Health and Well Being under the sex and gender lens: the gateway to precision medicine

Women's Brain Project

An international non-profit organization advocating for women's brain and mental health

Dr. Antonella Santuccione Chadha
Womensbrainproject.com

The information and views set out in this presentation are those of the author and do not necessarily reflect the official opinion of Roche, which is the official employer of Dr. Santuccione - Chadha

Medicine is androcentric

Historically biomedical research reflects predominantly a male perspective assimilating women to men

- Men and women differ in the way they experience diseases:
  - Symptom
  - Progression
  - Diagnosis
- Response to drug Pharmocokinetics
  - Pharmacodynamics
  - Polypharmacy
  - Adverse events

The Aspirin Example

Medicine is androcentric

GAO
Accountability • Integrity • Reliability

United States General Accounting Office
Washington, DC 20548

January 19, 2001

The Honorable Tom Harkin
The Honorable Olympia J. Snowe
The Honorable Barbara A. Mikulski
United States Senate

The Honorable Henry A. Waxman
House of Representatives

Subject: Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women

8 out of 10 drugs that were pulled pose more of a threat for women

Gender differences in preclinical studies

Fighting a persistent sex bias in animal studies

Some researchers warn that stereotypes can warp tests leading to new drugs

BY JOANNA KLEIN

Say you are prescribed medication for depression, anxiety or even just to sleep. Would you want to take it if you knew that the drug had only been tested on men and male animals?

Rebecca Shansky, a neuroscientist at Northeastern University in Boston, thinks you might not.

When she tells nonscientific audiences that researchers "for the most part don't study female animals, people are blown away," she said.

She added: "It seems like such an obvious thing to a normal person. But when you come up in the academic and science world, it's like, 'Oh no, females are so complicated, so we just don't study them.'"

In 2016, the National Institutes of Health and its Canadian counterpart mandated that all preclinical research they fund must include female subjects.

Now, Dr. Shansky and other scientists wonder if that requirement will do enough to improve how research is conducted.

In an essay published Thursday in Science, Dr. Shansky questions whether simply adding female organisms to experiments or looking for sex differences misses the point.

She warns that this is a public health problem — with implications beyond neuroscience — and says scientists should design experiments better suited to both biological sexes.

If scientists don't stop looking through a male lens, outdated gender stereotypes will continue to foster dangerous assumptions about the brain and behavior, resulting in clinical studies and eventual treatments that don't work equally for all people on the gender spectrum.

Basic research is the foundation for clinical studies and practice, and that often begins with animals, which offer controlled settings for research of human diseases.

"Because we start there, that does end up affecting human studies and the drugs that go to market, and the way they're marketed to men and women, and how we know if they work differently in men and women," said Tory Eisenlohr-Moul, a researcher and clinician who works with conditions related to hormones in women.

Women make up about half of the population, but female animals make up a far smaller percentage of biomedical research subjects. In neuroscience studies, males outnumbered females nearly six to one.

Dr. Shansky and others say this is a public health issue because women are more vulnerable to mood or anxiety disorders like major depression or post traumatic stress than men.

At the same time, men are more vulnerable to autism and attention deficit disorder. Men and women may express symptoms of these conditions differently. And of course some conditions, like postpartum depression and premenstrual dysphoric disorder, are only found in women.

By only looking at male animals in initial research, "we may be missing big pieces of the puzzle," said Liisa Hantsoo, who studies stress, premenstrual syndrome and premenstrual dysphoric disorder at the University of Pennsylvania's medical school.

The reasons women and female animals are often omitted from research are the same: ovarian hormones. In the Victorian era, the idea that women were inferior to men was replaced by the notion that women were hysterical, disorganized, emotional — the hormone-driven counterpoints to rational, stable men.

For years experiments used mostly male animals. An essay published in the journal Science suggests that researchers should design experiments better suited to both sexes.

By studying males only, mostly male scientists believed they could more easily identify the most basic ways the brain worked without the "messiness" of fluctuating female hormones. This stereotype is so pervasive that some biomedical researchers still don't question why they aren't looking at female rats or mice. It also set up men as the norm.

"We live in a world where the assumption is that males are the standard, the reference population, and females are the ones that are odd," said Daniela Polak, a neurobiologist who wrote an essay on the problem earlier this year.

In recent years, analyses of hundreds of neuroscience studies offered clear evidence disproving the idea that males are less hormonal.

In some cases, male rodents living in groups were messier because their testosterone (which essentially works on the brain like estrogen) fluctuates, depending on dominance hierarchies in groups. That males were hormonal, emotional and messy still didn't get them kicked out of studies.

Even if scientists had shown that females were more complex subjects, "it would not suffice as an excuse," Dr. Polak said. "Scientists are not meant to give up on a problem just because it starts becoming complicated."

Encouraged by the N.I.H. and Canadian mandates, scientists are reconsidering the effects of sex in their research. But this may not be enough to improve the outcomes if it primarily results in researchers just using more female subjects without understanding the ways stereotypes influence animal studies.

Dr. Shansky offered an example of how females were expected to behave in tasks designed to model post-traumatic stress in male rodents. Instead of freezing as males did, the females darted around during experimental tests. Without recognizing this behavior as different, rather than wrong, one might say females failed the task.

"We've gone from excluding women and female animals to this ham-handed implementation of sex as biological variable," said Anu Fink, a feminist neuroscientist and gender scholar at Lehigh University.

She emphasized that sex is biological and gender is a social construct, and that using gender stereotypes to study basic biological concepts first contributed to omitting female subjects from research. But drawing conclusions about gender from animal subjects that don't have this social construct potentially reaffirms damaging stereotypes or encourages dangerous practices.

In 2013, for example, the Food and Drug Administration issued an advisory recommending women take half the dose of the sleeping pill Ambien, because women were reporting more severe side effects than men.

But body weight, not sex, was the cause of the incorrect dosing. Telling doctors the problem was a sex difference could have resulted in overweight women being underdosed, and underweight men being overdosed.

Dr. Fink pointed out that many researchers are now looking for sex differences because they think that's what they have to do to adhere to the mandate, but that wasn't its intention.

"The socially accepted way to go is to give into the fact that you must consider female subjects," Dr. Pollak said. "That's good for science studies, but if you also want to tackle the mind-set for the future, we need to go deeper."

"In the academic and science world, it's like, 'Oh no, females are so complicated, so we just don't study them.'"

Attitudes are changing about studying both sexes. Within five years, we'll know if the mandate worked as intended. And within a couple of decades, we'll see if it leads to more personalized treatments.

Until then, Dr. Shansky said, research can be improved by studying the sexes in parallel or in the same cohort, instead of experimenting on one sex after the other and making the first set of results the standard.

And when a study tries to model a condition that may be more prevalent in one sex, researchers should start with just a few of the other sex, then look for hints that there might be a sex difference.

If one is found, she added, scientists should repeat the experiment with enough animals of both sexes. By opening their minds to the idea that variability, or messiness, can be a positive thing, researchers can improve their outcomes.

"All of this is about embracing the diversity of the brain, and variable data should not be ignored or seen as a negative thing," Dr. Shansky said.

PERSPECTIVES

NEUROSCIENCE

Are hormones a "female problem" for animal research?

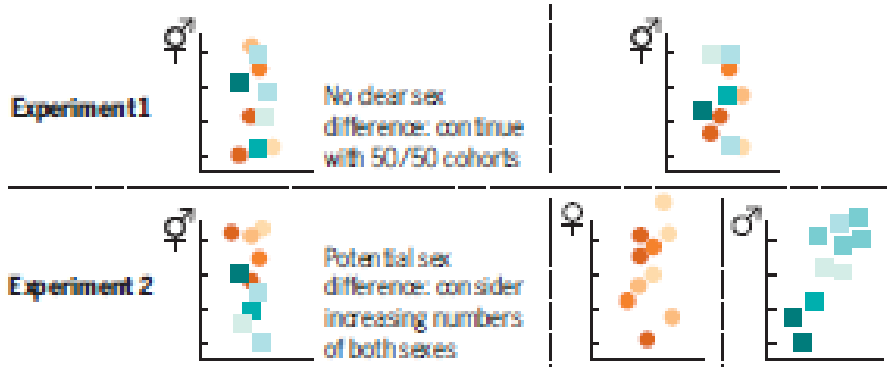
Outdated gender stereotypes are influencing experimental design in laboratory animals

By **Rebecca M. Shansky**

very practice of preclinical animal research, it also poses a public health problem.

Animal studies in both sexes

Researchers should start with mixed-sex cohorts and examine data for potential sex differences. If there are no clear sex differences (experiment 1), it is reasonable to proceed with mixed-sex cohorts. If data suggest a sex difference (experiment 2), studying cohorts of each sex may be appropriate.



What to do about it?

- Increase the number of women recruited in all phases of clinical trials
- Pharmacodynamics and pharmacokinetics should be reported separately in men and women
- Serious adverse events should be reported separately in men and women
- Educatate to sex and gender medicine already in medical schools

Sex and gender facor as the gateway to Precision Medicine

The **4 main workstreams** of Women's Brain Project

WS2 preclinical science

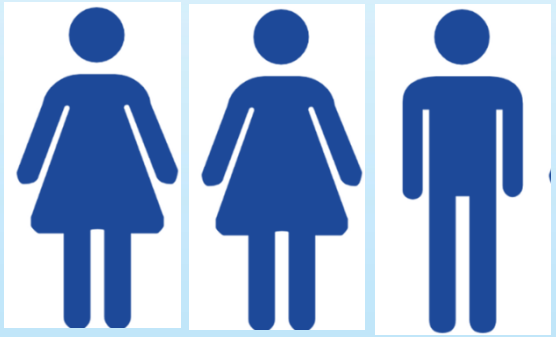
WKS2 drug development

WKS3 novel technologies

WS4 caregiving and policy science

Common mental disorders

Depression, anxiety and somatic complaints affect 1 in 3 persons worldwide



Of these, 2 out of 3 are women

‘Gender differences occur particularly in the rates of common mental disorders - depression, anxiety and somatic complaints. These disorders, in which women predominate, affect approximately 1 in 3 people in the community and constitute a serious public health problem.’ https://www.who.int/mental_health/prevention/genderwomen/en/

Prevalence of diseases is modulated by sex

Dementia
Migraine

Depression (also in teenagers)

Meningiomas
Prolactinoma

Multiple sclerosis
NMDA-R encephalitis

Anorexia
Bulimia
Late-onset schizophrenia

Parkinson's disease
Amyotrophic lateral sclerosis

Midlife stroke

Gliomas
Neuroblastoma

Suicide
Substance abuse

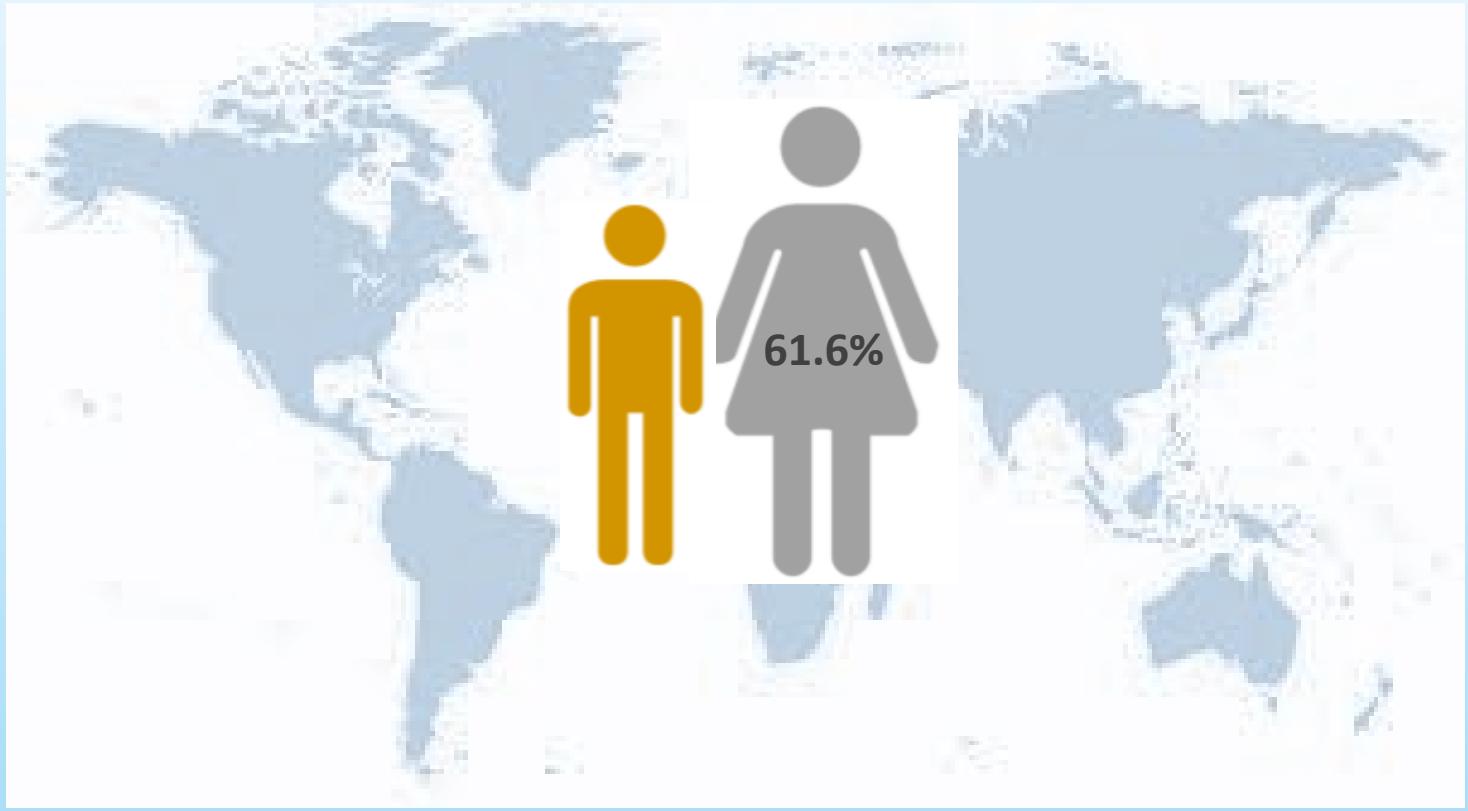
Early onset Schizophrenia
Autism

Tourette syndrome

Sex differences -the gateway to Precision Medicine in brain and mental diseases

Alzheimer’s as a case in point

Majority of Alzheimer’s patients worldwide are women



- **43.8 million** individuals suffer of Alzheimer’s and other dementias worldwide
- Of these, **27 millions** are women

Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016

Women and dementia in Europe

Women have greater frequency and prevalence of dementia in Europe

Table 3. The frequency of dementia in Europe (EU-28) according to sex

Country	Men	Women
Austria	45,938	99,494
Belgium	62,972	128,309
Bulgaria	37,851	72,042
Croatia	20,394	46,682
Cyprus	4,333	6,917
Czech Republic	45,532	97,778
Denmark	29,715	55,847
Estonia	5,469	16,252
Finland	29,287	62,945
France	375,843	799,113
Germany	517,136	1,054,968
Greece	75,392	126,375
Hungary	43,636	105,291
Ireland	17,895	31,574
Italy	414,975	857,341
Latvia	8,902	26,812
Lithuania	12,567	34,768
Luxembourg	2,327	4,662
Malta	1,878	3,423
Netherlands	83,247	162,314
Poland	150,371	350,721
Portugal	62,260	120,266
Romania	90,484	179,820
Slovakia	17,834	40,774
Slovenia	9,324	22,711
Spain	280,149	538,197
Sweden	60,479	112,656
United Kingdom	360,581	677,210
Total	**2,866,771**	**5,835,262**

WOMEN AND DEMENTIA IN EUROPE

POSITION PAPER

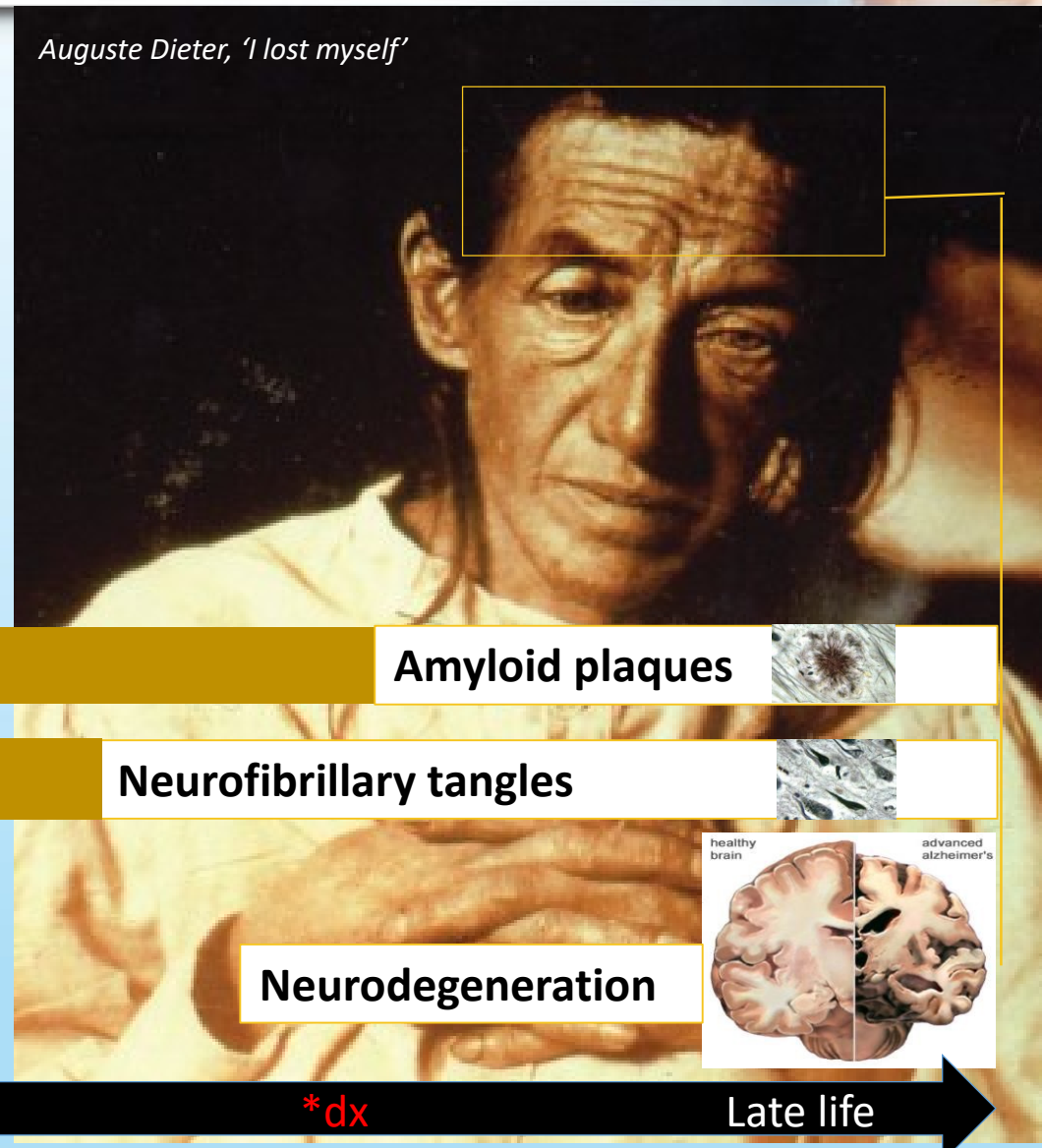
Addressing the Disproportionate Burden of Dementia on Women

WBP

EIWH Eurohealth

Alzheimer's pathology starts in midlife

Current clinical **diagnosis** (***dx**) occurs decades **after** the pathological process has started



Current challenges

- **No cure**
- **Diagnosis** comes too late
- High **interpersonal variability** in biomarkers and progression
- Focus on **prevention**

under the sex and gender lens

Maria Teresa Feretti, Maria Florencia Lulita, Enrica Cavedo, Patrizia Andrea Chiesa, Annemarie Schumacher Dimech, Antonella Santuccione Chadha, Francesca Baracchi, Hélène Girouard, Sabina Misoch, Ezio Giacobini, Herman Depyrere, Harald Hampel & for the Women's Brain Project and the Alzheimer Precision Medicine Initiative

Nature Reviews Neurology **14,** 457-469 (2018)

1. Early diagnosis – A Patient Journey

My journey to figure out what was wrong with me started the summer of 2014. I was so tired all the time. At the time we lived in the city Varberg in Sweden. I studied at a university to become a Health pedagog. I went to a doctor and he took some test on me that showed that I had iron deficiency. So I got some medicine but after 3 month I was still tired. I started to feel confused and forgetful, I took contact with a new doctor who sent me to a check of my memory. It went so well that they did not want to continue to investigate what was wrong with me. I told them about my grandmother, my father and his brother that al died in the disease so they continued to do test´s. Now I think, I was so early that it would not matter how many test they would have done. The test to draw a line from A to 1 then B to 2 and so on is still not my problem. But it was horrible to not be taken seriously. So we moved down south in Sweden to where I'm from. I contacted my father's old doctor and he helped me get in contact with the right people. And so a year and a half after I started, I got my diagnosis. Now I have the most wonderful team around me. And a couple of days ago I was on a check up at my doctor Moa Wibom and I have the same test results as I had a year ago. In my world that is great!

Sofia Petersson,

41 years, mother of two
teenagers, diagnosed with Early Onset
Alzheimer's disease
Patient Advocate

Excerpt from: www.womensbrainproject.com

Early diagnosis has to consider the sex of the patient

ARTICLES

Better verbal memory in women than men in MCI despite similar levels of hippocampal atrophy

Erin E. Sundermann, PhD
Anat Biegon, PhD
Leah H. Rubin, PhD
Richard B. Lipton, MD
Wenzhu Mowrey, PhD
Susan Landau, PhD
Pauline M. Maki, PhD
For the Alzheimer's Disease Neuroimaging Initiative

ABSTRACT

Objective: To examine sex differences in the relationship between clinical symptoms related to Alzheimer disease (AD) (verbal memory deficits) and neurodegeneration (hippocampal volume/intracranial volume ratio [HpVR]) across AD stages.

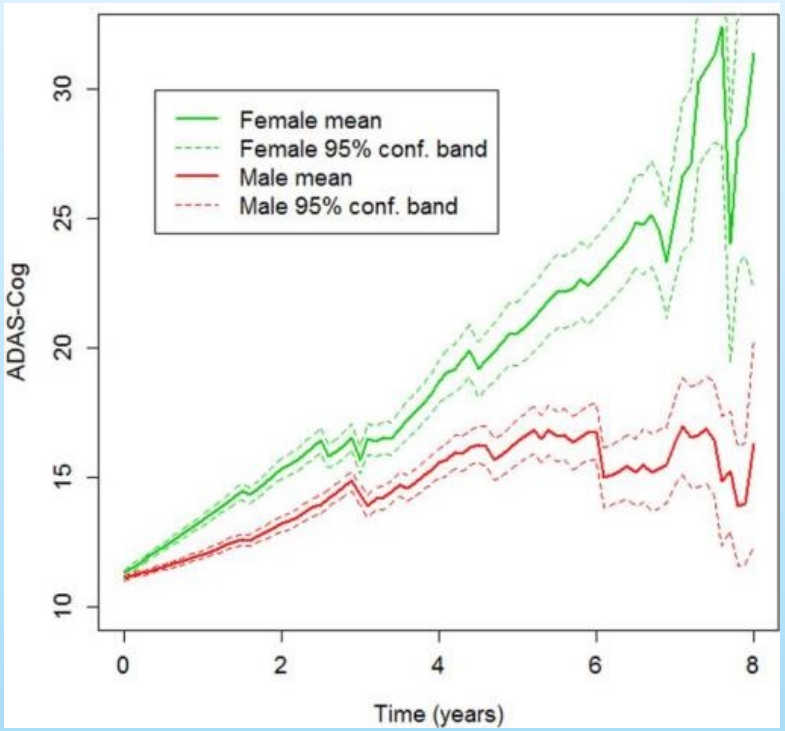
Methods: The sample included 379 healthy participants, 694 participants with amnestic mild cognitive impairment (aMCI), and 235 participants with AD and dementia from the Alzheimer's Disease Neuroimaging Initiative who completed the Rey Auditory Verbal Learning Test (RAVLT). Cross-sectional analyses were conducted using linear regression to examine the interaction between sex and HpVR on RAVLT across and within diagnostic groups adjusting for age, education, and *APOE* ε4 status.

Results: Across groups, there were significant sex × HpVR interactions for immediate and delayed

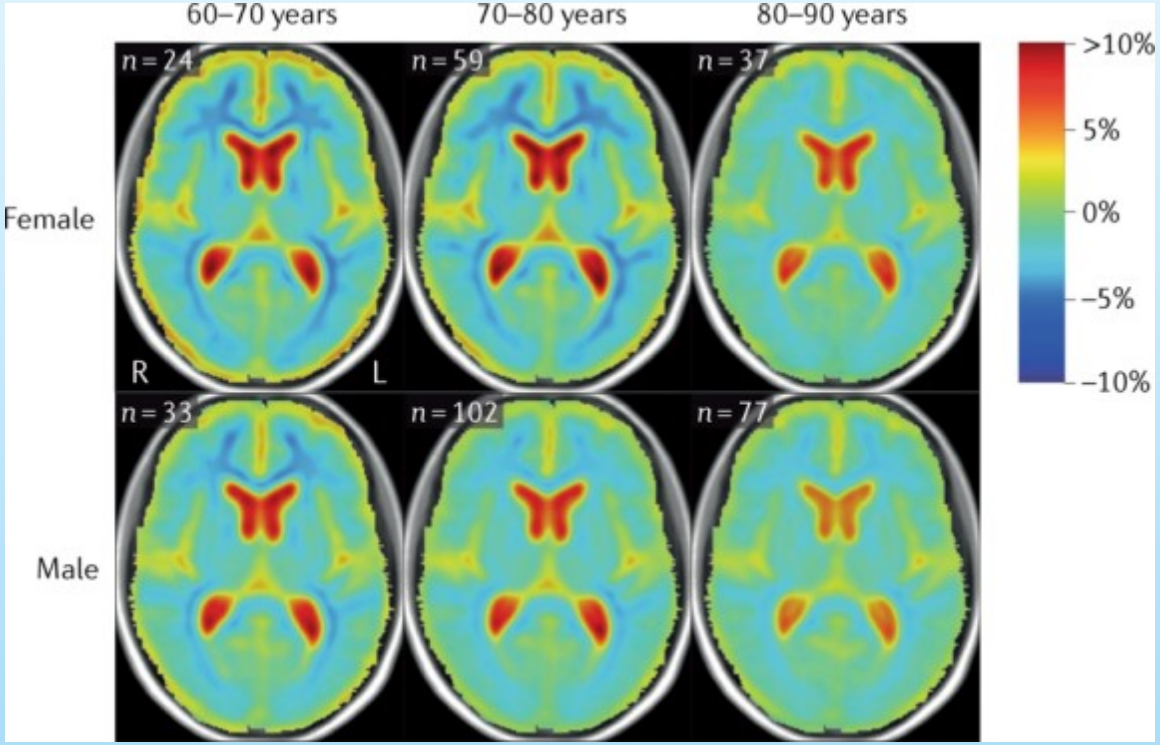
Sundermann et al., Neurology 2016

2. Interpersonal variability – Faster disease progression in women

2x faster cognitive decline

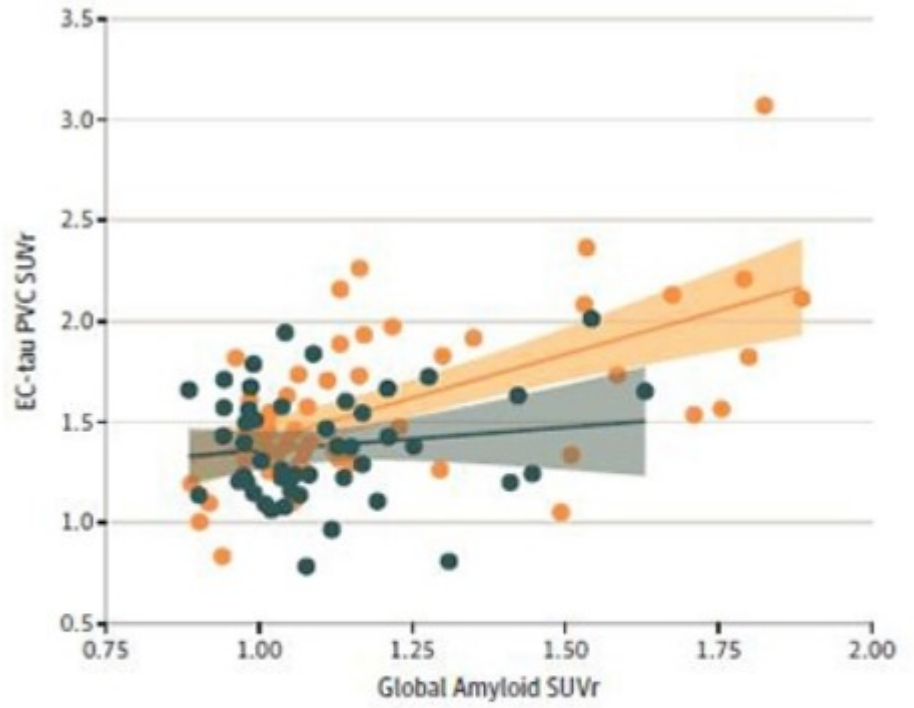


Faster brain shrinkage (darker blue)



Lin et al., 2015, A&D Hua et al, Neurobiol of aging 2010

Interpersonal variability – sex differences in biomarkers



Faster Tau Accumulation? *The more amyloid in the brain, the more tau tangles in entorhinal cortices of cognitively normal women (orange) compared to men (gray). [Courtesy of © 2019 American Medical Association. All rights reserved.]*

JAMA Network

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Amyloid and Regional Tau Deposition Measured By Positron Emission Tomography in Clinically Normal Older Adults

Rachel F. Buckley, PhD[1,2,3,4]; Elizabeth C. Mormino, PhD[5]; Jennifer S. Rabin, PhD[6]; et al

» Author Affiliations | Article Information

JAMA Neurol. Published online February 4, 2019. doi:10.1001/jamaneurol.2018.4693

Key Points

Questions Do sex differences exist in regional tauopathy, as measured with positron emission tomography, and is this largely driven by higher global amyloid burden?

Findings In this study of 2 cross-sectional cohorts of 296 clinically normal adults, women with higher amyloid burden showed greater entorhinal cortical tau signal compared with men with higher amyloid burden. Sex differences did not exist in amyloid load or apolipoprotein E ε4 frequency.

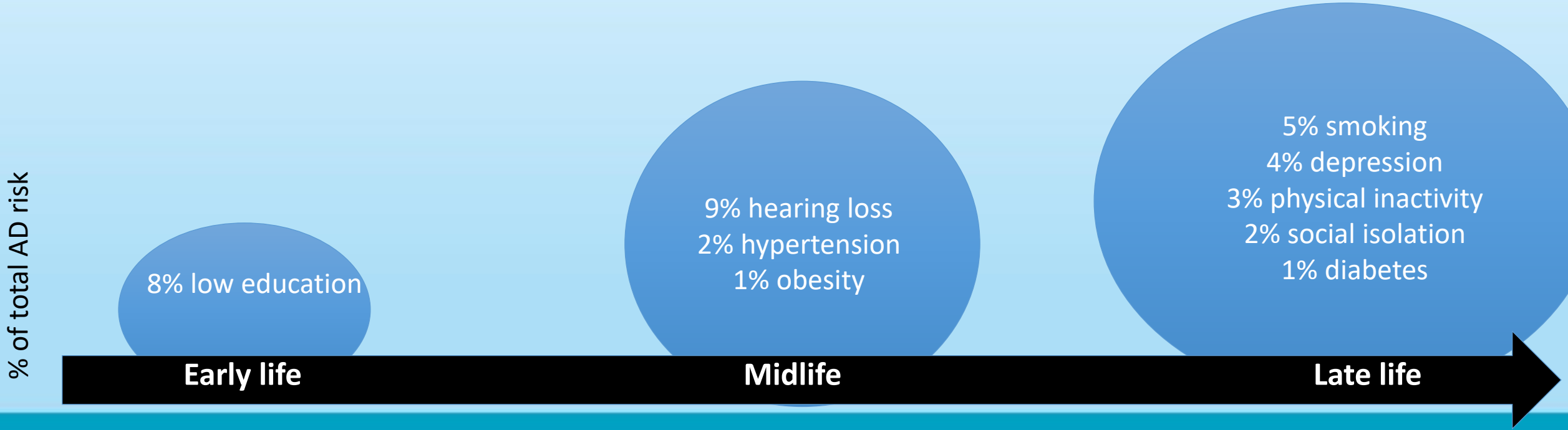
Meaning In conjunction with this finding, mounting evidence supports the notion that sex differences in the Alzheimer disease pathologic trajectory may well appear downstream of abnormal amyloid burden in the acceleration of tau deposition and brain atrophy.

3. Prevention of AD – the role of sex and gender

- ApoE, apolipoprotein E; DMT, disease-modifying therapy
- Livingston G, et al. Lancet 2017;390:2673–734.

35% of Alzheimer risk is **modifiable**

Sex and gender affect modifiable risk factors



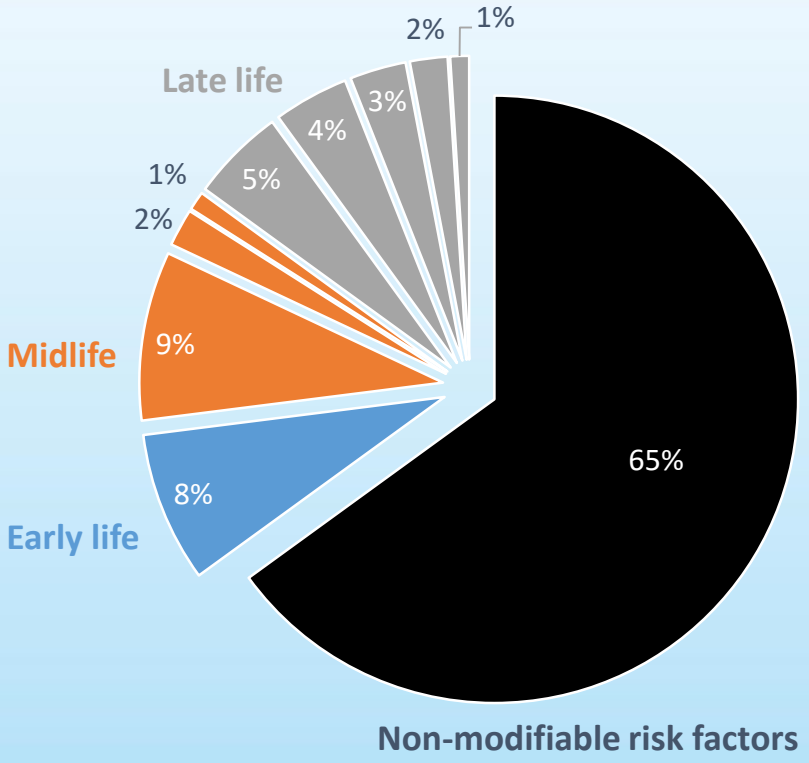
Female-specific risk-factors

Potential female-specific risk factors:

- Early menopause
- Hypertensive complications during pregnancy
- Pregnancies

Effective prevention of AD

- Delaying AD onset would benefit patients, despite the lack of curative treatments
- While some risk factors for AD are non-modifiable (e.g. age), there is growing interest in those that are modifiable:
  - Management of risk factors including low education, hypertension, obesity, poor social engagement, physical inactivity, smoking and diabetes may prove crucial, even if DMTs become available
- A decline in prevalence of age-specific dementia has been noted in some countries, despite an overall increase in the number of people with dementia
  - This may be attributed to increased education of these populations

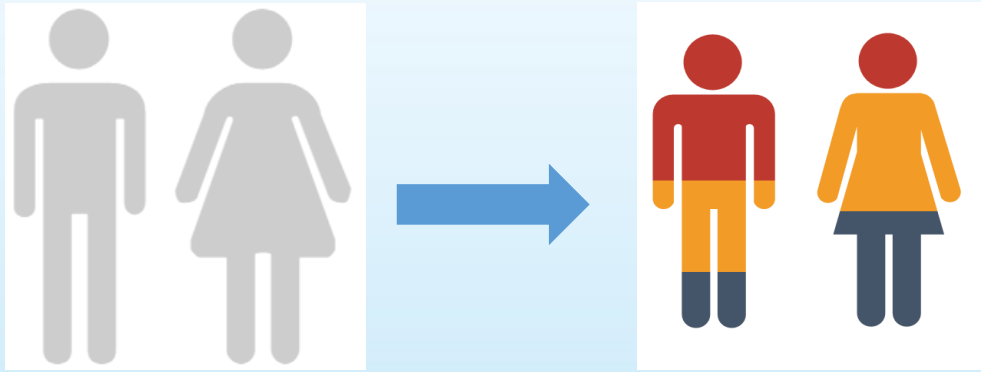


- **Early life:** low education (8%)
- **Midlife:** hearing loss (9%); hypertension (2%); obesity (1%)
- **Late life:** smoking (5%); depression (4%); physical inactivity (3%); social isolation (2%); diabetes (1%)

- ApoE, apolipoprotein E; DMT, disease-modifying therapy
- Livingston G, et al. Lancet 2017;390:2673–734. Figure adapted from Livingston G, et al. 2017

Call to action

Moving from 'one size fits all' medicine....



...to Precision Medicine

Consider sex and gender in:

- all mental health **awareness** campaigns
- **Policies** for mental health, to properly address the specificities of women and men
- **Early diagnosis** and **treatment** of mental diseases
- **Clinical trial design**
- **Brain research,** disaggregate data by sex to ensure precision medicine application for both women and men

Meet the WBP Team!