

Marios K. Georgakis[a], Eleni I. Kalogirou[a], Andreas-Antonios Diamantaras[a,b], Stella S. Daskalopoulou[c], Cynthia A. Munro[d], Constantine G. Lyketsos[d], Alkistis Skalkidou[e], Eleni Th. Petridou[a,*]

[a] Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Athens, 11527, Greece
[b] Program Medical Neurosciences, Charité-Universitätsmedizin, Berlin, 10117, Germany
[c] Division of Internal Medicine, Department of Medicine, Faculty of Medicine, McGill University, Montreal, Quebec, H3G 1A4, Canada
[d] Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD, 21287, USA
[e] Department of Women's and Children's Health, Uppsala University, Uppsala, 751 85, Sweden

ARTICLE INFO

*Article history:*
Received 26 March 2016
Received in revised form 27 July 2016
Accepted 2 August 2016

*Keywords:*
Dementia
Cognitive impairment
Cognition
Menopause
Postmenopausal women
Female hormones

ABSTRACT

*Introduction:* The preponderance of dementia among postmenopausal women compared with same-age men and the female sex hormones neuroprotective properties support a tentative role of their deficiency in the dement

*Methods:* Pairs for MEDLINE with (i) deme and authors analysis.

*Results:* Age participants) [0.78–1.21]) in both analys assessment, s In 9/13 studie significantly no meta-analy

*Conclusions:* E female hormo mance and de aging. Curren priorities in th

* Corresponding author at: Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, 75 Mikras Asias Str, Athens 11527, Greece.
*E-mail addresses:* mgeorgakis91@gmail.com (M.K. Georgakis), lenia_91@yahoo.com (E.I. Kalogirou), diam_ant@hotmail.com (A.-A. Diamantaras), stella.daskalopoulou@mcgill.ca (S.S. Daskalopoulou), cmunro@jhmi.edu (C.A. Munro), kostas@jhmi.edu (C.G. Lyketsos), alkistis.skalkidou@kbh.uu.se (A. Skalkidou), epetrid@med.uoa.gr (E.Th. Petridou).

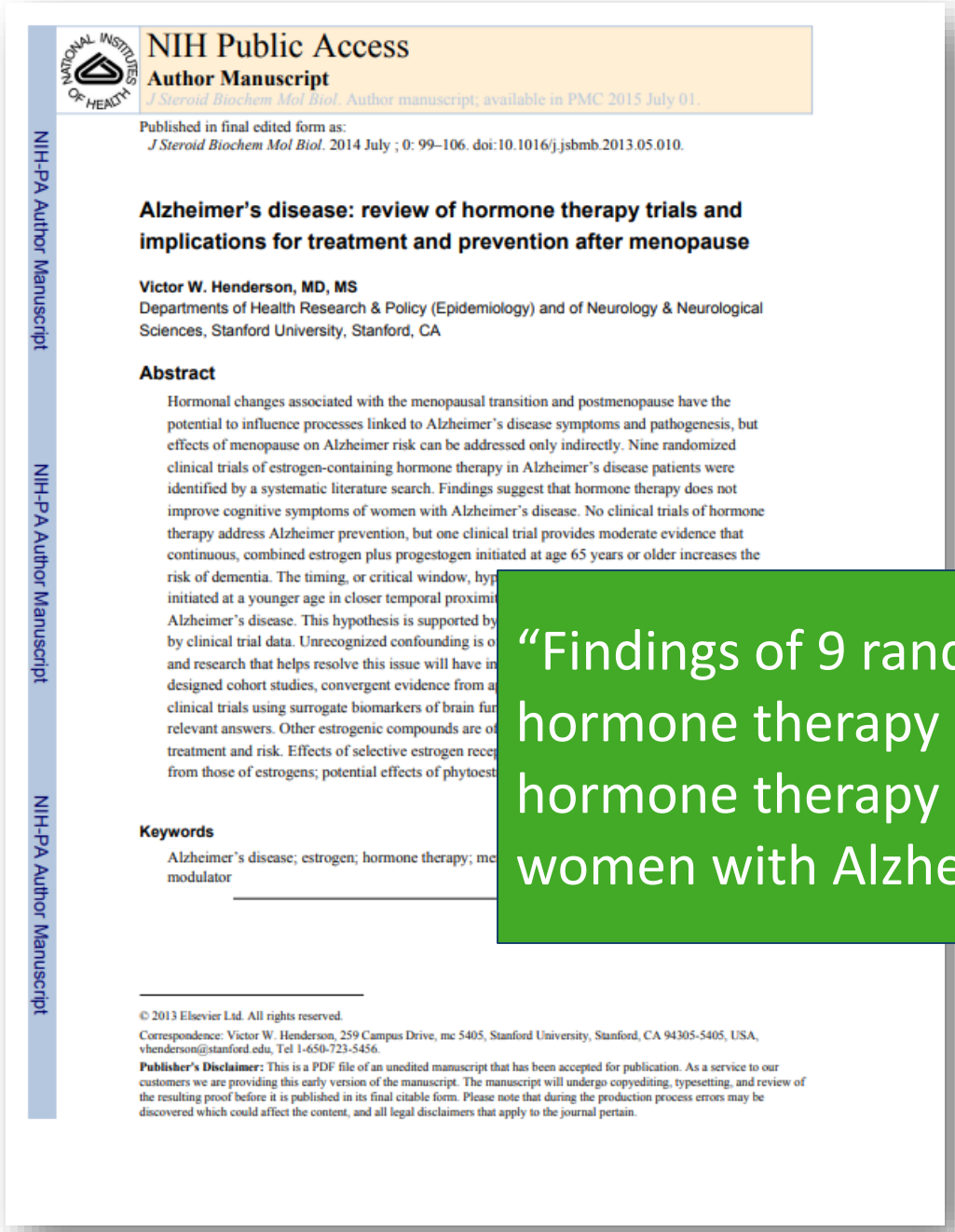
http://dx.doi.org/10.1016/j.psyneuen.2016.08.003


mainly sex steroids, occur (Butler and Santoro, 2011). Consequently, the nervous system, closely regulated by steroid hormones, undergoes a sequence of biochemical, structural and functional changes (Sellers et al., 2015). There is evidence in support of a role of female hormone deprivation following menopause in the pathogenesis of dementia. Indeed, a higher incidence of dementia, especially Alzheimer's disease (AD), is observed in elderly

"Existing evidence does not support an association between indices of prolonged exposure to female hormones and lower dementia risk. There are indications, however, for better cognitive performance and delayed cognitive decline, supporting a link between female hormone deficiency and cognitive aging."

GENOVA DIAGNOSTICS

Georgakis MK, et al. *Psychoneuroendocrinology*. 2016;73:224-43.



NIH Public Access
Author Manuscript
*J Steroid Biochem Mol Biol*. Author manuscript; available in PMC 2015 July 01.

Published in final edited form as:
*J Steroid Biochem Mol Biol*. 2014 July ; 0: 99–106. doi:10.1016/j.jsbmb.2013.05.010.

**Alzheimer's disease: review of hormone therapy trials and implications for treatment and prevention after menopause**

**Victor W. Henderson, MD, MS**
Departments of Health Research & Policy (Epidemiology) and of Neurology & Neurological Sciences, Stanford University, Stanford, CA

**Abstract**

Hormonal changes associated with the menopausal transition and postmenopause have the potential to influence processes linked to Alzheimer's disease symptoms and pathogenesis, but effects of menopause on Alzheimer risk can be addressed only indirectly. Nine randomized clinical trials of estrogen-containing hormone therapy in Alzheimer's disease patients were identified by a systematic literature search. Findings suggest that hormone therapy does not improve cognitive symptoms of women with Alzheimer's disease. No clinical trials of hormone therapy address Alzheimer prevention, but one clinical trial provides moderate evidence that continuous, combined estrogen plus progestogen initiated at age 65 years or older increases the risk of dementia. The timing, or critical window, hyp
initiated at a younger age in closer temporal proximit
Alzheimer's disease. This hypothesis is supported by
by clinical trial data. Unrecognized confounding is o
and research that helps resolve this issue will have in
designed cohort studies, convergent evidence from a
clinical trials using surrogate biomarkers of brain fun
relevant answers. Other estrogenic compounds are of
treatment and risk. Effects of selective estrogen recep
from those of estrogens; potential effects of phytoest

**Keywords**

Alzheimer's disease; estrogen; hormone therapy; me
modulator



Correspondence: Victor W. Henderson, 259 Campus Drive, mc 5405, Stanford University, Stanford, CA 94305-5405, USA, vhenderson@stanford.edu, Tel 1-650-723-5456.

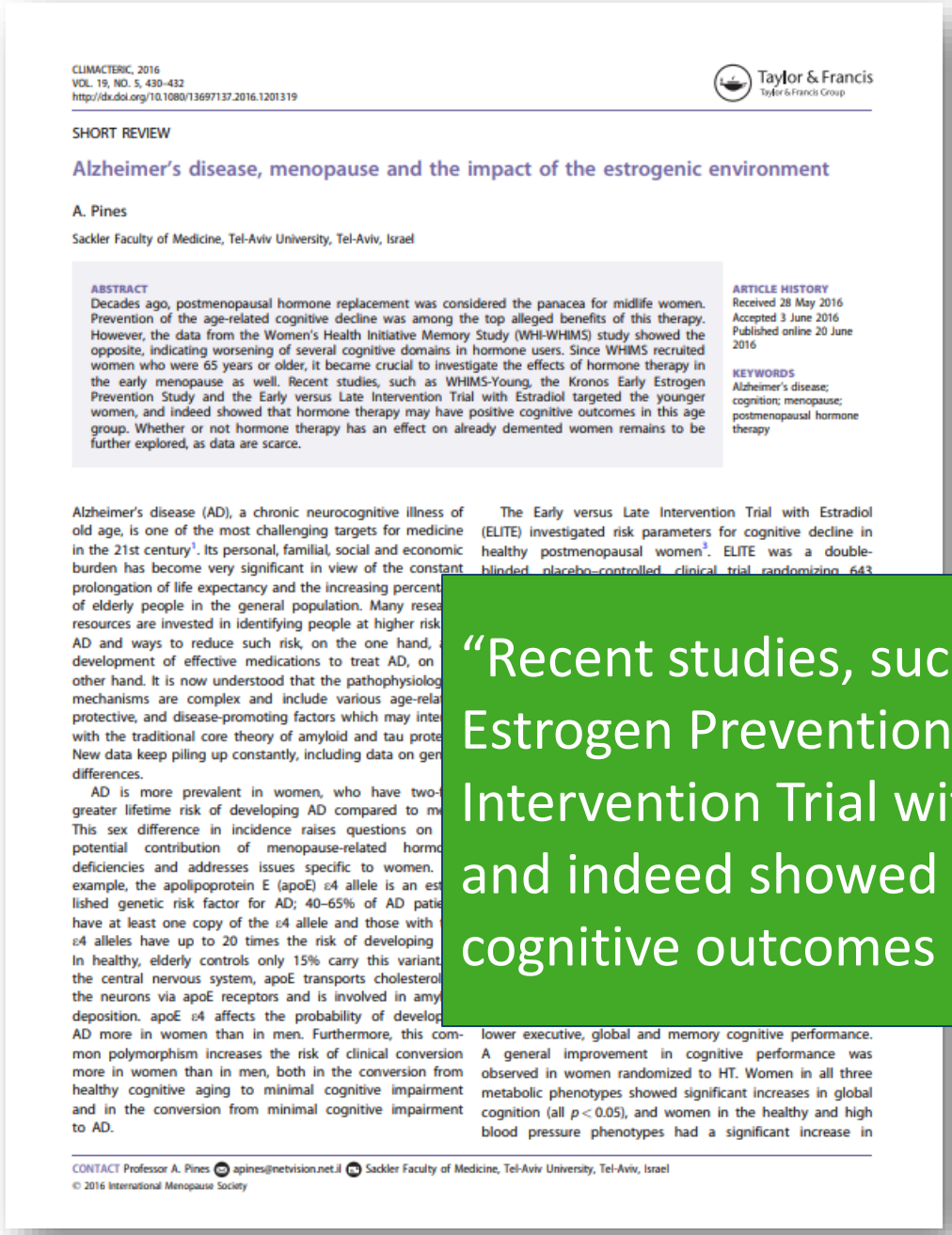




"Findings of 9 randomized clinical trials of estrogen containing hormone therapy in Alzheimer's disease suggested that hormone therapy does not improve cognitive symptoms of women with Alzheimer's disease."

GENOVA DIAGNOSTICS

Henderson VW. *J Steroid Biochem Mol Biol*. 2014;142:99-106.



CLIMACTERIC, 2016
VOL. 19, NO. 5, 430–432
http://dx.doi.org/10.1080/13697137.2016.1201319

Taylor & Francis
Taylor & Francis Group

SHORT REVIEW

# Alzheimer's disease, menopause and the impact of the estrogenic environment

A. Pines

Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

**ABSTRACT**

Decades ago, postmenopausal hormone replacement was considered the panacea for midlife women. Prevention of the age-related cognitive decline was among the top alleged benefits of this therapy. However, the data from the Women's Health Initiative Memory Study (WHI-WHIMS) study showed the opposite, indicating worsening of several cognitive domains in hormone users. Since WHIMS recruited women who were 65 years or older, it became crucial to investigate the effects of hormone therapy in the early menopause as well. Recent studies, such as WHIMS-Young, the Kronos Early Estrogen Prevention Study and the Early versus Late Intervention Trial with Estradiol targeted the younger women, and indeed showed that hormone therapy may have positive cognitive outcomes in this age group. Whether or not hormone therapy has an effect on already demented women remains to be further explored, as data are scarce.

**ARTICLE HISTORY**
Received 28 May 2016
Accepted 3 June 2016
Published online 20 June 2016

**KEYWORDS**
Alzheimer's disease; cognition; menopause; postmenopausal hormone therapy

Alzheimer's disease (AD), a chronic neurocognitive illness of old age, is one of the most challenging targets for medicine in the 21st century[1]. Its personal, familial, social and economic burden has become very significant in view of the constant prolongation of life expectancy and the increasing percent of elderly people in the general population. Many resea resources are invested in identifying people at higher risk AD and ways to reduce such risk, on the one hand, development of effective medications to treat AD, on other hand. It is now understood that the pathophysiolog mechanisms are complex and include various age-rela protective, and disease-promoting factors which may inte with the traditional core theory of amyloid and tau prote New data keep piling up constantly, including data on ger differences.

AD is more prevalent in women, who have two- greater lifetime risk of developing AD compared to m This sex difference in incidence raises questions on potential contribution of menopause-related hormo deficiencies and addresses issues specific to women. example, the apolipoprotein E (apoE) ε4 allele is an est lished genetic risk factor for AD; 40–65% of AD patie have at least one copy of the ε4 allele and those with ε4 alleles have up to 20 times the risk of developing In healthy, elderly controls only 15% carry this variant the central nervous system, apoE transports cholesterol the neurons via apoE receptors and is involved in amy deposition. apoE ε4 affects the probability of develop AD more in women than in men. Furthermore, this com- mon polymorphism increases the risk of clinical conversion more in women than in men, both in the conversion from healthy cognitive aging to minimal cognitive impairment and in the conversion from minimal cognitive impairment to AD.

The Early versus Late Intervention Trial with Estradiol (ELITE) investigated risk parameters for cognitive decline in healthy postmenopausal women[3]. ELITE was a double-blinded, placebo–controlled, clinical trial randomizing 643

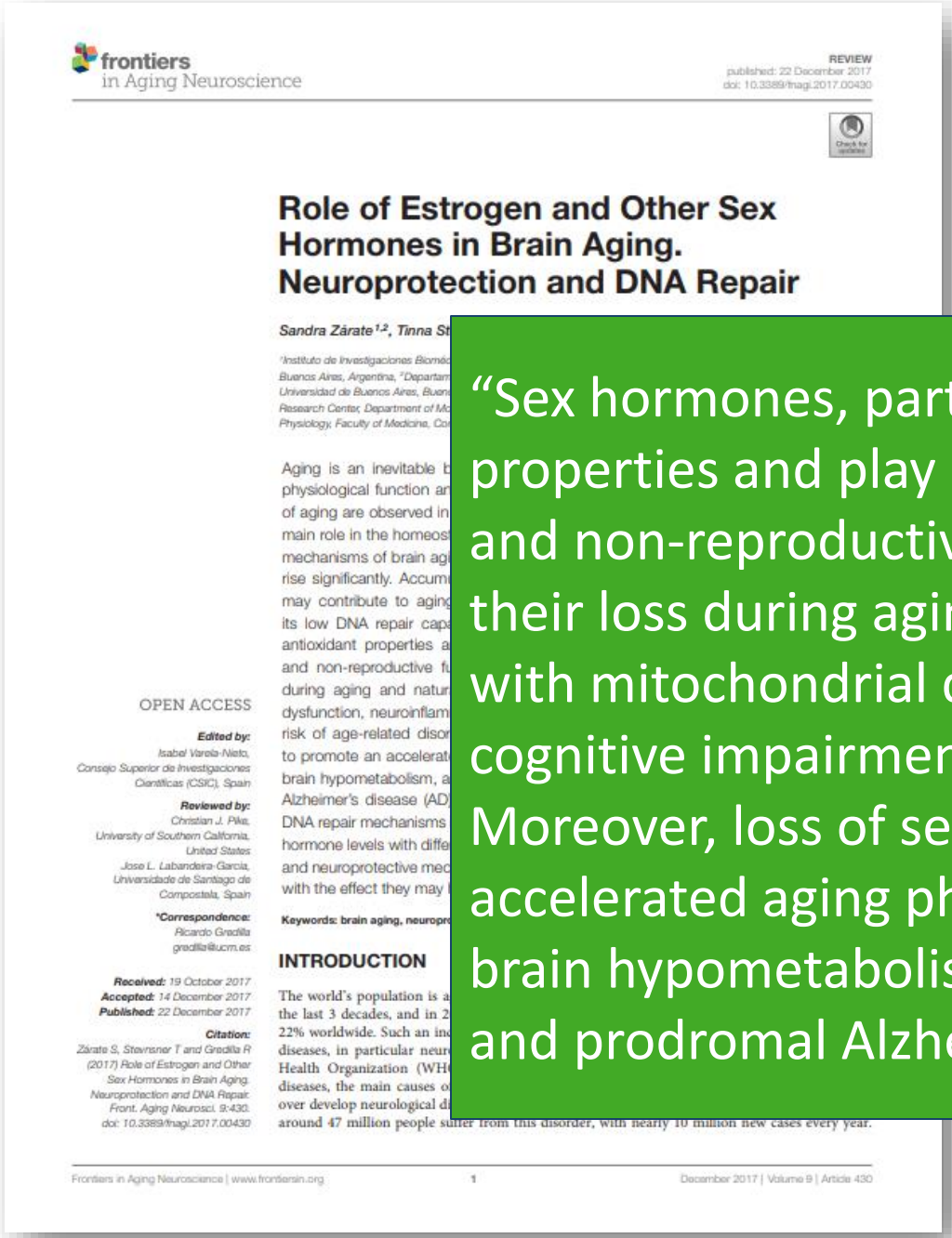
lower executive, global and memory cognitive performance. A general improvement in cognitive performance was observed in women randomized to HT. Women in all three metabolic phenotypes showed significant increases in global cognition (all $p < 0.05$), and women in the healthy and high blood pressure phenotypes had a significant increase in

CONTACT Professor A. Pines apines@netvision.net.il Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel


"Recent studies, such as WHIMS-Young, the Kronos Early Estrogen Prevention Study and the Early versus Late Intervention Trial with Estradiol targeted the younger women, and indeed showed that hormone therapy may have positive cognitive outcomes in this age group."

GENOVA DIAGNOSTICS

Pines A. *Climacteric.* 2016;19(5):430-432.



frontiers in Aging Neuroscience

REVIEW
published: 22 December 2017
doi: 10.3389/fnagi.2017.00430

# Role of Estrogen and Other Sex Hormones in Brain Aging. Neuroprotection and DNA Repair

Sandra Zárate[1,2], Tinna St

[1]Instituto de Investigaciones Biomed
Buenos Aires, Argentina, [2]Departam
Universidad de Buenos Aires, Buen
Research Center, Department of Mo
Physiology, Faculty of Medicine, Co

Aging is an inevitable b
physiological function ar
of aging are observed in
main role in the homeost
mechanisms of brain ag
rise significantly. Accum
may contribute to aging
its low DNA repair cape
antioxidant properties a
and non-reproductive fu
during aging and natur
dysfunction, neuroinflam
risk of age-related disor
to promote an accelerat
brain hypometabolism, a
Alzheimer's disease (AD)
DNA repair mechanisms
hormone levels with diffe
and neuroprotective mec
with the effect they may

Keywords: brain aging, neuropro

OPEN ACCESS

Edited by:
Isabel Varela-Nieto,
Consejo Superior de Investigaciones Científicas (CSIC), Spain

Reviewed by:
Christian J. Pike,
University of Southern California, United States
Jose L. Labandeira-Garcia,
Universidade de Santiago de Compostela, Spain

*Correspondence:
Ricardo Gredilla
gredilla@ucm.es

Received: 19 October 2017
Accepted: 14 December 2017
Published: 22 December 2017

Citation:
Zárate S, Stevnsner T and Gredilla R (2017) Role of Estrogen and Other Sex Hormones in Brain Aging. Neuroprotection and DNA Repair. Front. Aging Neurosci. 9:430. doi: 10.3389/fnagi.2017.00430

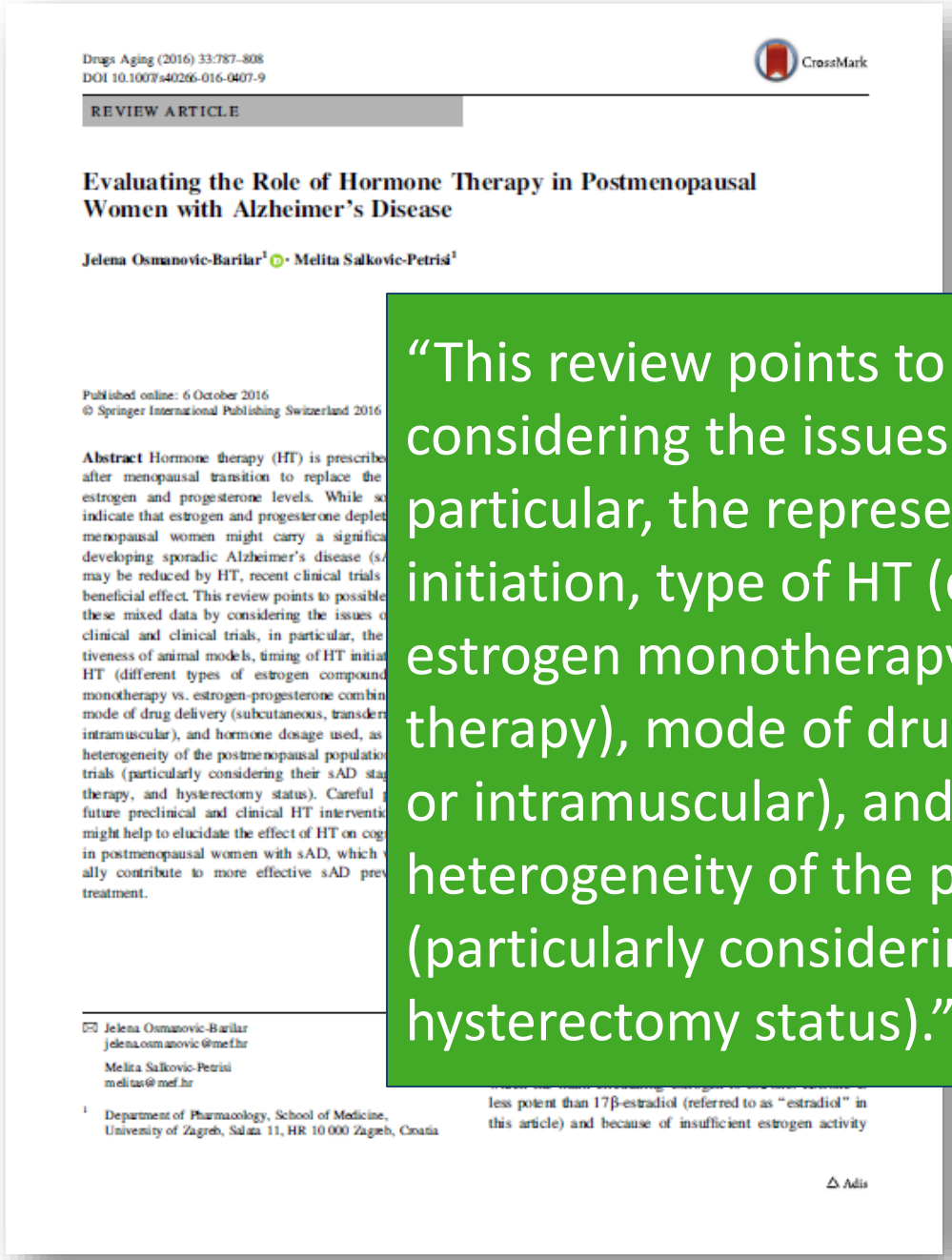
## INTRODUCTION

The world's population is a
the last 3 decades, and in 2
22% worldwide. Such an in
diseases, in particular neur
Health Organization (WH
diseases, the main causes o
over develop neurological d
around 47 million people suffer from this disorder, with nearly 10 million new cases every year.

Frontiers in Aging Neuroscience | www.frontiersin.org 1 December 2017 | Volume 9 | Article 430

"Sex hormones, particularly estrogens possess potent antioxidant properties and play important roles in maintaining normal reproductive and non-reproductive functions. They exert neuroprotective actions and their loss during aging and natural or surgical menopause is associated with mitochondrial dysfunction, neuroinflammation, synaptic decline, cognitive impairment and increased risk of age-related disorders. Moreover, loss of sex hormones has been suggested to promote an accelerated aging phenotype eventually leading to the development of brain hypometabolism, a feature often observed in menopausal women and prodromal Alzheimer's disease (AD)."

Zárate S, et al. *Front Aging Neurosci*. 2017;9:430.



Drugs Aging (2016) 33:787–808
DOI 10.1007/s40266-016-0407-9

REVIEW ARTICLE

# Evaluating the Role of Hormone Therapy in Postmenopausal Women with Alzheimer's Disease

Jelena Osmanovic-Barilar[1] · Melita Salkovic-Petrisi[1]

Published online: 6 October 2016


**Abstract** Hormone therapy (HT) is prescribe
after menopausal transition to replace the
estrogen and progesterone levels. While s
indicate that estrogen and progesterone deplet
menopausal women might carry a significa
developing sporadic Alzheimer's disease (sA
may be reduced by HT, recent clinical trials
beneficial effect. This review points to possible
these mixed data by considering the issues o
clinical and clinical trials, in particular, the
tiveness of animal models, timing of HT initiat
HT (different types of estrogen compound
monotherapy vs. estrogen-progesterone combin
mode of drug delivery (subcutaneous, transder
intramuscular), and hormone dosage used, as
heterogeneity of the postmenopausal populatio
trials (particularly considering their sAD sta
therapy, and hysterectomy status). Careful
future preclinical and clinical HT interventi
might help to elucidate the effect of HT on cog
in postmenopausal women with sAD, which
ally contribute to more effective sAD prev
treatment.

✉ Jelena Osmanovic-Barilar
jelena.osmanovic@mef.hr

Melita Salkovic-Petrisi
melitas@mef.hr

[1] Department of Pharmacology, School of Medicine, University of Zagreb, Salata 11, HR 10 000 Zagreb, Croatia

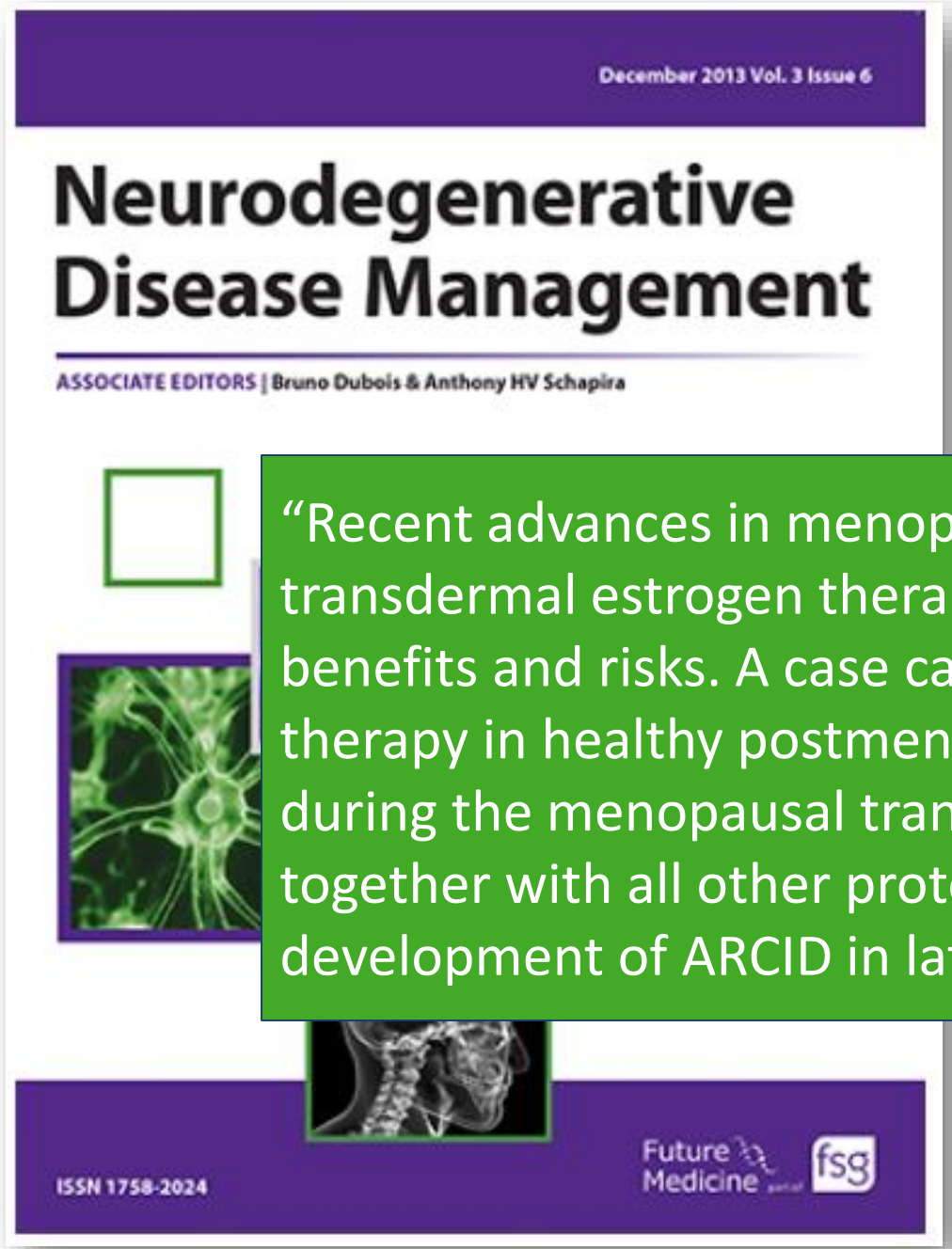
less potent than 17β-estradiol (referred to as "estradiol" in this article) and because of insufficient estrogen activity

Adis

"This review points to possible reasons for these mixed data by considering the issues of both preclinical and clinical trials, in particular, the representativeness of animal models, timing of HT initiation, type of HT (different types of estrogen compounds, estrogen monotherapy vs. estrogen-progesterone combined therapy), mode of drug delivery (subcutaneous, transdermal, oral, or intramuscular), and hormone dosage used, as well as the heterogeneity of the postmenopausal population in clinical trials (particularly considering their sAD stage, anti-AD therapy, and hysterectomy status)."

GENOVA DIAGNOSTICS

Osmanovic-Barilar J, et al. *Drugs Aging*. 2016;33(11):787-808.



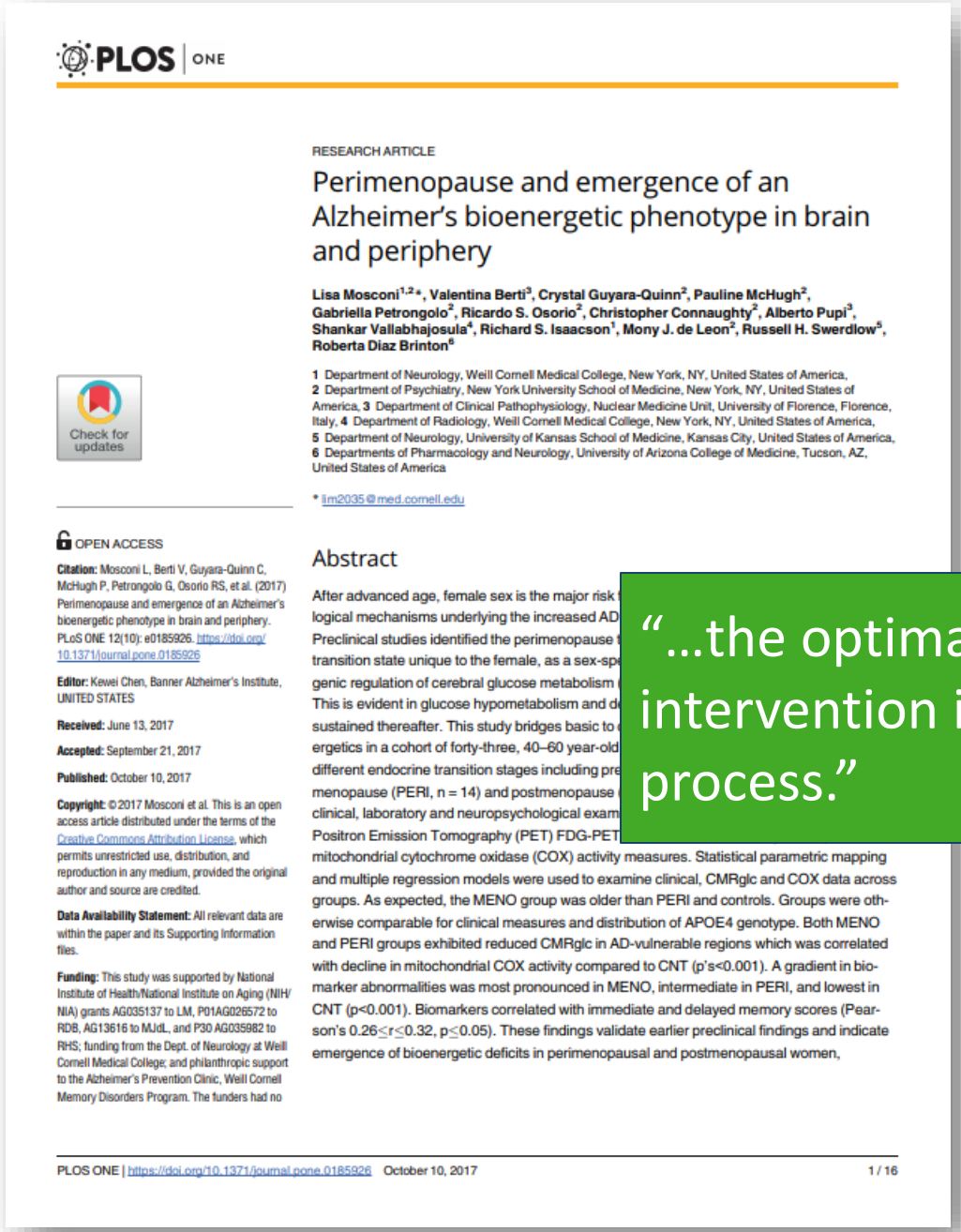

"Recent advances in menopause hormone therapy including transdermal estrogen therapy have favorably influenced the balance of benefits and risks. A case can be made for menopause hormone therapy in healthy postmenopausal women for 5–10 years starting during the menopausal transition (the 'window of opportunity'), together with all other protective measures, to delay or prevent the development of ARCID in later life."

GENOVA DIAGNOSTICS

Davey DA. *Neurodegener Dis Manag*. 2017;7(1):85-94.

# Given all this, how do you approach the menopausal woman?

GENOVA DIAGNOSTICS



PLOS ONE

RESEARCH ARTICLE

# Perimenopause and emergence of an Alzheimer's bioenergetic phenotype in brain and periphery

**Lisa Mosconi[1,2]*, Valentina Berti[3], Crystal Guyara-Quinn[2], Pauline McHugh[2], Gabriella Petrongolo[2], Ricardo S. Osorio[2], Christopher Connaughty[2], Alberto Pupi[3], Shankar Vallabhajosula[4], Richard S. Isaacson[1], Mony J. de Leon[2], Russell H. Swerdlow[5], Roberta Diaz Brinton[6]**

1 Department of Neurology, Weill Cornell Medical College, New York, NY, United States of America, 2 Department of Psychiatry, New York University School of Medicine, New York, NY, United States of America, 3 Department of Clinical Pathophysiology, Nuclear Medicine Unit, University of Florence, Florence, Italy, 4 Department of Radiology, Weill Cornell Medical College, New York, NY, United States of America, 5 Department of Neurology, University of Kansas School of Medicine, Kansas City, United States of America, 6 Departments of Pharmacology and Neurology, University of Arizona College of Medicine, Tucson, AZ, United States of America

* lim2035@med.cornell.edu

Check for updates

OPEN ACCESS

**Citation:** Mosconi L, Berti V, Guyara-Quinn C, McHugh P, Petrongolo G, Osorio RS, et al. (2017) Perimenopause and emergence of an Alzheimer's bioenergetic phenotype in brain and periphery. PLoS ONE 12(10): e0185926. https://doi.org/10.1371/journal.pone.0185926

**Editor:** Kewei Chen, Banner Alzheimer's Institute, UNITED STATES

**Received:** June 13, 2017

**Accepted:** September 21, 2017

**Published:** October 10, 2017



**Data Availability Statement:** All relevant data are within the paper and its Supporting Information files.

**Funding:** This study was supported by National Institute of Health/National Institute on Aging (NIH/NIA) grants AG035137 to LM, P01AG026572 to RDB, AG13616 to MJdL, and P30 AG035982 to RHS; funding from the Dept. of Neurology at Weill Cornell Medical College; and philanthropic support to the Alzheimer's Prevention Clinic, Weill Cornell Memory Disorders Program. The funders had no

## Abstract

After advanced age, female sex is the major risk f
logical mechanisms underlying the increased AD
Preclinical studies identified the perimenopause t
transition state unique to the female, as a sex-spe
genic regulation of cerebral glucose metabolism (
This is evident in glucose hypometabolism and de
sustained thereafter. This study bridges basic to c
ergetics in a cohort of forty-three, 40–60 year-old
different endocrine transition stages including pre
menopause (PERI, n = 14) and postmenopause (
clinical, laboratory and neuropsychological exam
Positron Emission Tomography (PET) FDG-PET
mitochondrial cytochrome oxidase (COX) activity measures. Statistical parametric mapping and multiple regression models were used to examine clinical, CMRglc and COX data across groups. As expected, the MENO group was older than PERI and controls. Groups were otherwise comparable for clinical measures and distribution of APOE4 genotype. Both MENO and PERI groups exhibited reduced CMRglc in AD-vulnerable regions which was correlated with decline in mitochondrial COX activity compared to CNT ($p's<0.001$). A gradient in biomarker abnormalities was most pronounced in MENO, intermediate in PERI, and lowest in CNT ($p<0.001$). Biomarkers correlated with immediate and delayed memory scores (Pearson's $0.26 \leq r \leq 0.32$, $p \leq 0.05$). These findings validate earlier preclinical findings and indicate emergence of bioenergetic deficits in perimenopausal and postmenopausal women,



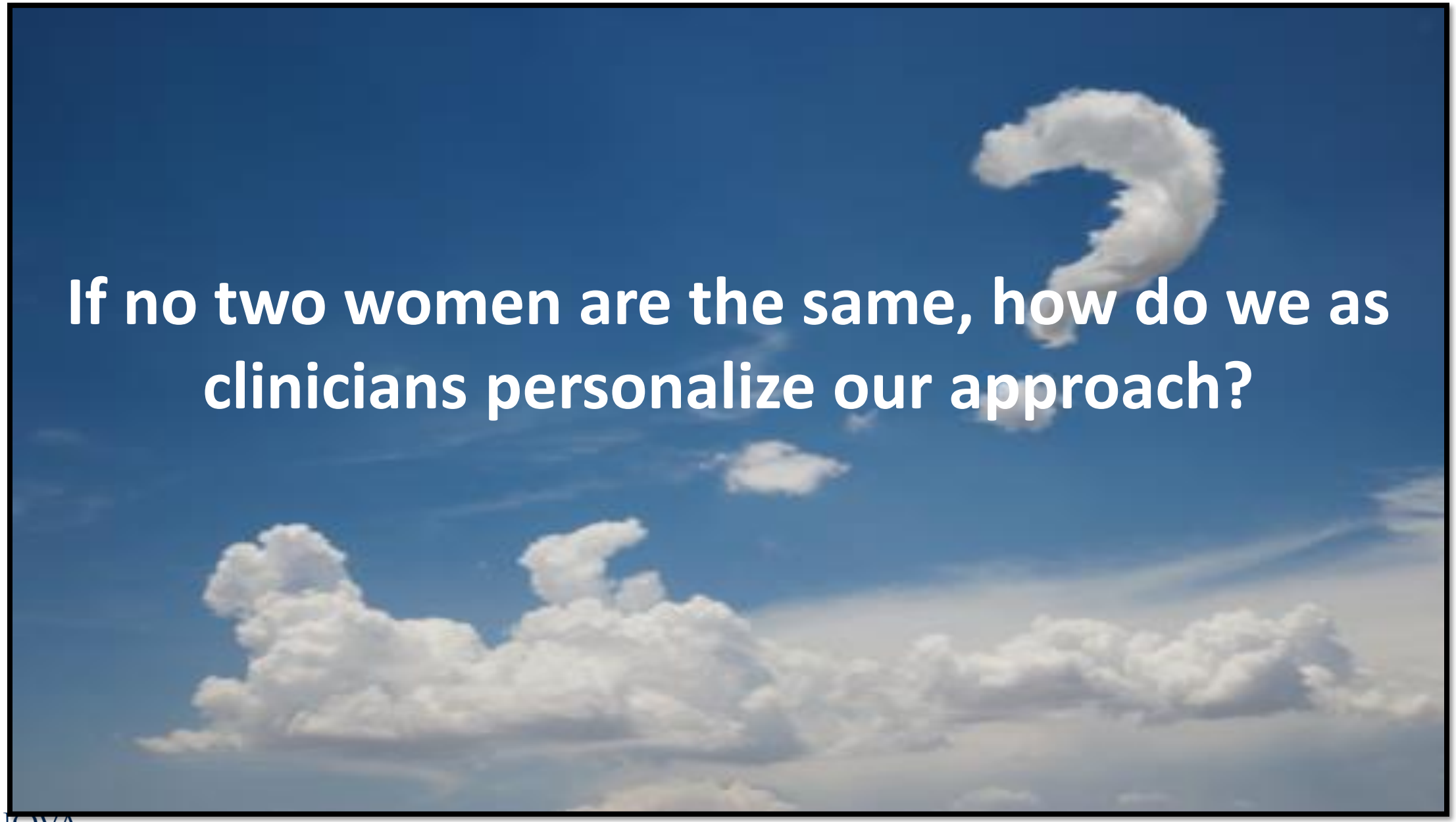
"…the optimal window of opportunity for therapeutic intervention in women is early in the endocrine aging process."

GENOVA DIAGNOSTICS

Mosconi L, et al. *PLoS One*. 2017;12(10):e0185926.

# No Two Women Are The Same

GENOVA DIAGNOSTICS




GENOVA DIAGNOSTICS

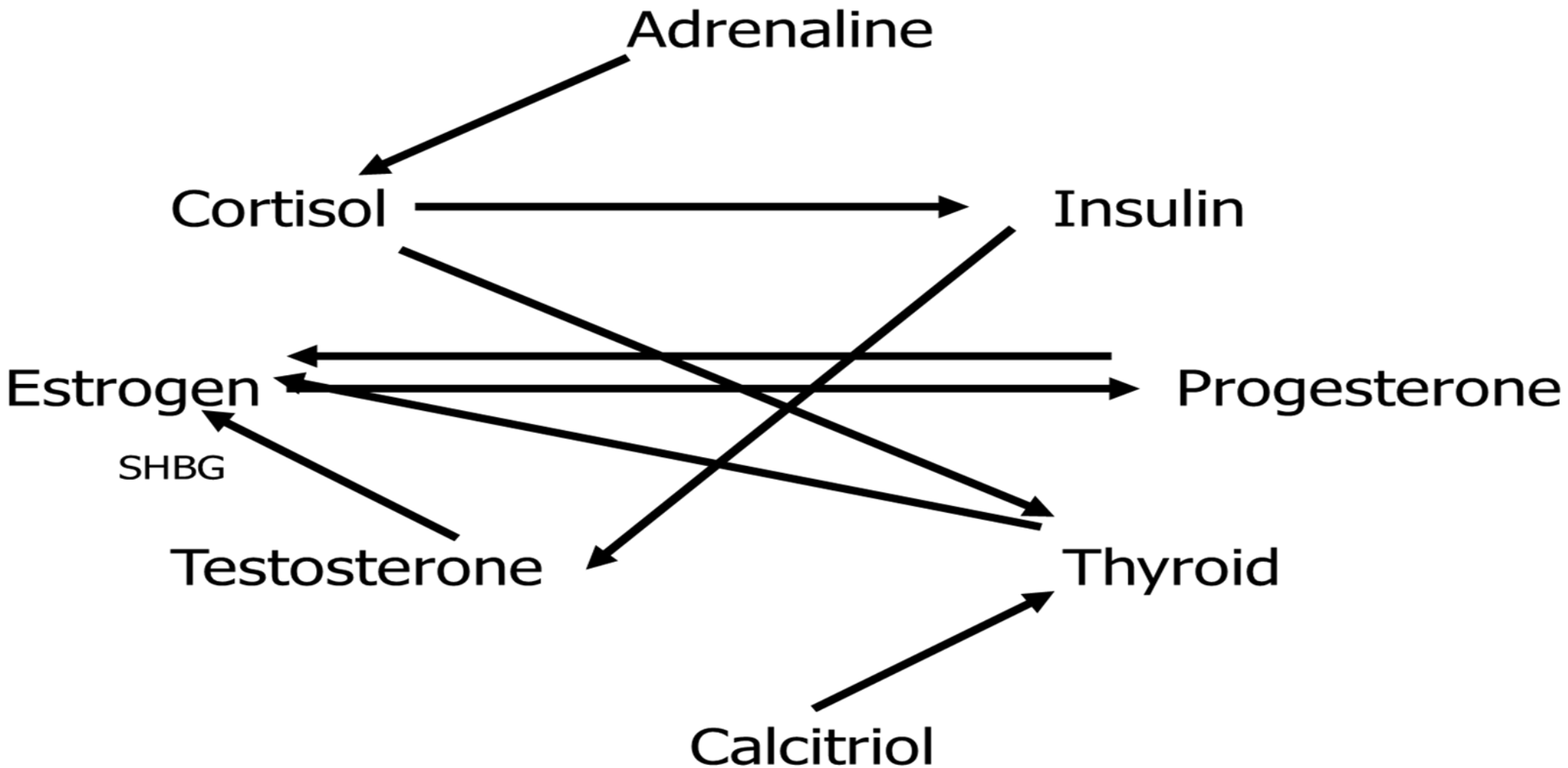
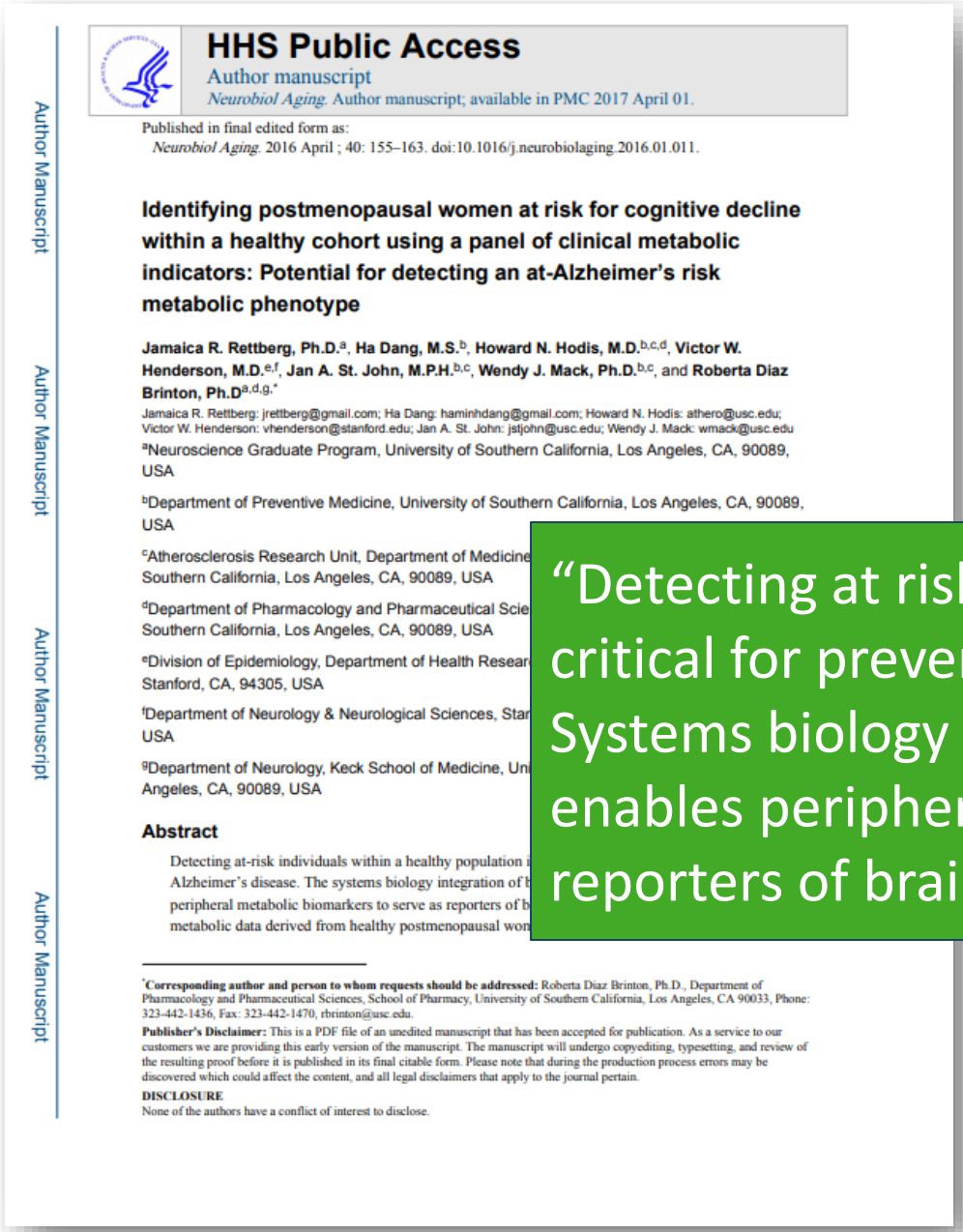



Image Reference: http://www.nutritionqed.com/blog/2017/05/thyroid-symptoms/



HHS Public Access

Author manuscript

*Neurobiol Aging*. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

*Neurobiol Aging*. 2016 April ; 40: 155–163. doi:10.1016/j.neurobiolaging.2016.01.011.

**Identifying postmenopausal women at risk for cognitive decline within a healthy cohort using a panel of clinical metabolic indicators: Potential for detecting an at-Alzheimer's risk metabolic phenotype**

**Jamaica R. Rettberg, Ph.D.**[a], **Ha Dang, M.S.**[b], **Howard N. Hodis, M.D.**[b,c,d], **Victor W. Henderson, M.D.**[e,f], **Jan A. St. John, M.P.H.**[b,c], **Wendy J. Mack, Ph.D.**[b,c], and **Roberta Diaz Brinton, Ph.D**[a,d,g,*]

Jamaica R. Rettberg: jrettberg@gmail.com; Ha Dang: haminhdang@gmail.com; Howard N. Hodis: athero@usc.edu; Victor W. Henderson: vhenderson@stanford.edu; Jan A. St. John: jstjohn@usc.edu; Wendy J. Mack: wmack@usc.edu

[a]Neuroscience Graduate Program, University of Southern California, Los Angeles, CA, 90089, USA

[b]Department of Preventive Medicine, University of Southern California, Los Angeles, CA, 90089, USA

[c]Atherosclerosis Research Unit, Department of Medicine Southern California, Los Angeles, CA, 90089, USA

[d]Department of Pharmacology and Pharmaceutical Scie Southern California, Los Angeles, CA, 90089, USA

[e]Division of Epidemiology, Department of Health Resear Stanford, CA, 94305, USA

[f]Department of Neurology & Neurological Sciences, Star USA

[g]Department of Neurology, Keck School of Medicine, Un Angeles, CA, 90089, USA

**Abstract**

Detecting at-risk individuals within a healthy population i Alzheimer's disease. The systems biology integration of b peripheral metabolic biomarkers to serve as reporters of b metabolic data derived from healthy postmenopausal wom

[*]**Corresponding author and person to whom requests should be addressed:** Roberta Diaz Brinton, Ph.D., Department of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, University of Southern California, Los Angeles, CA 90033, Phone: 323-442-1436, Fax: 323-442-1470, rbrinton@usc.edu.



**DISCLOSURE**

None of the authors have a conflict of interest to disclose.

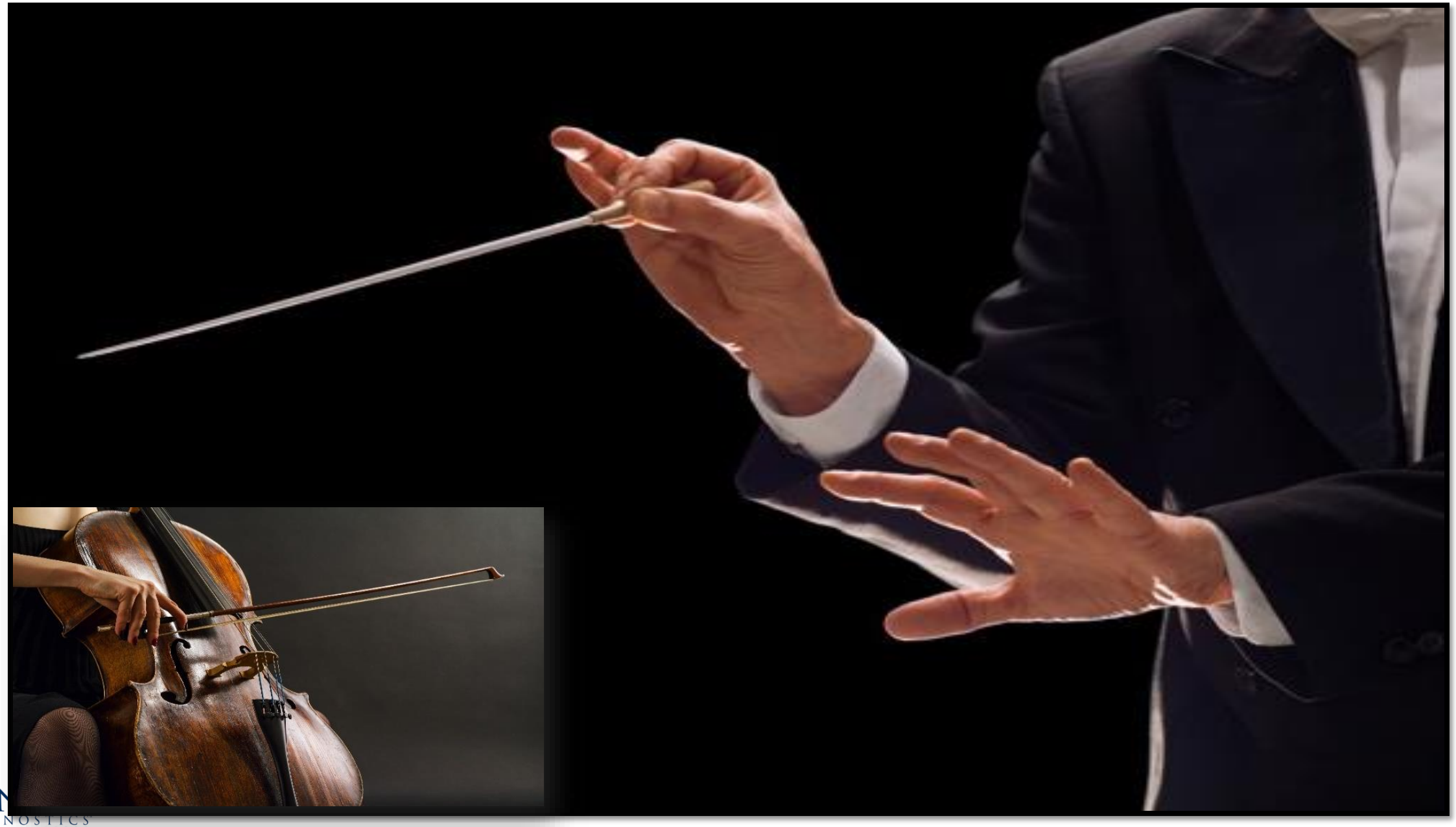


"Detecting at risk individuals within a healthy population is critical for preventing or delaying Alzheimer's disease. Systems biology integration of brain and body metabolism enables peripheral metabolic biomarkers to serve as reporters of brain bioenergetic status."

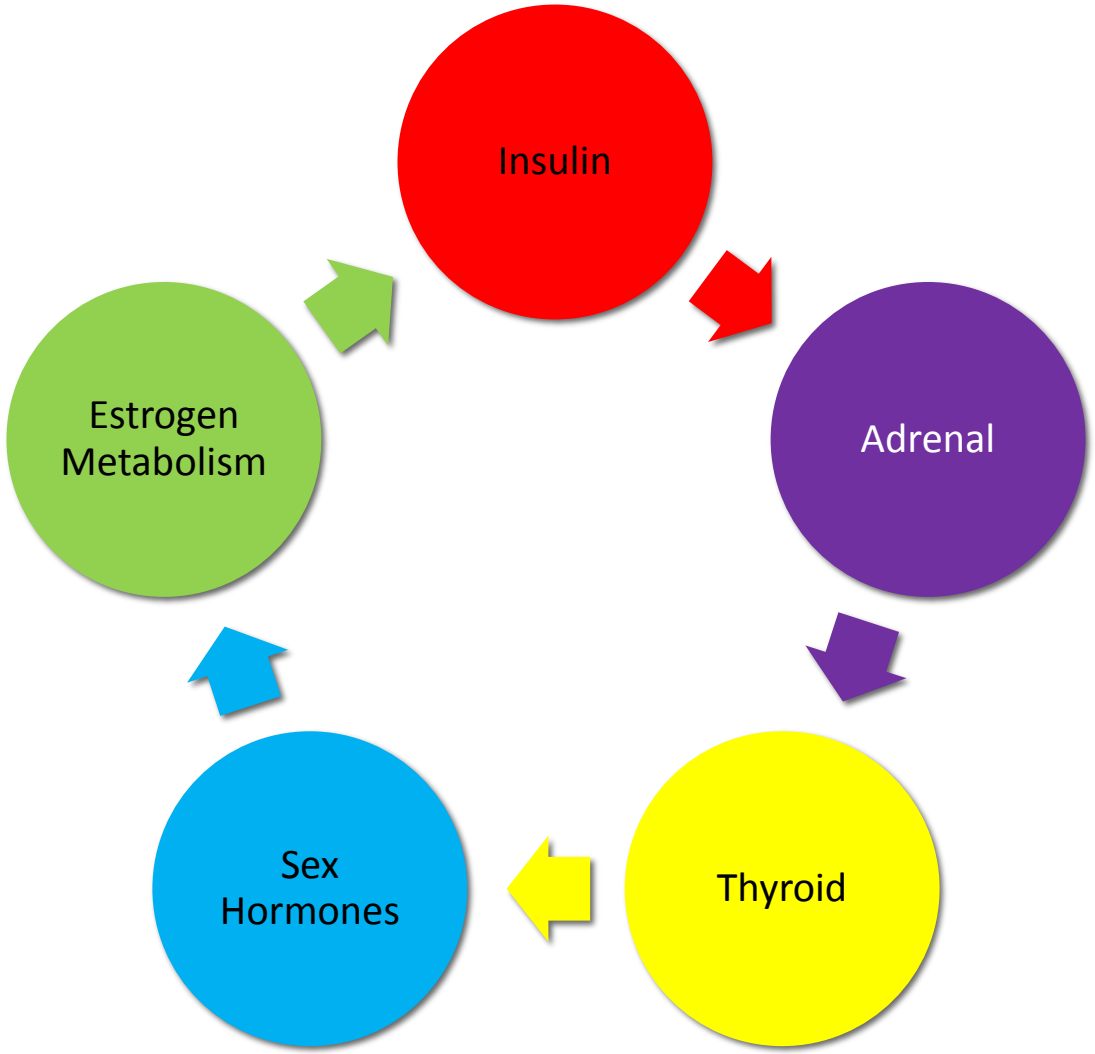
GENOVA DIAGNOSTICS

Rettberg JR, et al. *Neurobiol Aging*. 2016;40:155-63.

GENOVA DIAGNOSTICS



# The Saudade Hormonal Symphony™




GENOVA DIAGNOSTICS

# Disruptors of Hormonal Function

- Traumatic emotional events
- Physical trauma
- Chronic sleep deprivation
- Infections
- Aging
- Inflammatory diseases
- Single nucleotide polymorphisms (SNPs)
- Exogenous toxins
- Acute physical stress
- Nutritional insufficiencies
- Food allergy, intolerance, or sensitivity
- Changes in gut microbiota
- Altered biotransformation
- Pharmaceuticals

GENOVA DIAGNOSTICS

# "*Listen* to your patient, (s)he is telling you the diagnosis."

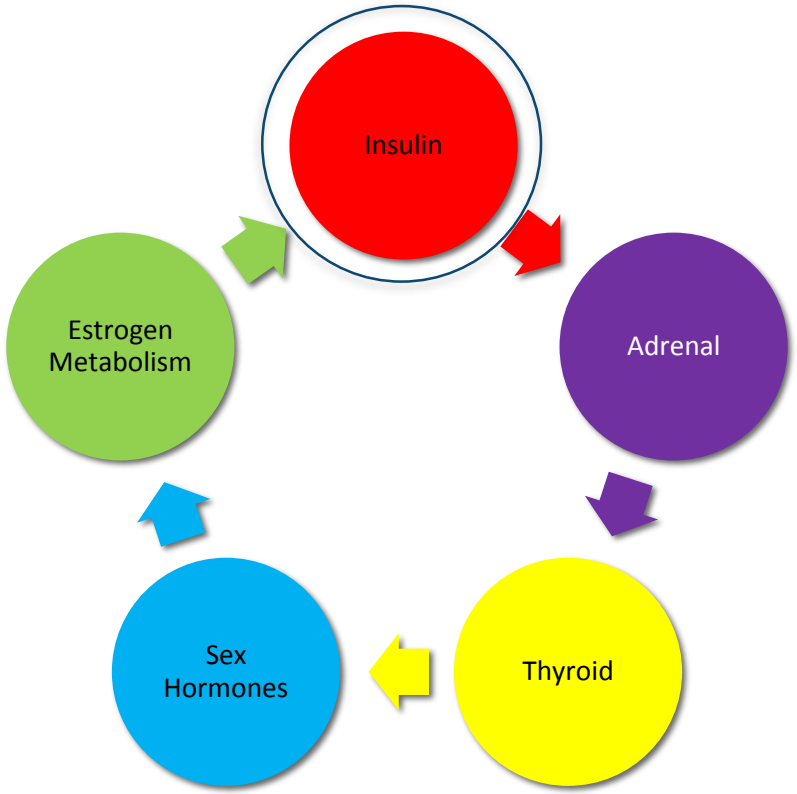
**-Sir William Osler**

GENOVA DIAGNOSTICS

# That Story Is Typically Told As…


GENOVA DIAGNOSTICS

# The Saudade Hormonal Symphony™




GENOVA DIAGNOSTICS

# Insulin's Effects

- Effects CBO, lipid, metabolism
- Insulin effects thyroid function… and thyroid function effects insulin production
- Insulin effects endothelial function
- Other hormones…

Rezzonico J, et al. *Thyroid*. 2008;18(4):461-64.
Kapadia KB, et al. *J Pharmacol Pharmacother*. 2012;3(2):156-60.
Brenta G; et al. *J Thyroid Res*. 2011;2011:152850.
Rezzónico J, et al. *Metab Syndr Relat Disord*. 2011;9(1):69-75.

# Menopausal Complaints Are Associated With Cardiovascular Risk Factors

Gerrie-Cor M. Gast, Diederick E. Grobbee, Victor J.M. Pop, Jules J. Keyzer,
Colette J.M. Wijnands-van Gent, Göran N. Samsioe, Peter M. Nilsson, Yvonne T. van der Schouw

***Abstract***—It has been hypothesized that women with vasomotor symptoms differ from those without with respect to cardiovascular risk factors or responses to exogenous hormone therapy. We studied whether the presence and extent of menopausal complaints are associated with cardiovascular risk profile. Data were used from a population-based sample of 5523 women, aged 46 to 57 years, enrolled between 1994 and 1995. Data on menopausal complaints and potential confounders were collected by questionnaires. Total cholesterol, systolic and diastolic blood pressures, and body mass index were measured. Linear and logistic regression analyses were used to analyze the data. Night sweats were reported by 38% and flushing by 39% of women. After multivariate adjustment, women with complaints of flushing had a 0.27-mmol/L (95% CI: 0.15 to 0.39) higher cholesterol level, a 0.60-kg/m$^2$ (95% CI: 0.35 to 0.84) higher BMI, a 1.59-mm Hg (95% CI: 0.52 to 2.67) higher systolic blood pressure, and a 1.09-mm Hg (95% CI: 0.48 to 1.69) higher diastolic blood pressure compared with asymptomatic women. Flushing was also associated with hypercholesterolemia (odds ratio: 1.52; 95% CI: 1.25 to 1.84) and hypertension (OR: 1.20; 95% CI: 1.07 to 1.34). Results were similar for complaints of night sweating. The findings support the view that menopausal complaints are associated with a less favorable cardiovascular risk profile. These findings substantiate the view that differences in the presence of menopausal symptoms as a reason for using hormone therapy could explain discrepant findings between observational research and trials. (***Hypertension***. **2008;51:1492-1498.)**

**Key Words:** menopausal complaints ■ cholesterol ■ blood pressure ■ body mass index ■ cardiovascular risk profile ■ women

A number of observational studies demonstrated a protective association between hormone therapy (HT) and cardiovascular disease (CVD).[1–3] Placebo-controlled, randomized trials, however, could not confirm a cardioprotective effect and showed no overall benefit of HT on the risk of cardiovascular events.[4,5]

Many potential reasons have been proposed to explain this apparent discrepancy between the observational studies and the trials. An important difference is that, in the observational studies, the most common reason to initiate HT was to relieve menopausal complaints. In contrast, in the trials, women with severe complaints were either excluded or composed only a minority of the total randomized population. Results of a recent subgroup analysis of the combined Women's Health Initiative trials showed that women who initiated HT closer to menopause had a reduced coronary heart disease (CHD) risk compared with the increase in CHD risk among women initiating HT more distant from menopause.[6] Moreover, among women 50 to 59 years old at enrollment in the Women's Health Initiative, end-of-trial coronary calcium scores were lower in women assigned to estrogens than in those assigned to placebo.[7] A younger age is likely to

of menopausal complaint

We hypothesized pre

symptoms may differ

cardiovascular risk fact

Indeed, women with n

level of plasma antioxid

vascular reactivity to

studies demonstrated th

increased blood pressu

analysis of the combin

showed that the higher

from menopause appea

subset of women with

toms.[6] We examined whether the presence of menopausal complaints is associated with CVD risk profile in a large, community-based sample of perimenopausal women.

Received November 29, 2007; first decision December 30, 2007; revision accepted March 17, 2008.

From the Julius Center for Health Sciences and Primary Care (G.C.M.G., D.E.G., Y.T.v.d.S.), University Medical Center Utrecht, Utrecht, The Netherlands; the Department of Clinical Health Psychology (V.J.M.P.), University of Tilburg, Tilburg, The Netherlands; Research Unit (J.J.K., C.J.M.W.-v.G.), Diagnostic Center Eindhoven, Eindhoven, The Netherlands; the Department of Obstetrics and Gynaecology (G.C.M.G., G.N.S.), Lund University Hospital, Lund, Sweden; and the Department of Clinical Sciences Medicine (P.M.N.), University Hospital, University of Lund, Malmö, Sweden.

Correspondence to Gerrie-Cor M. Gast, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Room STR 6.131, PO Box 85500, 3508 GA Utrecht, The Netherlands. E-mail G.C.M.Gast@umcutrecht.nl



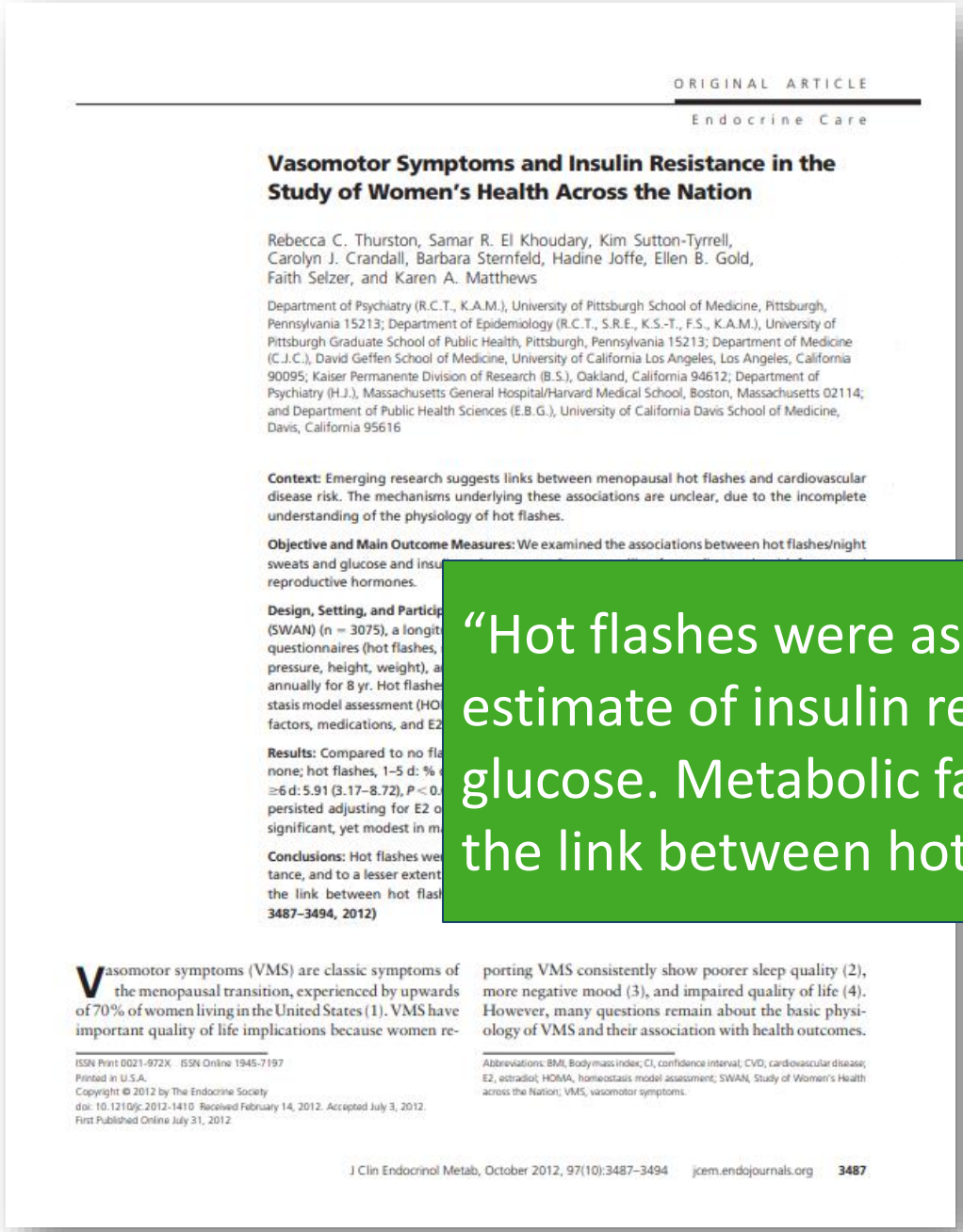
*Hypertension* **is available at http://hypertension.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.107.106526**



"The findings support the view that menopausal complaints are associated with a less favorable cardiovascular risk profile."

GENOVA DIAGNOSTICS

Gast GC, et al. *Hypertension.* 2008;51(6):1492-98.



ORIGINAL ARTICLE

Endocrine Care

## Vasomotor Symptoms and Insulin Resistance in the Study of Women's Health Across the Nation

Rebecca C. Thurston, Samar R. El Khoudary, Kim Sutton-Tyrrell, Carolyn J. Crandall, Barbara Sternfeld, Hadine Joffe, Ellen B. Gold, Faith Selzer, and Karen A. Matthews

Department of Psychiatry (R.C.T., K.A.M.), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213; Department of Epidemiology (R.C.T., S.R.E., K.S.-T., F.S., K.A.M.), University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania 15213; Department of Medicine (C.J.C.), David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California 90095; Kaiser Permanente Division of Research (B.S.), Oakland, California 94612; Department of Psychiatry (H.J.), Massachusetts General Hospital/Harvard Medical School, Boston, Massachusetts 02114; and Department of Public Health Sciences (E.B.G.), University of California Davis School of Medicine, Davis, California 95616

**Context:** Emerging research suggests links between menopausal hot flashes and cardiovascular disease risk. The mechanisms underlying these associations are unclear, due to the incomplete understanding of the physiology of hot flashes.

**Objective and Main Outcome Measures:** We examined the associations between hot flashes/night sweats and glucose and insu… reproductive hormones.

**Design, Setting, and Particip…** (SWAN) (n = 3075), a longit… questionnaires (hot flashes, … pressure, height, weight), a… annually for 8 yr. Hot flashe… stasis model assessment (HO… factors, medications, and E2…

**Results:** Compared to no fla… none; hot flashes, 1–5 d: % … ≥6 d: 5.91 (3.17–8.72), $P < 0.$… persisted adjusting for E2 o… significant, yet modest in m…

**Conclusions:** Hot flashes we… tance, and to a lesser extent… the link between hot flash… 3487–3494, 2012)

Vasomotor symptoms (VMS) are classic symptoms of the menopausal transition, experienced by upwards of 70% of women living in the United States (1). VMS have important quality of life implications because women reporting VMS consistently show poorer sleep quality (2), more negative mood (3), and impaired quality of life (4). However, many questions remain about the basic physiology of VMS and their association with health outcomes.

ISSN Print 0021-972X. ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2012-1410 Received February 14, 2012. Accepted July 3, 2012.
First Published Online July 31, 2012

Abbreviations: BMI, Body mass index; CI, confidence interval; CVD, cardiovascular disease; E2, estradiol; HOMA, homeostasis model assessment; SWAN, Study of Women's Health across the Nation; VMS, vasomotor symptoms.



"Hot flashes were associated with a higher HOMA index, an estimate of insulin resistance, and to a lesser extent higher glucose. Metabolic factors may be relevant to understanding the link between hot flashes and cardiovascular disease risk."

GENOVA DIAGNOSTICS

Thurston RC, et al. *J Clin Endocrinol Metab*. 2012;97(10):3487–94.

ORIGINAL ARTICLE

Endocrine Care

## Vasomotor Symptoms and Insulin Resistance in the Study of Women's Health Across the Nation

Rebecca C. Thurston, Samar R. El Khoudary, Kim Sutton-Tyrrell, Carolyn J. Crandall, Barbara Sternfeld, Hadine Joffe, Ellen B. Gold, Faith Selzer, and Karen A. Matthews

Department of Psychiatry (R.C.T., K.A.M.), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213; Department of Epidemiology (R.C.T., S.R.E., K.S.-T., F.S., K.A.M.), University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania 15213; Department of Medicine (C.J.C.), David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California 90095; Kaiser Permanente Division of Research (B.S.), Oakland, California 94612; Department of Psychiatry (H.J.), Massachusetts General Hospital/Harvard Medical School, Boston, Massachusetts 02114; and Department of Public Health Sciences (E.B.G.), University of California Davis School of Medicine, Davis, California 95616

**Context:** Emerging research suggests links between menopausal hot flashes and cardiovascular disease risk. The mechanisms underlying these associations are unclear, due to the incomplete understanding of the physiology of hot flashes.

**Objective and Main Outcome Measures:** We examined
sweats and glucose and insulin resistance over 8 yr, cor
reproductive hormones.

**Design, Setting, and Participants:** Participants in the St
(SWAN) (n = 3075), a longitudinal cohort study, were
questionnaires (hot flashes, night sweats: none, 1–5 d,
pressure, height, weight), and a fasting blood draw [s
annually for 8 yr. Hot flashes/night sweats were examin
stasis model assessment (HOMA) in mixed models, adju
factors, medications, and E2/FSH.

**Results:** Compared to no flashes, hot flashes were ass
none; hot flashes, 1–5 d: % difference (95% confidenc
≥6 d: 5.91 (3.17–8.72), $P < 0.0001$] in multivariable mod
persisted adjusting for E2 or FSH, and were similar fo
significant, yet modest in magnitude, for the outcome

**Conclusions:** Hot flashes were associated with a higher
tance, and to a lesser extent higher glucose. Metabolic
the link between hot flashes and cardiovascular di
3487–3494, 2012)

Vasomotor symptoms (VMS) are classic symptoms of the menopausal transition, experienced by upwards of 70% of women living in the United States (1). VMS have important quality of life implications because women reporting VMS consistently show poorer sleep quality (2), more negative mood (3), and impaired quality of life (4). However, many questions remain about the basic physiology of VMS and their association with health outcomes.

ISSN Print 0021-972X. ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2012-1410 Received February 14, 2012. Accepted July 3, 2012.
First Published Online July 31, 2012

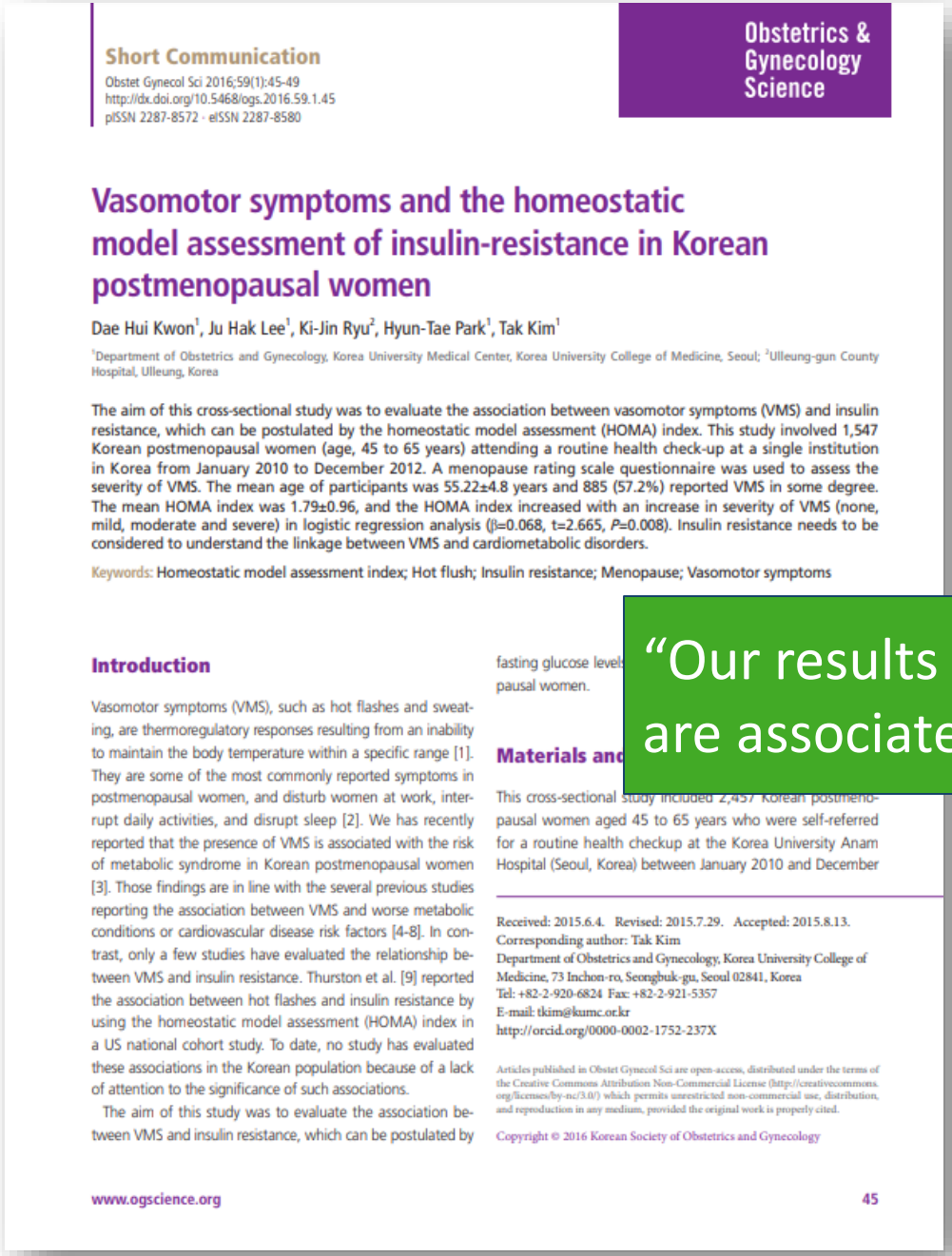
Abbreviations: BMI, Body mass index; CI, confidence interval; CVD, cardiovascular disease; E2, estradiol; HOMA, homeostasis model assessment; SWAN, Study of Women's Health across the Nation; VMS, vasomotor symptoms.



"In summary, VMS were associated with insulin resistance, as measured by the HOMA index, over a period of approximately 8 yr. These findings may contribute to ongoing efforts to better understand any mechanisms linking hot flashes to cardiovascular health."

GENOVA DIAGNOSTICS

Thurston RC, et al. *J Clin Endocrinol Metab*. 2012;97(10):3487–94.



Short Communication

Obstet Gynecol Sci 2016;59(1):45-49
http://dx.doi.org/10.5468/ogs.2016.59.1.45
pISSN 2287-8572 · eISSN 2287-8580

Obstetrics & Gynecology Science

# Vasomotor symptoms and the homeostatic model assessment of insulin-resistance in Korean postmenopausal women

Dae Hui Kwon[1], Ju Hak Lee[1], Ki-Jin Ryu[2], Hyun-Tae Park[1], Tak Kim[1]

[1]Department of Obstetrics and Gynecology, Korea University Medical Center, Korea University College of Medicine, Seoul; [2]Ulleung-gun County Hospital, Ulleung, Korea

The aim of this cross-sectional study was to evaluate the association between vasomotor symptoms (VMS) and insulin resistance, which can be postulated by the homeostatic model assessment (HOMA) index. This study involved 1,547 Korean postmenopausal women (age, 45 to 65 years) attending a routine health check-up at a single institution in Korea from January 2010 to December 2012. A menopause rating scale questionnaire was used to assess the severity of VMS. The mean age of participants was 55.22±4.8 years and 885 (57.2%) reported VMS in some degree. The mean HOMA index was 1.79±0.96, and the HOMA index increased with an increase in severity of VMS (none, mild, moderate and severe) in logistic regression analysis (β=0.068, t=2.665, *P*=0.008). Insulin resistance needs to be considered to understand the linkage between VMS and cardiometabolic disorders.

Keywords: Homeostatic model assessment index; Hot flush; Insulin resistance; Menopause; Vasomotor symptoms

## Introduction

Vasomotor symptoms (VMS), such as hot flashes and sweating, are thermoregulatory responses resulting from an inability to maintain the body temperature within a specific range [1]. They are some of the most commonly reported symptoms in postmenopausal women, and disturb women at work, interrupt daily activities, and disrupt sleep [2]. We has recently reported that the presence of VMS is associated with the risk of metabolic syndrome in Korean postmenopausal women [3]. Those findings are in line with the several previous studies reporting the association between VMS and worse metabolic conditions or cardiovascular disease risk factors [4-8]. In contrast, only a few studies have evaluated the relationship between VMS and insulin resistance. Thurston et al. [9] reported the association between hot flashes and insulin resistance by using the homeostatic model assessment (HOMA) index in a US national cohort study. To date, no study has evaluated these associations in the Korean population because of a lack of attention to the significance of such associations.

The aim of this study was to evaluate the association between VMS and insulin resistance, which can be postulated by

fasting glucose level
pausal women.

## Materials and

This cross-sectional study included 2,457 Korean postmenopausal women aged 45 to 65 years who were self-referred for a routine health checkup at the Korea University Anam Hospital (Seoul, Korea) between January 2010 and December

Received: 2015.6.4. Revised: 2015.7.29. Accepted: 2015.8.13.
Corresponding author: Tak Kim
Department of Obstetrics and Gynecology, Korea University College of Medicine, 73 Inchon-ro, Seongbuk-gu, Seoul 02841, Korea
Tel: +82-2-920-6824 Fax: +82-2-921-5357
E-mail: tkim@kumc.or.kr
http://orcid.org/0000-0002-1752-237X





"Our results suggest that VMS in postmenopausal women are associated with increased insulin resistance."

GENOVA DIAGNOSTICS

Kwon DH, et al. *Obstet Gynecol Sci*. 2016;59(1):45-49.

# Dietary Management for the Patient with Insulin Resistance

- Decrease insulin stimulation
  - Dietary modifications which decrease insulin release:
    - Fiber, 10-12 servings of vegetables and low glycemic load fruits
    - ‘Good’ (vs. ‘bad’) fat
    - ‘Good’ (vs. ‘bad’) carbohydrates
    - Protein at every meal
    - Elimination of most inflammatory food: Wheat, dairy, soy, corn, nightshades….
- Modify Gut Microbiota
  - Food first, high fiber
  - Fermented foods
  - Probiotics/prebiotics

# Dietary Management for the Patient with Insulin Resistance

- Increase cellular responsiveness to insulin
  - Agents that modify insulin responsiveness at the cellular level:
    - Spices
    - Herbs
    - Chromium
    - Vitamin D
    - Magnesium
    - Omega-3

Neuropharmacology 136 (2018) 223–242

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

# Brain insulin signalling, glucose metabolism and females' reproductive aging: A dangerous triad in Alzheimer's disease

A.I. Duarte [a, b, *], M.S. Santos [a, c], C.R. Oliveira [a, d], P.I. Moreira [a, e, **]

[a] CNC- Center for Neuroscience and Cell Biology, University of Coimbra, 3004-517 Coimbra, Portugal
[b] Institute for Interdisciplinary Research (IIIUC), University of Coimbra, Casa Costa Alemão - Pólo II, Rua D. Francisco de Lemos, 3030-789 Coimbra, Portugal
[c] Life Sciences Department, University of Coimbra, Largo Marquês de Pombal, 3004-517 Coimbra, Portugal
[d] Institute of Biochemistry, Faculty of Medicine, University of Coimbra, 3004-504 Coimbra, Portugal
[e] Institute of Physiology, Faculty of Medicine, University of Coimbra, 3004-504 Coimbra, Portugal

ARTICLE INFO

*Article history:*
Received 13 October 2017
Received in revised form
22 January 2018
Accepted 29 January 2018
Available online 20 February 2018

*Keywords:*
Alzheimer's disease
Insulin signalling
Estrogen signalling
Brain (mitochondrial) metabolism
Female aging/reproductive senescence

ABSTRACT

Alzheimer's disease (AD) constitutes a major socioeconomic challenge due to its disabling features and the rise in prevalence (especially among (peri)menopausal women and type 2 diabetes patients).

The precise etiopathogenesis of AD remains poorly understood. Importantly, its neurodegenerative perspective has been challenged towards a more "systemic" view. Amyloid-β (Aβ) and hyperphosphorylated Tau protein (P-Tau) (the main AD neuropathological features) affect and are affected by peripheral and brain insulin signalling dysfunction, leading to glucose dysme
deficits. This may be anticipated and exacerbated by the p
with insulin) during females' aging, increasing their risk f

Under this perspective, we aimed to discuss the rec
ripheral view of AD, and the role for insulin deficits and
brain. We also focused on the metabolic shift and th
midlife/perimenopause) herein. We finally discussed A
therapeutic potential of restoring brain insulin levels or g
intranasal insulin and use of ketogenic diets.

In sum, AD appears to lie on an intricate crosstalk betw
genetic changes that challenge its traditional view. Hence
gender) and pathophysiological mechanisms will allow
markers and more efficient drugs – all urgent medical n

This article is part of the Special Issue entitled 'Meta
generative Disorders.'

Contents



* Corresponding author. CNC - Center for Neuroscience and Cell Biology, Rua Larga, Faculty of Medicine (1st Floor), University of Coimbra, 3004-517 Coimbra, Portugal.
** Corresponding author. CNC - Center for Neuroscience and Cell Biology, and Institute of Physiology, Faculty of Medicine, University of Coimbra, 3004-517 Coimbra, Portugal.
*E-mail addresses:* ana.duarte@cnc.uc.pt (A.I. Duarte), pimoreira@fmed.uc.pt, vental@ci.uc.pt (P.I. Moreira).

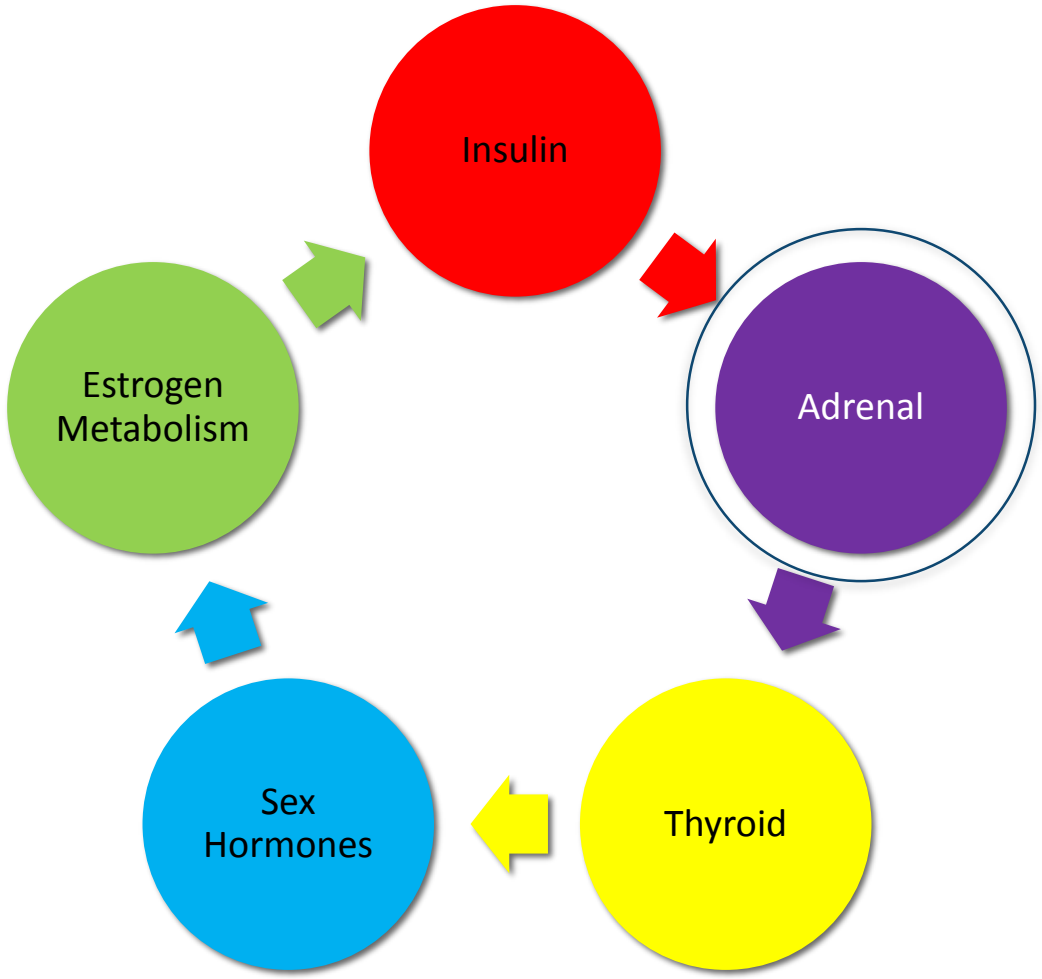
https://doi.org/10.1016/j.neuropharm.2018.01.044
0028-3908/

"We finally discussed AD as the potential type 3 diabetes, and the potential of restoring brain insulin levels or glucose energy metabolism via administration of intranasal insulin and use of ketogenic diets."

GENOVA DIAGNOSTICS

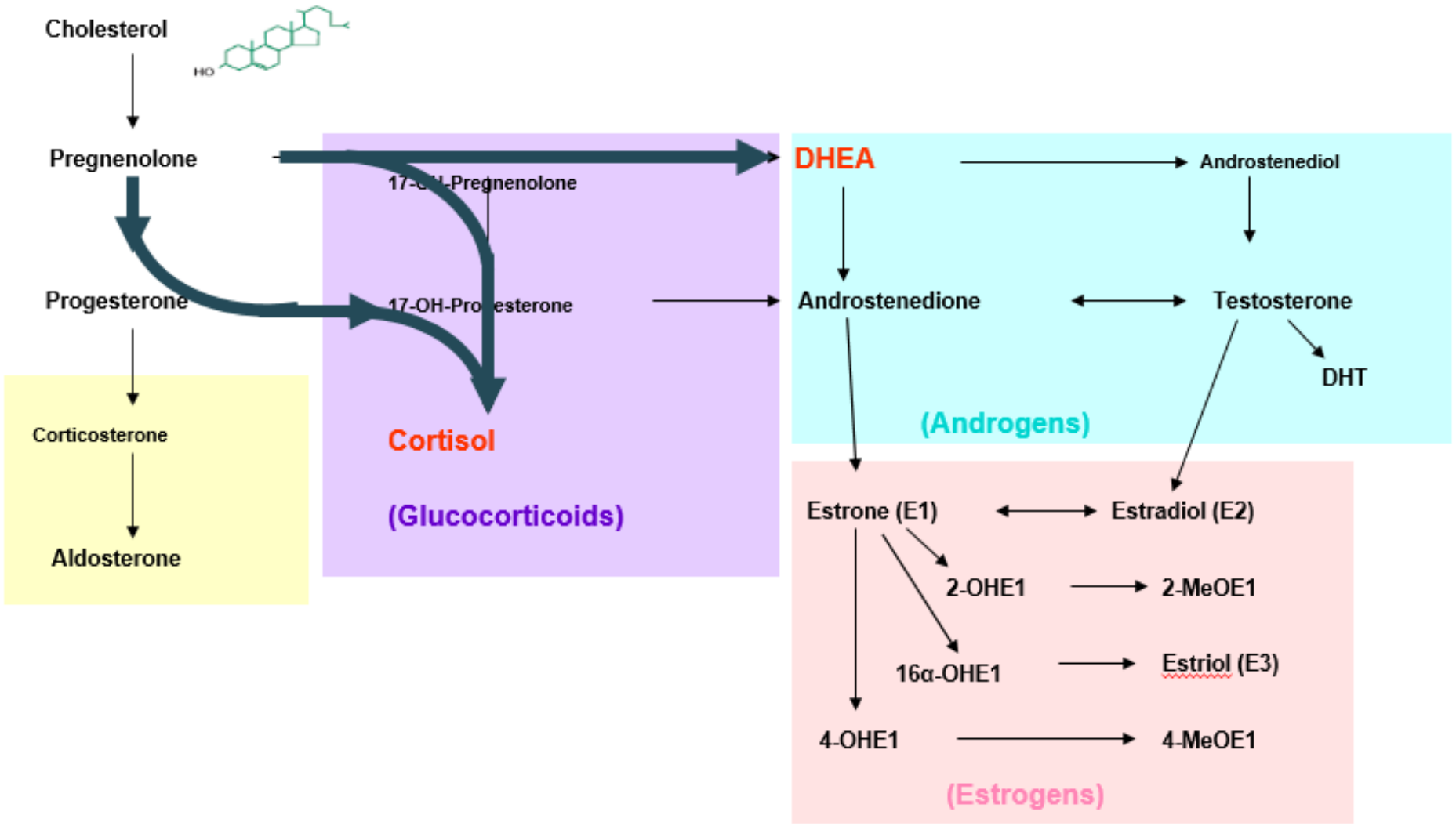
Duarte AI, et al. *Neuropharmacology*. 2018;136(2018):223-42.

# The Saudade Hormonal Symphony™

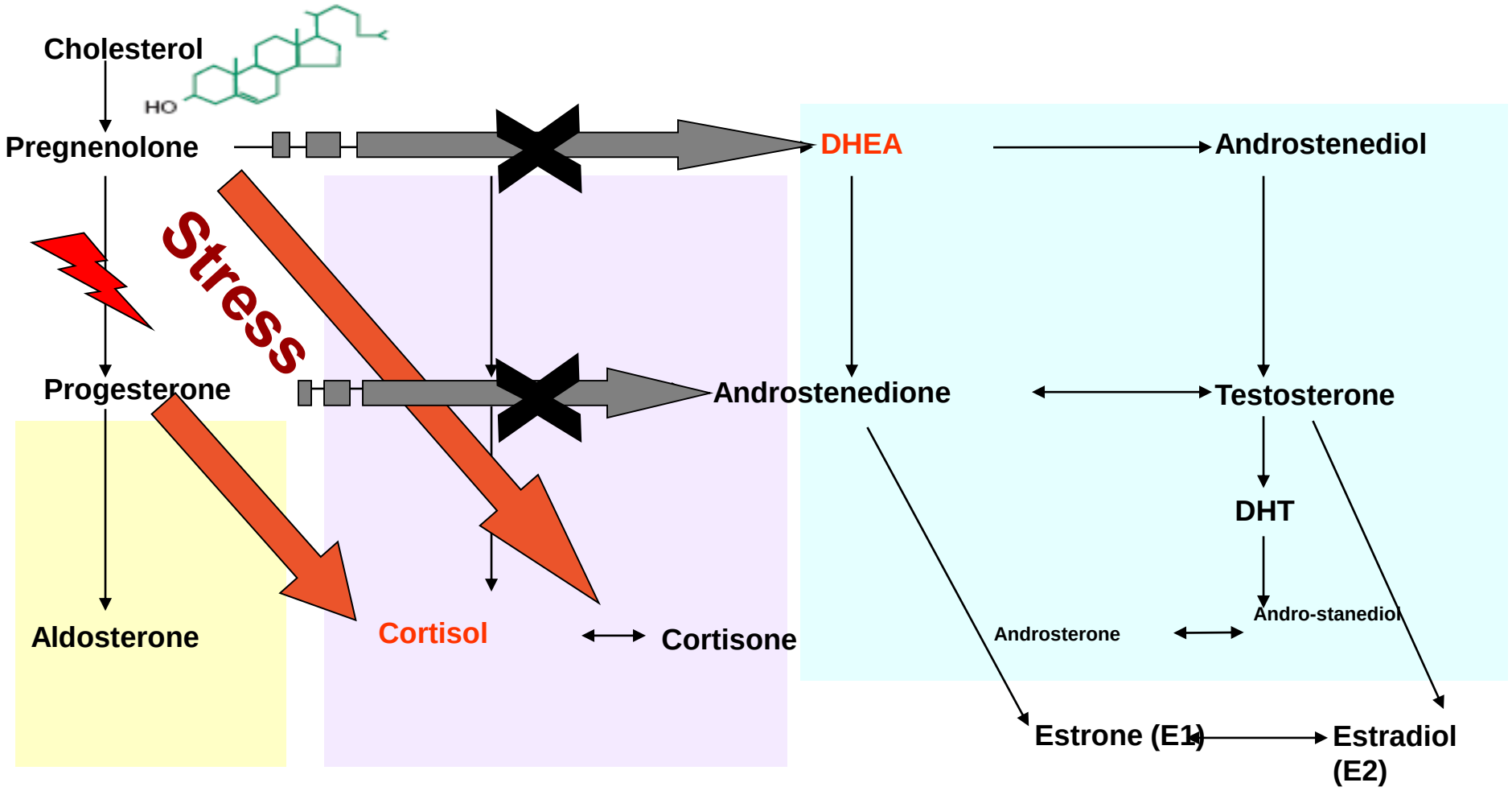



GENOVA DIAGNOSTICS

# Cortisol and DHEA Derive from Same Precursors




GENOVA DIAGNOSTICS




GENOVA DIAGNOSTICS

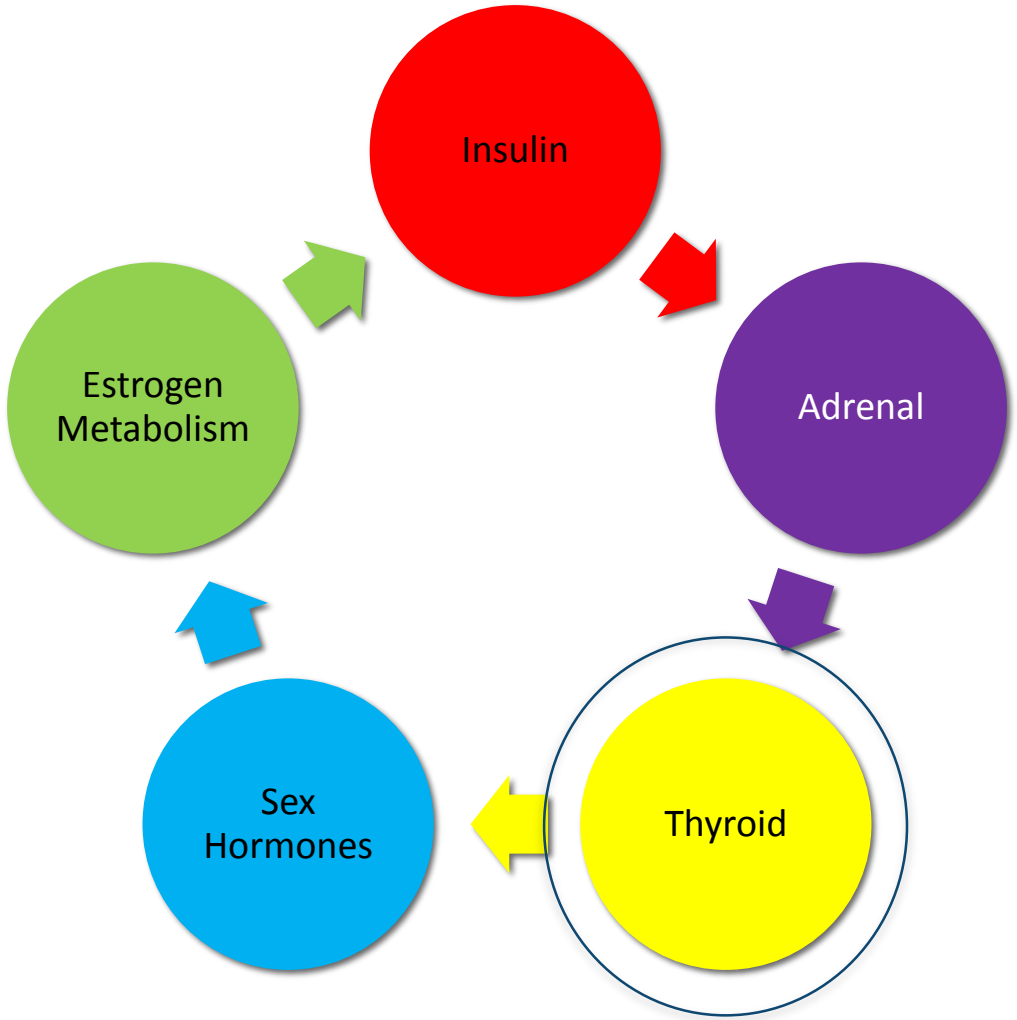
# The Big Picture: Selye's General Adaptation Syndrome

- Stage 1: **Arousal**
  - Both cortisol and DHEA increase with episodic stress, but recovery occurs to baseline
  - This may be asymptomatic
- Stage 2: **Adaptation**
  - Cortisol chronically elevated, but DHEA declines
  - "Stressed," anxiety attacks, mood swings, depression
- State 3: **Exhaustion**
  - Adrenal insufficiency / low cortisol and DHEA
  - Depression and fatigued

GENOVA DIAGNOSTICS

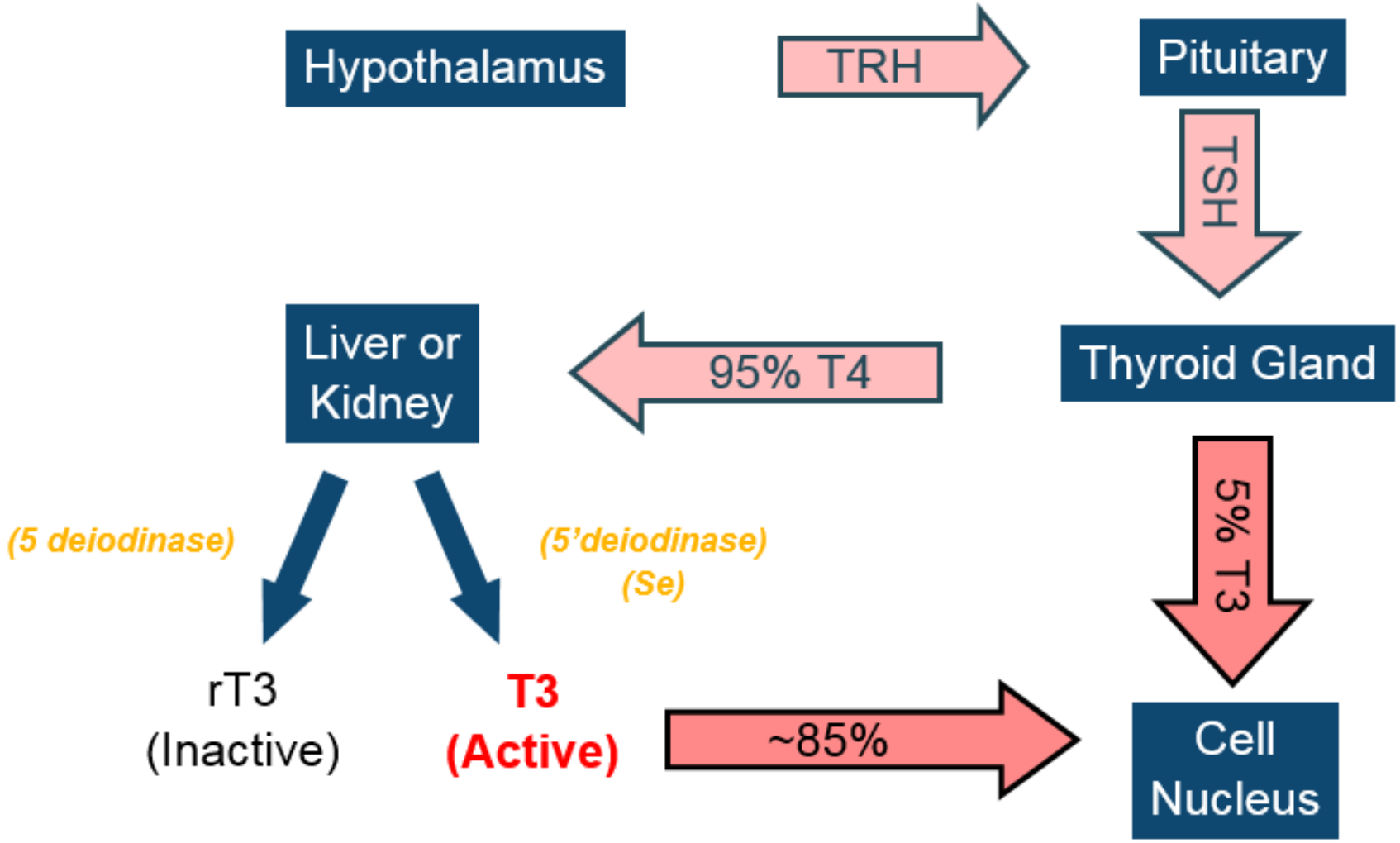
Selye H. 1956. The stress of life. New York: McGraw-Hill Book Co.

# The Saudade Hormonal Symphony™



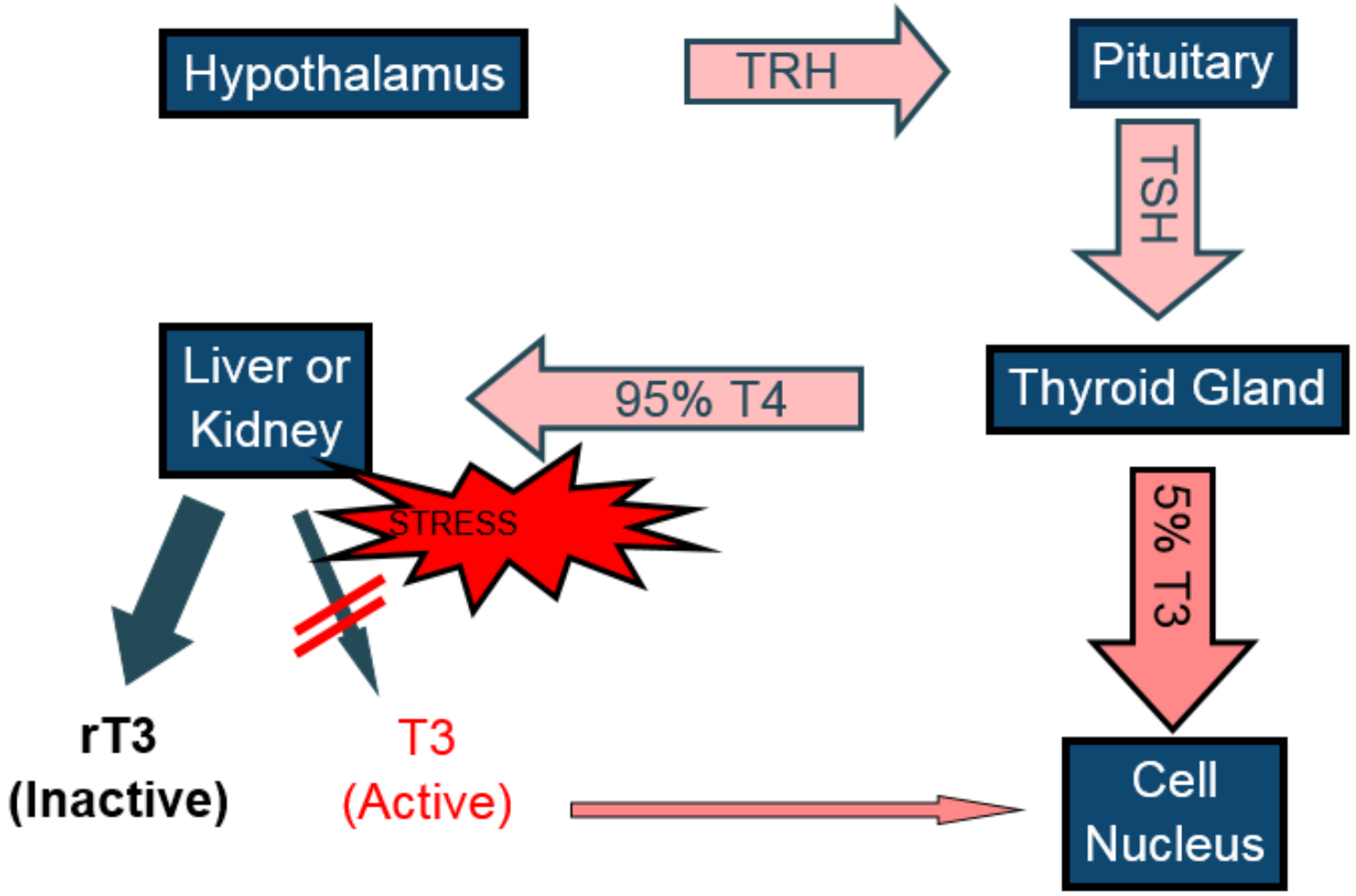

GENOVA DIAGNOSTICS

# Thyroid Function

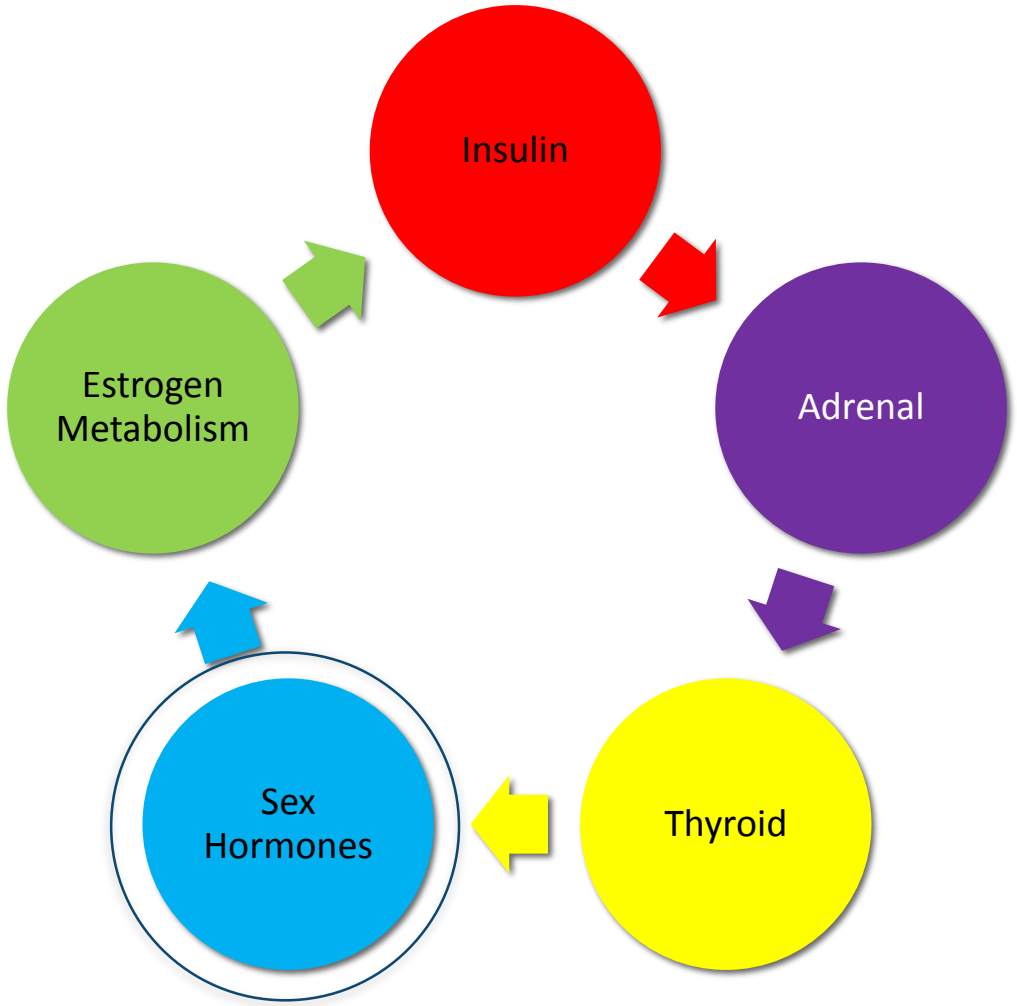



GENOVA DIAGNOSTICS

# Stress and Thyroid Function

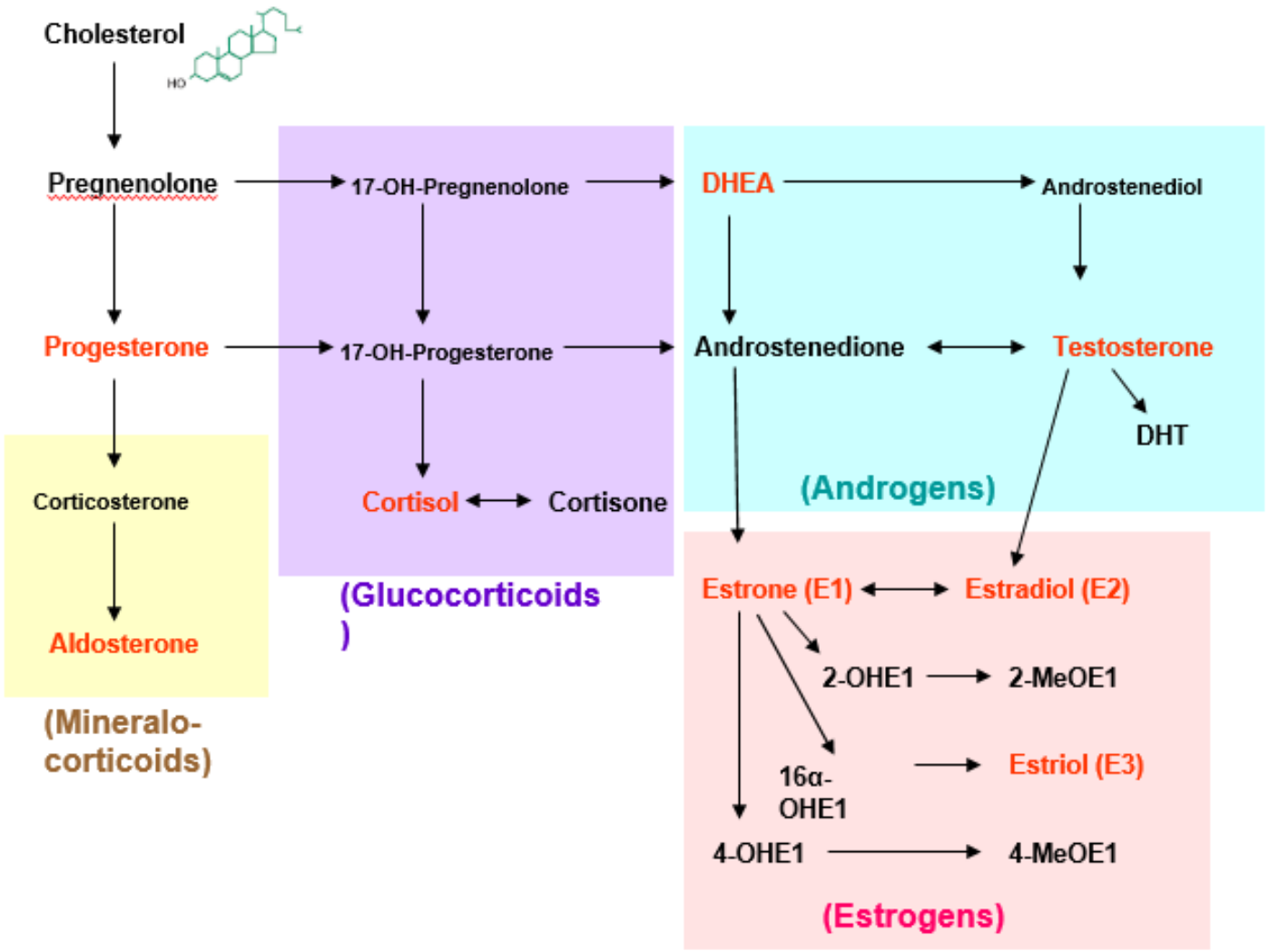


# The Saudade Hormonal Symphony™



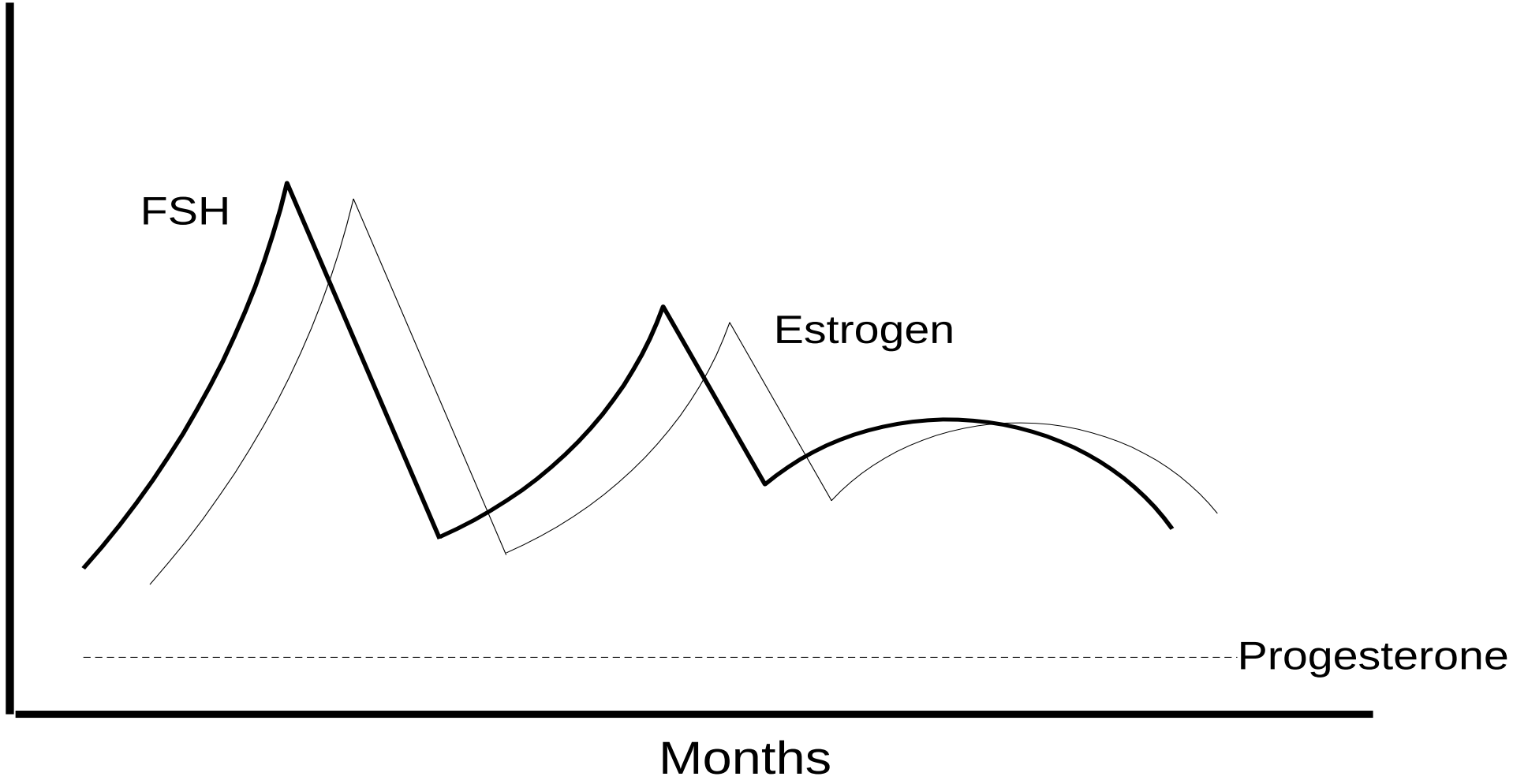

GENOVA DIAGNOSTICS

# The Steroidogenic Pathways




GENOVA DIAGNOSTICS

# Perimenopause




GENOVA DIAGNOSTICS

# Breast Cancer Risks and HRT

- Follow-up on the French E3N cohort study
  - 80,377 postmenopausal women found “when combined with an estrogen, progesterone has a safer risk profile in the breast compared with some other progestogens.”

GENOVA DIAGNOSTICS

Fournier A. Breast Cancer Res Treat. 2008;107(1):103–11.

Published in final edited form as:
*Fertil Steril*. 2011 August ; 96(2): 399–403. doi:10.1016/j.fertnstert.2011.05.079.

# Differential effects of estrogen and micronized progesterone or medroxyprogesterone acetate on cognition in postmenopausal women

**Barbara B. Sherwin, Ph.D.** and **Miglena Grigorova, Ph.D.**
Department of Psychology, McGill University, Montreal, Quebec, Canada

## Abstract

**Objective—**To investigate possible differential effects of the coadministration of conjugated equine estrogen (CEE) and a placebo (CEE + PL), CEE and medroxyprogesterone acetate (CEE + MPA), or CEE and micronized P (CEE + MP) on aspects of cognitive functioning in naturally postmenopausal women.

**Design—**Double-blind, randomized, controlled trial.

**Setting—**Gynecologic screening occurred at a university hospital, and neuropsychological testing took place in a university laboratory.

**Patient(s)—**Twenty-four naturally menopausal w
hormone therapy were recruited by means of news

**Intervention(s)—**A battery of mood and neurops
were randomly assigned to receive CEE + PL (n =
The tests were readministered 12 weeks later.

**Main Outcome Measure(s)—**Standardized test
spatial abilities, and visual–spatial sequencing, and

**Result(s)—**Mood improved after treatment in all groups. No changes in scores occurred over time in any cognitive test in the group that received CEE + PL. Only the CEE + MP group had a significant decrease in their delayed verbal memory scores from baseline to after treatment. The CEE + MP-treated women performed significantly better on a test of working memory than women in the other two groups.

**Conclusion(s)—**Coadministration of CEE with MPA or MP caused differential effects on aspects of memory in postmenopausal women. These findings need to be replicated with a larger sample size before their potential clinical implications can be determined.

## Keywords

Postmenopause; micronized progesterone; medroxyprogesterone acetate; estrogen; cognition; mood

Reprint requests: Barbara B. Sherwin, Ph.D., McGill University, Department of Psychology, 1205 Dr. Penfield Ave., Montreal, QC H3A 1B1, Canada (barbara.sherwin@mcgill.ca).

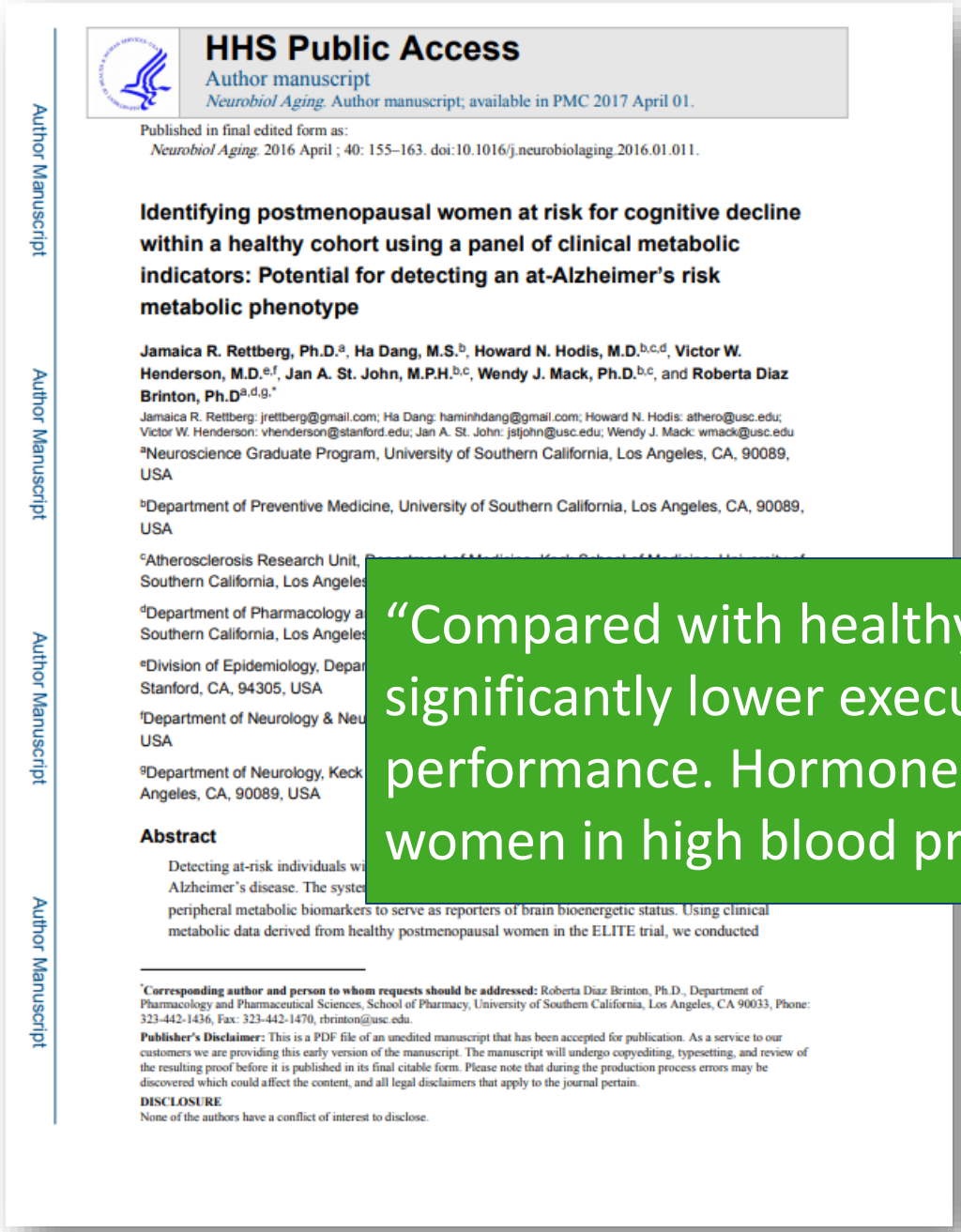
B.B.S. has nothing to disclose. M.G. has nothing to disclose.



"Co-administration of CEE with MPA or MP caused differential effects on memory in postmenopausal women."

GENOVA DIAGNOSTICS

Sherwin BB, et al. *Fertil steril*. 2011;96(2):399-403.



HHS Public Access

Author manuscript

*Neurobiol Aging*. Author manuscript; available in PMC 2017 April 01.

Published in final edited form as:

*Neurobiol Aging*. 2016 April ; 40: 155–163. doi:10.1016/j.neurobiolaging.2016.01.011.

**Identifying postmenopausal women at risk for cognitive decline within a healthy cohort using a panel of clinical metabolic indicators: Potential for detecting an at-Alzheimer's risk metabolic phenotype**

**Jamaica R. Rettberg, Ph.D.**[a], **Ha Dang, M.S.**[b], **Howard N. Hodis, M.D.**[b,c,d], **Victor W. Henderson, M.D.**[e,f], **Jan A. St. John, M.P.H.**[b,c], **Wendy J. Mack, Ph.D.**[b,c], and **Roberta Diaz Brinton, Ph.D**[a,d,g,*]

Jamaica R. Rettberg: jrettberg@gmail.com; Ha Dang: haminhdang@gmail.com; Howard N. Hodis: athero@usc.edu; Victor W. Henderson: vhenderson@stanford.edu; Jan A. St. John: jstjohn@usc.edu; Wendy J. Mack: wmack@usc.edu

[a]Neuroscience Graduate Program, University of Southern California, Los Angeles, CA, 90089, USA

[b]Department of Preventive Medicine, University of Southern California, Los Angeles, CA, 90089, USA

[c]Atherosclerosis Research Unit, Southern California, Los Angeles

[d]Department of Pharmacology a Southern California, Los Angeles

[e]Division of Epidemiology, Depar Stanford, CA, 94305, USA

[f]Department of Neurology & Neu USA

[g]Department of Neurology, Keck Angeles, CA, 90089, USA

**Abstract**

Detecting at-risk individuals wi Alzheimer's disease. The syste peripheral metabolic biomarkers to serve as reporters of brain bioenergetic status. Using clinical metabolic data derived from healthy postmenopausal women in the ELITE trial, we conducted

[*]**Corresponding author and person to whom requests should be addressed:** Roberta Diaz Brinton, Ph.D., Department of Pharmacology and Pharmaceutical Sciences, School of Pharmacy, University of Southern California, Los Angeles, CA 90033, Phone: 323-442-1436, Fax: 323-442-1470, rbrinton@usc.edu.



**DISCLOSURE**

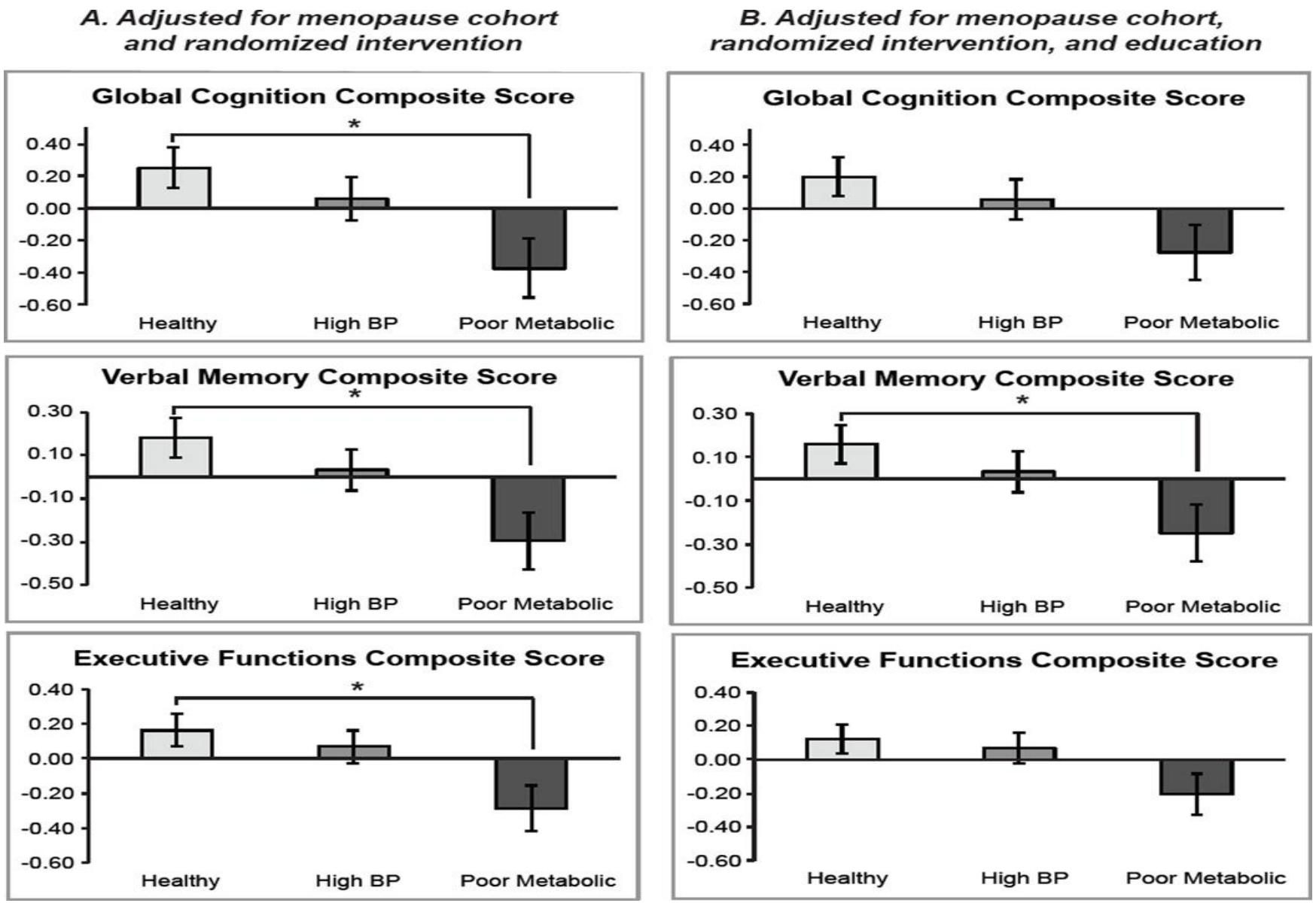
None of the authors have a conflict of interest to disclose.



"Compared with healthy women, poor metabolic women had significantly lower executive, global and memory cognitive performance. Hormone therapy provided metabolic benefit to women in high blood pressure and poor metabolic phenotypes."

GENOVA DIAGNOSTICS

Rettberg JR, et al. *Neurobiol Aging*. 2016;40:155-63.



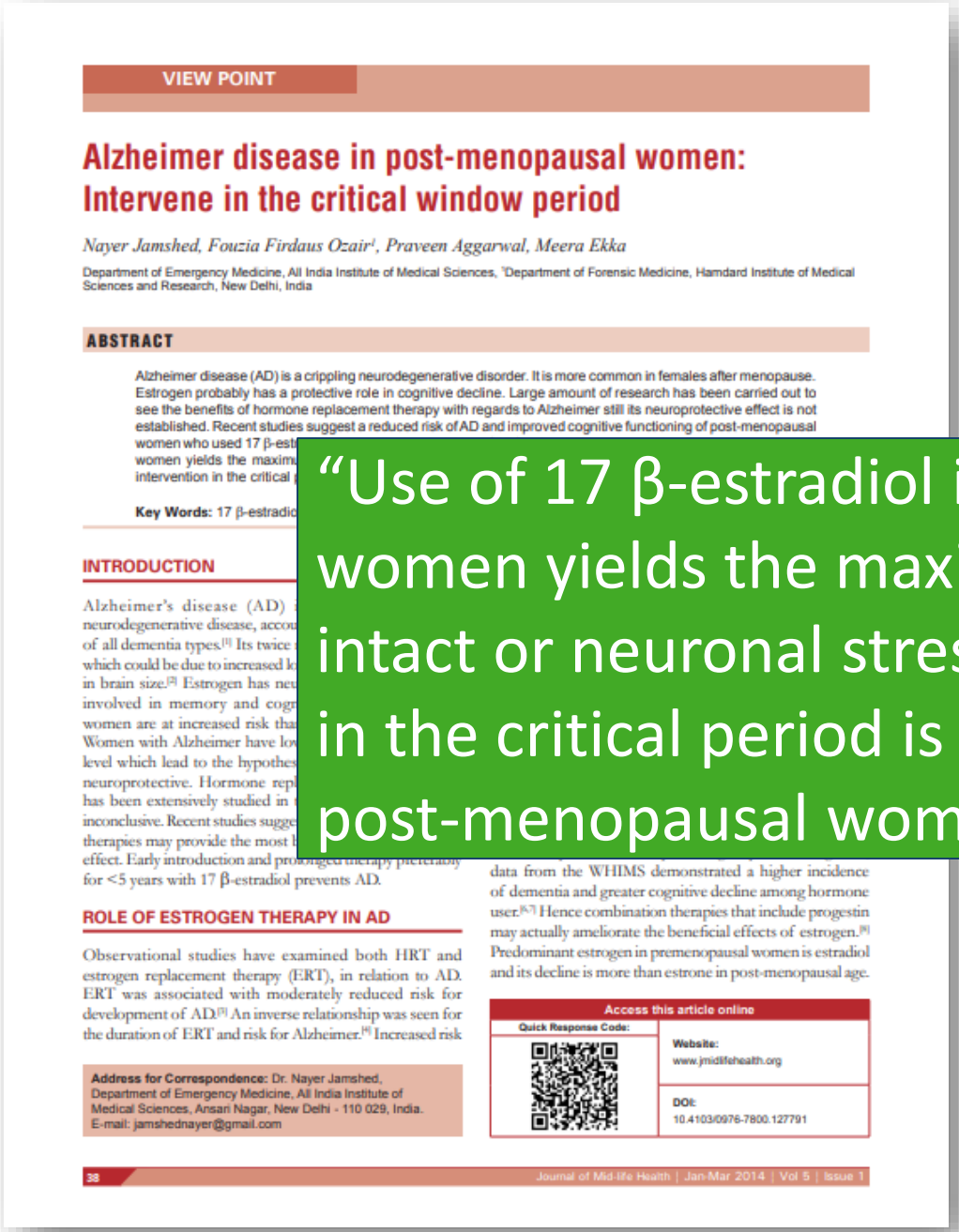

Rettberg JR, et al. *Neurobiol Aging*. 2016;40:155-63.

# Will Memory be Lost with Menopause

"It is possible that timing of the start of hormone replacement therapy exactly to the menopause could provide the best benefit of memory and inflammation processing."

GENOVA DIAGNOSTICS

Remes A, et al. *Duodecim*. 2015;131(16):1499-1505.



VIEW POINT

# Alzheimer disease in post-menopausal women: Intervene in the critical window period

*Nayer Jamshed, Fouzia Firdaus Ozair[1], Praveen Aggarwal, Meera Ekka*

Department of Emergency Medicine, All India Institute of Medical Sciences, [1]Department of Forensic Medicine, Hamdard Institute of Medical Sciences and Research, New Delhi, India

**ABSTRACT**

Alzheimer disease (AD) is a crippling neurodegenerative disorder. It is more common in females after menopause. Estrogen probably has a protective role in cognitive decline. Large amount of research has been carried out to see the benefits of hormone replacement therapy with regards to Alzheimer still its neuroprotective effect is not established. Recent studies suggest a reduced risk of AD and improved cognitive functioning of post-menopausal women who used 17 β-est
women yields the maxim
intervention in the critical

**Key Words:** 17 β-estradio

## INTRODUCTION

Alzheimer's disease (AD)
neurodegenerative disease, accou
of all dementia types.[1] Its twice
which could be due to increased l
in brain size.[2] Estrogen has neu
involved in memory and cogn
women are at increased risk tha
Women with Alzheimer have lo
level which lead to the hypothes
neuroprotective. Hormone repl
has been extensively studied in
inconclusive. Recent studies sugge
therapies may provide the most
effect. Early introduction and prolonged therapy preferably for <5 years with 17 β-estradiol prevents AD.

## ROLE OF ESTROGEN THERAPY IN AD

Observational studies have examined both HRT and estrogen replacement therapy (ERT), in relation to AD. ERT was associated with moderately reduced risk for development of AD.[3] An inverse relationship was seen for the duration of ERT and risk for Alzheimer.[4] Increased risk data from the WHIMS demonstrated a higher incidence of dementia and greater cognitive decline among hormone user.[5-7] Hence combination therapies that include progestin may actually ameliorate the beneficial effects of estrogen.[8] Predominant estrogen in premenopausal women is estradiol and its decline is more than estrone in post-menopausal age.

**Address for Correspondence:** Dr. Nayer Jamshed, Department of Emergency Medicine, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110 029, India. E-mail: jamshednayer@gmail.com

Access this article online

Quick Response Code:

Website: www.jmidlifehealth.org

DOI: 10.4103/0976-7800.127791

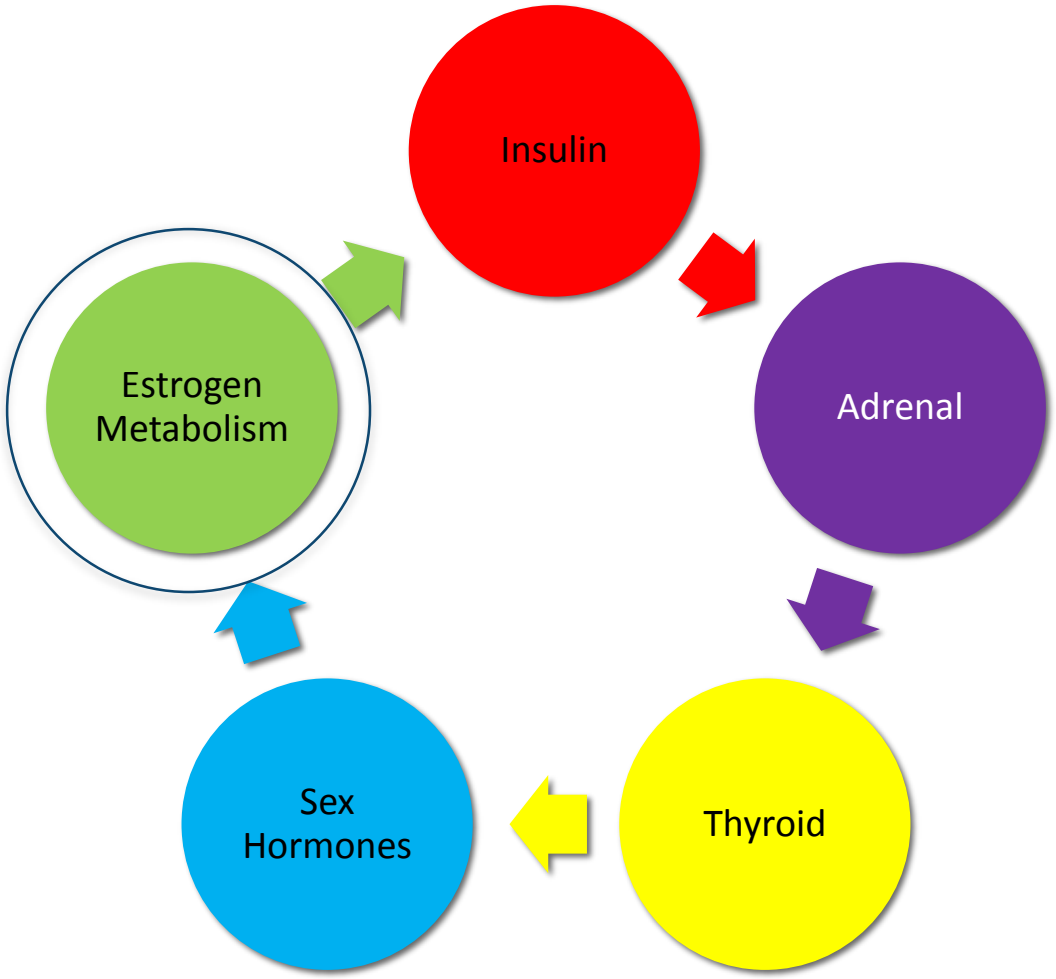


"Use of 17 β-estradiol in young and healthy post-menopausal women yields the maximum benefit when the neurons are intact or neuronal stress has just started. Hence intervention in the critical period is key in the prevention or delay of AD in post-menopausal women."

GENOVA DIAGNOSTICS

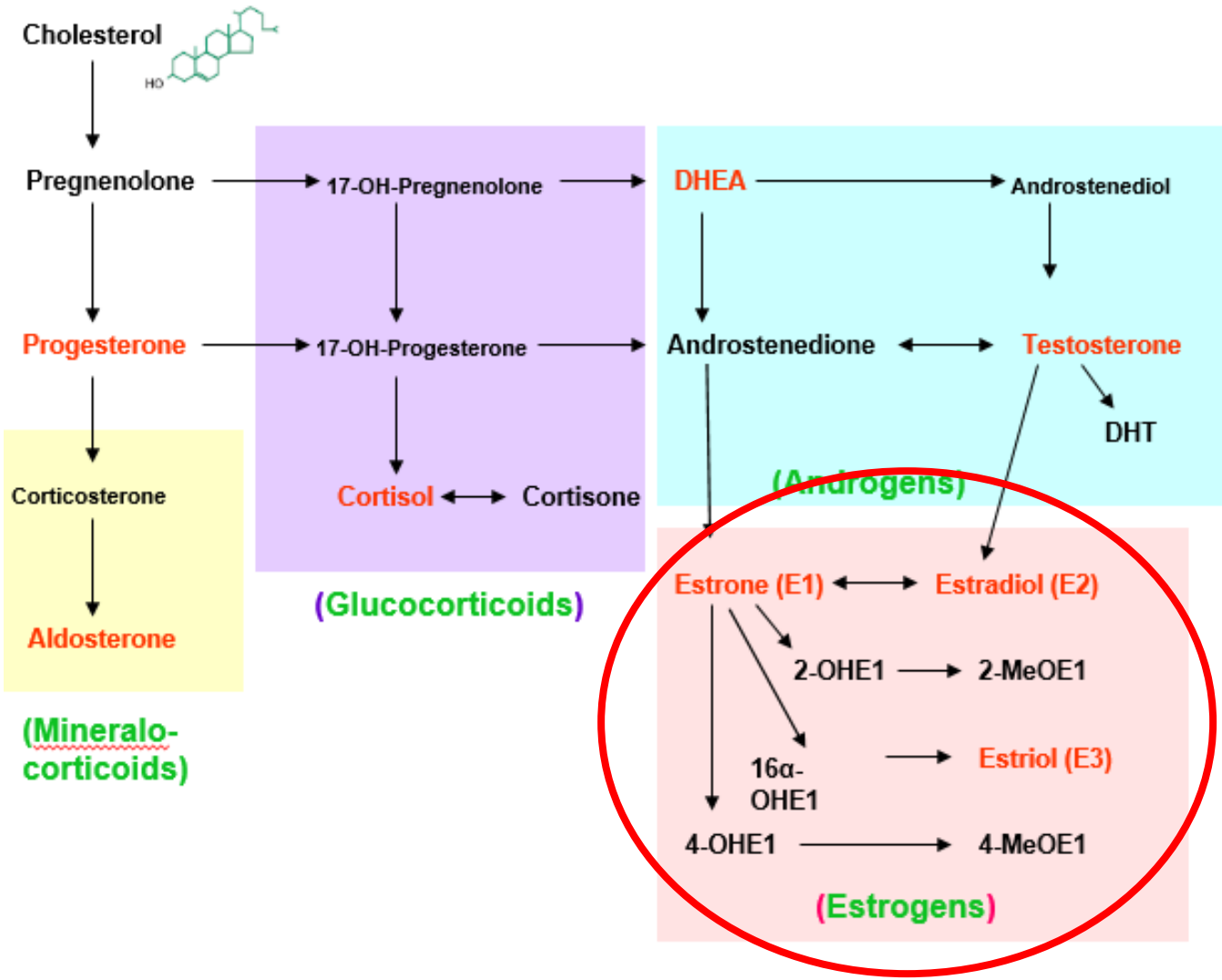
Jamshed N, et al. *J Midlife Health*. 2014;5(1):38-40.

# The Saudade Hormonal Symphony™

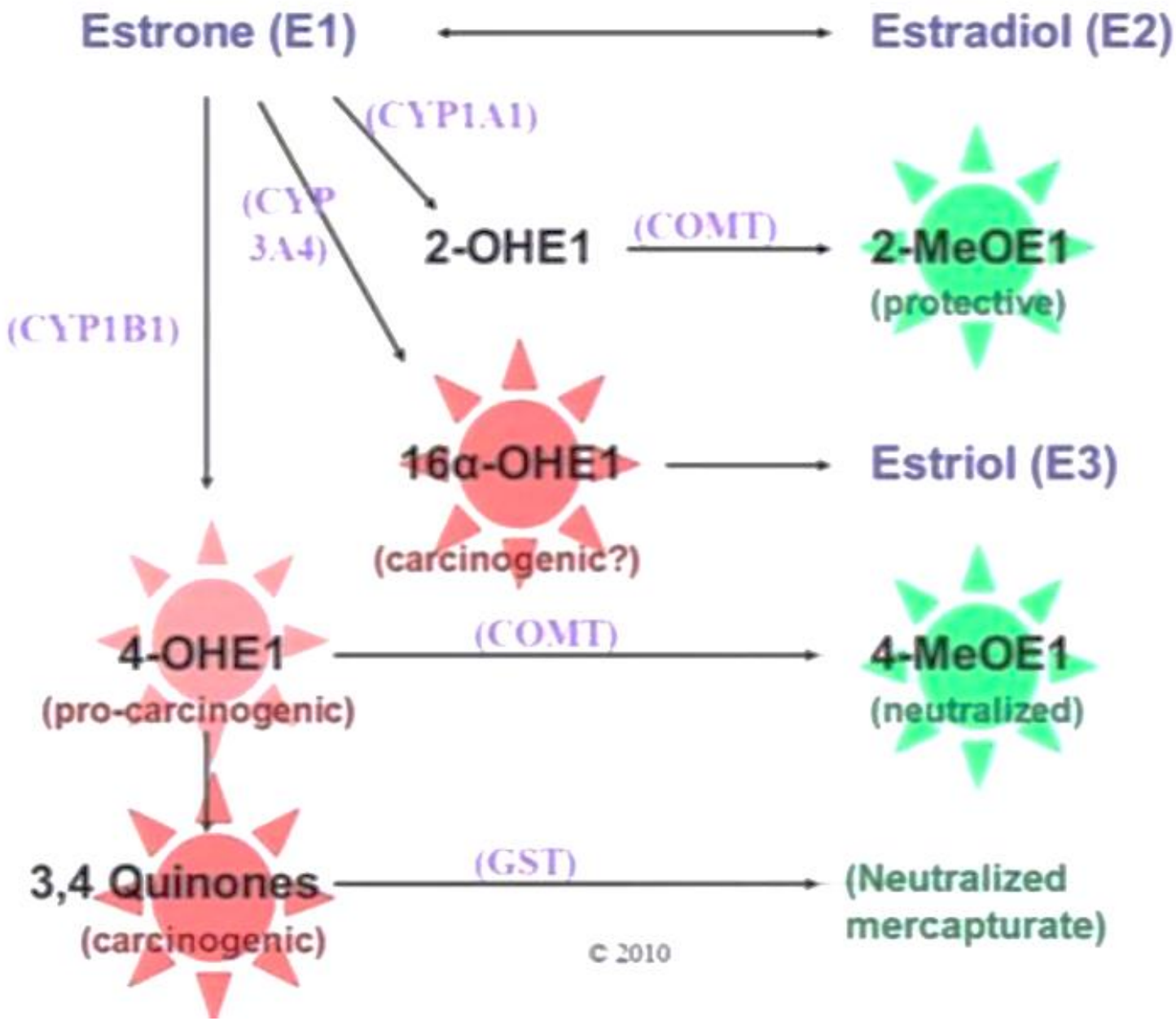



GENOVA DIAGNOSTICS

# Estrogen Metabolism




GENOVA DIAGNOSTICS




GENOVA DIAGNOSTICS

# Endocrine Disruptors

- Environmental xenobiotics act as “endocrine disruptors” that modify intercellular communication and function
- Chemicals commonly detected in people include DDT, Polychlorinated biphenyls (PCB's), Bisphenol A, Polybrominated diphenyl ethers (PBDE's)
- May play role in cancer and obesity
- Changes in DNA methylation (epigenetic modification) which can ultimately change ER activity
- A higher ratio of the 4 and 16 hydroxylated-estrogen derivatives that are potentially more genotoxic
  - Modifying members of the CYP450 enzyme family

GENOVA DIAGNOSTICS

Latini, et al. *Mini-Reviews in Medicinal Chemistry*. 2010;10;846-55.
Soto AM, et al. *Nat Rev Endocrinol.* 2010;6:363–70.

GENOVA DIAGNOSTICS

CONNECTING THE DOTS TO FIND THE ROOT CAUSE...

## Saudade Certification Program

Register at: http://www.drtrindade.com/for-practitioners

&

## Saudade Total Wellness Retreat

May 30th to June 3rd (5 Full Days)

The Sacred Island of Sao Jorge

Register at: http://www.drtrindade.com/saudadetotalwellnessretreat

***Advance your Knowledge in Functional Medicine, Rebuild and Rejuvenate with Dr. T***

**Filomena Trindade, MD, MPH, ABFM, ABOIM**
**Presenter**

**US Client Services: 800-522-4762**

**UK Client Services: 020.8336.7750**

***We look forward to hearing from you!***

# *Questions?*

GENOVA DIAGNOSTICS

# Upcoming LIVE GDX Webinar Topics

- Male Hormones: What You Need to Know (March 27, 2019)
  - Pam W. Smith, MD, MPH
- Hormone Testing: Selecting the Right Profile for Your Complex Patient (April 24, 2019)
  - Stephen Goldman, DC
- Epigenetics: Telling Your Genes How to Behave (May 22, 2019)
  - Ann Shippy, MD

Register for upcoming LIVE GDX webinars and
access archived webinars online at **WWW.GDX.NET/LIVEGDX**

GENOVA DIAGNOSTICS