WOMEN'S BRAIN PROJECT®

"SEX, GENDER AND THE BRAIN: TOWARDS AN INCLUSIVE RESEARCH AGENDA"

Overview of the WBP-Commissioned Economist Impact White Paper and Call to Action Prepared by the Women's Brain Project, March 2023

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INTRODUCTION

Health begins with human beings: individuals. Men and women are different when it comes to brain and mental disease risk factors, frequency, severity, symptoms, progression, treatment response and adherence. Women bear the greatest burden as both patients and caregivers.

At present, we still lack precision medicine that properly account for sex and gender differences. The current 'one-size fits all' approach neglects differences in patients' specific needs and clinical outcomes among specific groups of men and women resulting in shallow outcomes.

The Women's Brain Project (WBP), as the world experts in the field of sex (biological) and gender (societal) determinants of brain and mental health to achieve precision medicine and care, commissioned Economist Impact to examine the economic rationale for investing in sex-and-gender specific brain research.

IN A SNAPSHOT

At some point in their lives, one in three people will develop some type of neurological disorder— the leading cause of disability and the second leading cause of death (after heart disease)[1]. The cost of brain disorders is estimated to equal 10% of the world's gross domestic product (GDP)[2]. It is not widely known that neurological disorders affect men and women differently, with women overwhelmingly affected by the most prevalent disorders including dementia and migraine. Until today, the impact of sex and gender on the economic costs of neurological disorders has not been properly studied as most research is carried out on the basis of a one-size fits all approach.

Tackling brain diseases is not just a health problem, but also an economic one— including direct and indirect costs, loss of productivity and quality of life. In this context, sex-and-gender-specific outcomes from biomedical research may influence productivity, as well as national economic outcomes, both directly and indirectly. However, until now the impact of sex/gender in research and the economy has been neglected. It is therefore crucial to examine the economic impact of investing in sex and gender-differentiated brain research.

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will develop some sort of neurological disorder.

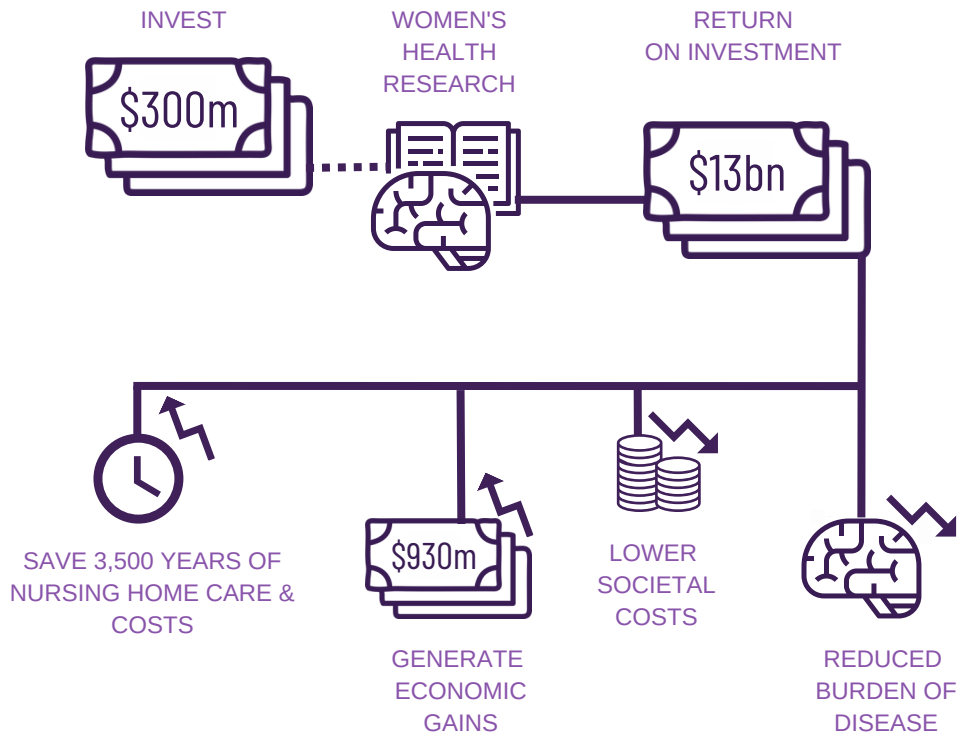
The cost of brain disorders is estimated to equal

of the world's GDP.

Neurological disorders are the leading cause of disability.

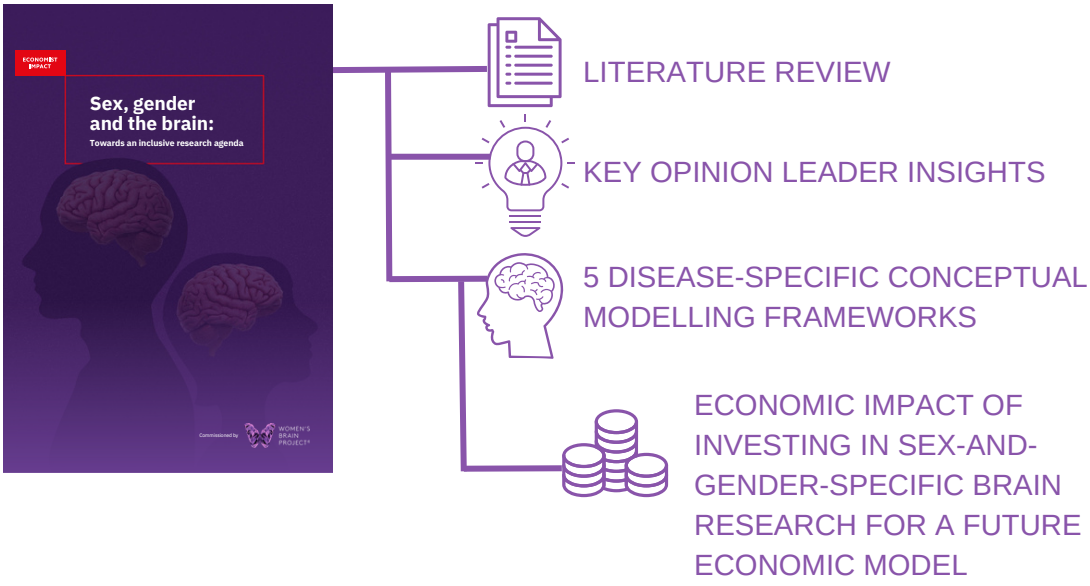
Neurological disorders are the second leading cause of death after heart disease.

Investing $300m in women's health research for Alzheimer's disease and other noncommunicable diseases could generate a return on investment (ROI) of $13bn through the reduced burden of disease and lower societal costs and can generate $930m in economic gains, as well as save 3,500 years of nursing home care and costs.[3]



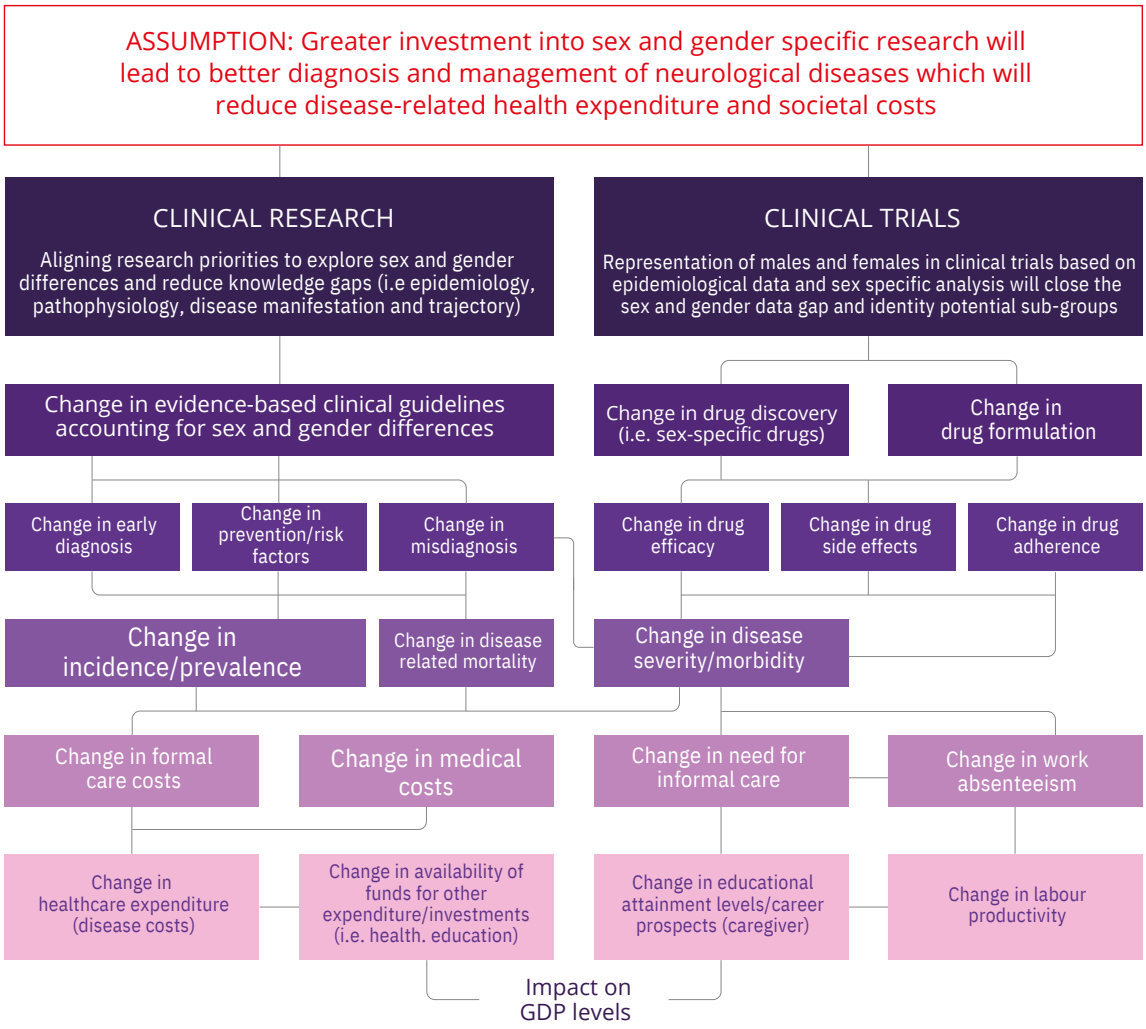
The White Paper provides a thematic review of identified sex and gender-based differences across five select brain diseases: Alzheimer's disease, Migraine, Multiple Sclerosis, Parkinson's disease and Stroke. The paper argues the need for greater efforts on sex-and-gender-specific brain research based on the beneficial economic consequences of early and more reliable diagnosis, prevention, more effective treatments and disease management; all of which could mitigate the impact of these conditions on individuals, families and society at large.

The White Paper was launched on the occasion of International Women's Day on 8 March 2023. It consists of a literature review, key opinion leader insights and the development of 5 disease-specific conceptual modelling frameworks demonstrating the economic impact of investing in sex-and-gender-specific brain research, providing the basis for a future economic model.



To make an economic case for greater investment in sex-and-gender-inclusive brain research, Economist Impact developed five novel conceptual frameworks, which convey how sex-and-gender-specific research can impact a country's overall GDP, for each of the brain diseases.

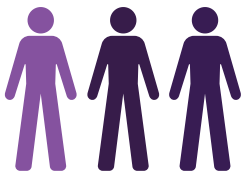
In the following figure is **a conceptual framework for investing in sex- and gender-specific research in the area of brain disorders** from the WBP-commissioned White Paper.



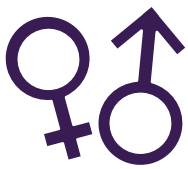
As a follow-up to the White Paper, there are plans to develop a robust economic model with inputs and assumptions derived from the conceptual framework. This will quantify the economic implications of sex-and-gender differences in brain diseases and build an evidence-based case for investment. The initial pilot will focus on one geography for one disease area.

KEY FINDINGS

Disease burden



1 in 3 people worldwide lives with a brain disease.



Sex and gender influence the **prevalence, onset and progression** of brain diseases.

The most prevalent brain diseases have a **higher prevalence** among females.

It's not only about incidence: there are also differences in terms of risk factors, biomarkers, symptoms, progression, treatment response and adherence.

Life Expectancy & Quality of Life

In general, **women live longer** than men do, but **women also live more years with disability than men do.**

Clinical research and practice

Biases in clinical practice lead to **delayed and misdiagnosis, undertreatment and poor prevention** primarily in women.

Females are "missing" from the science, and poor enrolment in clinical trials and lack of disaggregated research results in **gaps in the global understanding of the influence of sex and gender** on health outcomes.

Impact on life and the economy

Women are more likely to provide **unpaid caregiving** to family members. Both disability and caregiving responsibilities can limit full **participation in the workforce.**

Symptoms can make maintaining a job difficult for **patients and caregivers who are predominantly women.**

The economic burden of brain diseases has a significant impact on global markets, **influencing workforce productivity and health expenditure.**

CALL TO ACTION

WBP's commitment to precision medicine and care for all

The overarching goal of WBP is to transform the state of medical treatments and drug development through sex and gender factors as a gateway to precision medicine and care. WBP is committed to furthering the knowledge base through its plans to establish the Research Institute for Sex and Gender Precision Medicine.

Sex and gender biases are prevalent from the very early stages of preclinical research as there are 5.5 times more animal studies using only male animals than studies that include female animals.[4] Brain disease research has historically consistently favoured the use of males over females.[5]

To optimise care for patients with brain diseases, it is important to increase the enrolment of both sexes into clinical research and drug trials that are reflective of the sex distribution of the epidemiological burden. Better efficacy and safety of drugs, as well as fewer side effects – which would all result from more equitable clinical trial research – would improve adherence to treatment protocols for both males and females.

WBP cannot do this alone; collaborative efforts are needed.

Only by working together in a multistakeholder approach can we transform the clinical trial landscape and offer the right treatment to the right patient at the right time for all brain conditions. That is why WBP is committed to working with all relevant stakeholders to co-create on finding solutions (scientists, healthcare professionals, governments and policymakers, payers, regulators, pharmaceutical industry and, most importantly patients and caregivers) to ultimately drive policy change. WBP will advance discussions through various WBP events, as well as through scientific and policy papers to improve brain health for all worldwide.

Our recommendations to stakeholders to reach a **more inclusive research agenda in brain health** are gathered around **four main themes**:

1. Brain and mental health, through a sex and gender lens, must be made a priority, through both policymaking and economic prioritisation

2. Robust data and research for informed decision-making

3. Further knowledge and understanding of healthcare professionals to ensure better diagnosis, access to treatment and management for all patients

4. Meaningful involvement of patients and caregivers in decision-making

1. Brain and mental health, through a sex and gender lens, must be made a priority, through both policymaking and economic prioritisation

Despite progress at global, EU and national levels, we need to further the momentum to reach a more inclusive research agenda.

Action at global, EU and national levels

- National governments, the EU and WHO need to establish and implement brain health strategies and policies, taking into account sex-and-gender-differences.
- Policymakers at global, EU and national levels must understand the necessity for sex-and-gender-specific precision medicine in brain and mental health.
- National governments should roll out public information campaigns to raise awareness of the risk factors of neurological conditions and to promote brain health across the life course, highlighting sex-and-gender-differences, as appropriate.
- National governments and the EU should increase brain research funding to better understand the brain and brain diseases.

Research funding

- More funding to drive momentum towards exploring more sex-and-gender-based differences in brain disease research is necessary. Tying funding to sex-and-gender-informed research design and participation will be important.
- We then need to share best practices in clinical research funding. Protocols governing access to clinical research funding are an important policy lever for change. For instance, US federal law dictates that applications for NIH studies that involve human subjects must address the inclusion of women, underrepresented racial and ethnic groups, and children in the proposed research.[6] As a result of this policy there is increased awareness of the importance of sex as a variable in many disciplines, including brain research. The Canadian Institutes of Health Research (CIHR) also expects research applicants to integrate sex and gender into research design and practices when appropriate.[7]
- Further to the European Commission's current requirement for all higher education and research organisations to have a Gender Equality Plan in place before they can receive research funding, improved informational strategies could also provide gender-sensitive health indicators that identify key differences between women and men in relation to health and social determinants of health to support policy changes.

Caregiving

- There are huge gender equality issues in terms of caregiving. We need to reduce the burden. In Europe, as a result of unpaid care responsibilities, a staggering 7.7 million women are not able to work.[8] The majority of caregivers are women. Caregivers need to be recognised and supported, including via access to training, financial support, pension and health prevention. Policy interventions aiming to reduce the burden borne by caregivers and help people with neurological disorders continue to live full, active lives will limit the economic and social costs felt by society. This will yield the greatest benefits for both those directly affected and the wider society.

2. Robust data and research for informed decision-making

There has been some progress towards gender equity in clinical trials. To ensure a more inclusive research agenda, further action is still required in several key areas.

Gender balance among researchers

- Further equity in the number of female scientists leading brain research is still required.

Basic Science

- More equitable preclinical and clinical research that addresses the biases that emerge from narrow trial populations would provide data to improve treatment protocols, adherence to drug regimens and overall disease outcomes.

Regulatory frameworks

- Regulators across the world must ensure we have regulatory frameworks that support precision medicine, based on sound science and data.
- Regulators need to design clinical trials and recruitment methodologies in ways that encourage broader participation.
- Market authorisation should require that pharmaceutical companies should establish added therapeutic value.

Data gathering

- WHO can promote and support national capacity for high-quality data gathering, research and development for the prevention and control of brain diseases.
- Research institutions, governments and global health actors can gather statistics on patient numbers, stratified by sex, to ensure that decision-makers are aware of the impact and urgency of these conditions.

- Multisectoral partnerships can play a key role in gathering data (in particular, patient insight data, real-world evidence and patient-reported outcome data) on brain diseases to increase awareness among decision-makers and the public, as exemplified through the Sex and Gender Patient Journey series that WBP has initiated.
- We need to further understand long COVID through the gathering and assessment of data. Long COVID appears to be more common in females compared to males. Studies have shown that females experience more prolonged neurological, neuropsychiatric, cognitive, and physical symptoms following COVID-19 infection.[9]

Clinical trials[9]

- More inclusive clinical trial design, as well as the inclusion of sex and gender sensitivity as a requirement for research funding, are examples of tools that can be used to enable a more inclusive brain research and policy agenda.
- More representative clinical study populations would produce more rigorous research and better outcomes, such as treatments that work effectively with minimal side effects. Clinical trial design can also be improved at every step, from diagnostic criteria to communications that ensure better cohort selection, to data analysis disaggregated by sex.
- More women need to be enrolled in clinical trials and there needs to be increased reporting of women's health variables (such as contraception, parity, use of hormonal replacement therapy) as well as sex and gender differences in observational data.
- National clinical practice guidelines for brain diseases must be kept up-to-date with the most recent best clinical evidence and therapeutic strategies to ensure their optimal use to improve health outcomes.
- There has been an urgent need for the development of disease-modifying therapies for major neurodegenerative disorders such as Alzheimer's and Parkinson's. We can bring these new therapies to the proper patient population through a precision-based research approach, taking into account sex differences in terms of adherence and side effects.

Pharmaceutical industry

- Pharmaceutical companies need to invest as much as possible in Research & Development, including both preclinical and clinical research, ensuring a focus on medically-valuable innovation and precision medicine.

Biomarkers

- Biomarkers play a vital role in detection and early diagnosis and can revolutionise the study of brain disorders with recent technological advances allowing measurements of neurological damage. Sex-specific differences in diagnostic accuracy have been suggested but need to be further explored, paving the way for more equitable diagnosis and management.

- Developing objective digital biomarkers that can pick up subtle biological and social distinctions will help ensure individuals are diagnosed earlier and receive optimal treatment. For example, a recent study by WBP and Altoida showed that Artificial Intelligence (AI) and augmented reality can depict sex-based differences in cognitive, functional, and motoric performance using digital biomarker data collected from a cognitive assessment test.

Health Economics and Outcomes Research

- Payers need to further understand the unmet needs and value in brain health. Value encompasses clinical outcomes, quality of life, and societal benefits. This will improve access to diagnosis, care and treatment and ensure access to innovative treatments.
- Health Economists should gather data on healthcare resource utilisation in brain diseases including direct healthcare and non-medical costs, and indirect costs. More in-depth cost-effectiveness and budget impact models should be developed that can solidify sex and gender unbalances in healthcare expenditures. These should highlight and report which are the critical trade-offs in investments between the achieved benefits and its costs.
- Pricing and reimbursement systems should be reformed to reward pharmaceutical companies developing medicines that provide added clinical benefit.

3. Further knowledge and understanding of healthcare professionals to ensure better diagnosis, access to treatment and management for all patients

Education of healthcare professionals, including primary care physicians, specialists and nurses, on sex and gender differences in brain research is of great importance. We need to involve the right people, with the right skills, at the right time to respond to patient needs. Further action is needed to educate healthcare professionals.

- Healthcare professionals need to be educated on the inextricable link between sex/gender and disease prevention, diagnosis, and management. Through medical curriculum and continuing medical education, we must ensure greater awareness amongst clinicians and healthcare workers on sex and gender differences in the symptoms manifested by brain diseases, their progression and their impact.
- Develop and support care pathways that fully address patients' needs, including the patient voices in the decision-making process and making sure the needs of both men and women are listened to.
- Primary care can help promote awareness, prevention, improve early case detection, provide integrated care, and ensure effective referral systems.

- A multidisciplinary team (MDT) approach has been shown to improve the quality of life for many patients and caregivers. This creates an enabling environment and supportive community targeted to individual needs ensuring optimal care and treatment.
- Last but not least, we must not forget the brain health and mental health of healthcare professionals themselves. Nurses and Doctors are at high risk of burnout. We need to retain the best healthcare professionals for the best possible outcomes.

4. Meaningful involvement of patients and caregivers in decision-making

Patients and caregivers need to be put at the centre of healthcare to ensure that we leave no one behind, which is the central, transformative promise of the 2030 Agenda for Sustainable Development and its Sustainable Development Goals (SDGs). Change must be informed by people living with neurological conditions as well as their caregivers.

- Ensure that patients are empowered to amplify their voices to the world. Patients can best ensure that their specific needs are addressed by telling their unique stories; the voices of both men and women with diseases need to be heard. National governments should involve patients in brain health-related public information campaigns.
- National governments should seek the expertise of people living with brain conditions, and their caregivers to provide insights and knowledge of the lived experience. Patient journeys need to be followed from the onset of symptoms, encompassing referral to a specialist, diagnosis, disease management and treatment, and lived experiences with the conditions.
- Involve patients as experts in research design and participants in research projects (patient research registries); ensure brain research addresses both sex and gender factors and supports precision medicine; share best practices and develop brain health policies.
- Most caregivers and people in need of long-term care are women. Women, on average, have lower incomes, including pensions, and are potentially less able to afford care, while at the same time living longer than men and thus more in need of care. We need to ensure they have adequate support. This will lead to better outcomes, ultimately reducing the health and economic burden.
- Maximise digital potential — develop telemedicine based on the needs of patients and caregivers.

WOMEN'S BRAIN PROJECT®

About the Women's Brain Project:

WBP is an international organisation studying sex and gender determinants of brain and mental health to achieve precision medicine and care. WBP is a global leading player in the field of brain research, supporting innovative science, precision medicine and care, unbiased AI and promoting gender health equity to make healthcare systems more sustainable. WBP is in the process of establishing the Research Institute for Sex and Gender Precision Medicine. WBP commissioned Economist Impact to examine the economic rationale for investing in sex-and-gender-specific brain research, resulting in the White Paper.

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Sponsored by Roche

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EXPERTS:

The list below (in alphabetical order) includes the experts involved in this research:

• Dr. Cheryl Carcel, Neurologist and early career researcher leading the sex differences in stroke group at the George Institute for Global Health, University of New South Wales, Australia

• Dr. Janine Clayton, Director, National Institutes of Health (NIH) Office of Research on Women's Health; Associate Director for Research on Women's Health, NIH, United States

• Anna Dé, Policy Advisor, Women's Brain Project, Switzerland

• Dr. Tarun Dua, Head of the Brain Health Unit in the Department of Mental Health and Substance Use, World Health Organization, Switzerland

• Dr. Maria Teresa Ferretti, Co-founder and Chief Scientific Officer, Women's Brain Project, Switzerland

• Professor Martin Knapp, Professor of Health and Social Care Policy, London School of Economics and Political Science, United Kingdom

• Dr. Antonella Santuccione Chadha, Co-founder and CEO of the Women's Brain Project and Chief Medical Officer, Altoida, Switzerland

• Professor Wiesje Van der Flier, Scientific Director, Alzheimer Center Amsterdam, Netherlands

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