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Integrating Gender in Health Research

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2023

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INTEGRATING GENDER IN HEALTH RESEARCH

Horizon Europe, the European Union's funding program for research and innovation spanning the years 2021 to 2027, has committed to address global challenges and enhancing European industrial competitiveness. The program is organized into distinct clusters, each designed to lead major research and innovation domains, aiming to advance knowledge and tackle the multifaceted issues of our time. Among these clusters, the Health Cluster of Horizon Europe is of importance, with high significance against the backdrop of our ever-evolving global landscape. This expansive domain of health research encompasses a wide spectrum of challenges and objectives, all with a central focus on the well-being and health of European citizens in a dynamic and evolving world. Its themes span critical areas, from navigating the maintenance of health within rapidly changing societies to ensuring sustainable, high-quality healthcare delivery. This strategic cluster opt to address the challenges of the 21st century with a comprehensive approach. In recognition of the pivotal role that gender, and sex inclusivity play in shaping effective, robust, and inclusive research, GENDER-IN, a collaborative initiative fostering bilateral connections between researchers in Greece and Norway, has undertaken a mission to incorporate gender and sex perspectives thoroughly into research content. This mission aligns perfectly with Horizon Europe's vision, acknowledging the essential value of gender and sex inclusivity. To this end, GENDER-IN carried out a series of workshops, each tailored to the main topics under the six clusters of Horizon Europe. Therefore, the aim of this report is to summarize the insights, discussions, and recommendations from the GENDER-IN workshop, with a dedicated focus on the Health Cluster. As health research continues to evolve, the importance of understanding gender and sex dimensions becomes increasingly clear.

Beyond the overarching themes of the Health Cluster, this report delves into several critical aspects that warrant in-depth consideration within the gender/sex-inclusive health research dimension. Furthermore, this report aims to describe what has happened so far by public programs, organizations, and individual researches in the effort to incorporate gender and sex in the research of medical conditions. Accordingly examples are included where research has failed to address this matter. Of note, we also discuss about the work of many researches that have incorporated gender or sex into the experimental questions and designs, and ultimately underlying that sex and gender inclusivity highly increases the chances of developing successful and with adequate efficacy treatment of numerous diseases and disorders. Through the exploration of these multifaceted facets, this report aspires to provide a comprehensive understanding of the significance of gender and sex inclusivity within the framework of Horizon Europe's Health Cluster. In doing so, our goal is to shed light on the broader impact of integrating gender in health research, ultimately working toward more equitable, inclusive, and effective healthcare solutions for everyone.

Main Topics Addressed by Cluster Health in Horizon Europe

The Health Cluster in Horizon Europe addresses a wide range of challenges and objectives, aiming to secure high standard well-being and health conditions for all European citizens.

Staying Healthy in a Rapidly Changing Society: In an era marked by swift societal shifts, this theme underlines the importance of understanding and tackling non-communicable diseases. Moreover, it emphasizes the need for health promotion and preventive measures maintaining the well-being of citizens in changing socio-environmental conditions. It is well established that the risk of numerous non-communicable diseases can vary significantly between sexes or genders. For instance, men and women have different susceptibilities to conditions like heart disease, diabetes, or certain cancers. Understanding these sex-based differences is crucial for tailoring preventive strategies effectively (Mauvais-Jarvis et al., 2020). Moreover, different gender roles and occupations may result in varying levels of exposure to environmental hazards. Understanding how these exposures differ by sex or gender and how they contribute to non-communicable diseases is of importance to develop targeted preventive measures.

Living and Working in a Health-Promoting Environment: This theme recognizes that our immediate environment plays a pivotal role in determining our health outcomes. By detecting the interrelation between pollution, sustainable food systems, and health, it supports research focused on creating environments that enhance overall well-being. Additionally, it highlights the importance of cultivating workplaces that support employee well-being for a productive workforce. A major point here is how health impacts work-life balance. Balancing work and family responsibilities can be different for men and women due to societal expectations. This can affect stress levels and overall well-being (Ip, Lindfelt, Tran, Do, & Barnett, 2020). Understanding how work-life balance relates to health and how it varies by gender is vital for creating supportive workplace environments. Overall, despite great efforts to promote gender balance across different professions and to ensure fair hiring practices, an ongoing gender gap remains, especially in top leadership positions. This imbalance is often linked to societal expectations that tend to prioritize women's roles within the family. These societal norms can sometimes act as obstacles to women's career advancement and their ability to take on leadership roles. It underscores the importance of ongoing initiatives to challenge and transform these traditional gender stereotypes, both professionally and personally.

Tackling Diseases and Reducing Disease Burden: One of the key goals of health-focused initiatives is to fight diseases and lessen their impact on society. This involves research on infectious diseases, as well as a deeper understanding of non-communicable diseases. Additionally, it supports the advancement of innovative tools, technologies, and digital solutions. A noteworthy aspect of this theme is its focus on personalized medicine, paving the way for healthcare solutions that cater to individual needs. Here, incorporating sex and gender analysis, in both empirical and theoretical data, is of paramount importance. It enables recognizing that diseases can affect individuals differently based on their biological sex and gender roles. For instance, certain infectious diseases may manifest differently in men and women due to hormonal differences or social behaviours. By including sex and gender analysis, tailored healthcare interventions can be proven more effective, ensuring that they

address the specific needs and vulnerabilities of all individuals. Additionally, personalized medicine, a central focus of this theme, can benefit immensely from considering sex and gender factors in treatment plans, leading to more precise and effective healthcare solutions.

Ensuring Access to Sustainable and High-Quality Healthcare: Central of any strong health system is the commitment to provide accessible and high-quality care. This theme explores the complexities of healthcare systems, policies, and research related to health services. By advocating for resilience, accessibility, and effectiveness, our goal is to ensure that all European citizens have access to sustainable and excellent healthcare services, irrespective of their socio-economic standing. For instance, certain nations have successfully integrated sex and gender aspects into their healthcare systems, utilizing advanced notification systems to inform individuals about regular health check-ups or tests that align with their specific needs. This established approach not only promotes preventive care but also provides a model for countries to consider following. Extending this practice to include a wider range of health services and encouraging more countries to embrace similar strategies can contribute to a future where personalized, gender-sensitive healthcare becomes a standard practice.

Unlocking the Full Potential of New Tools, Technologies, and Digital Solutions for a Healthy Society: The modern age is defined by remarkable technological advancements, and this theme aims to utilize that potential to improve healthcare. So far, many applications such as wearable devices have been utilised to monitor the progression and alleviate some of the symptomatology of certain disorders. A great example has been seen in Parkinson's disease (REF). Similarly to the previous topic, in the context of telemedicine, many health apps offer the ability to schedule follow-up appointments, updating medical history by registering new symptoms live, and overall having a more direct communication with practitioners and doctors (Haleem, Javaid, Singh, & Suman, 2021). During the development of such healthcare tools, sex and gender specific factors must be considered, aiming to enhance their accessibility, usability, and accuracy for diverse populations.

Maintaining an Active and Healthy Aging Population: Aging is an inevitable aspect of the human life, but how we age can be influenced by research and innovation. This theme explores the factors influencing the course of aging, with a focus on finding solutions that help older adults to have active, independent and healthy lives. In a continent where the aging population is a significant demographic, this theme is both timely and crucial. As people age, gender-sensitive healthcare services become increasingly important. It is understandable that people based on their sex and gender have different healthcare needs and preferences, a notion that can influence the quality of care provided when older. Moreover, it is crucial to note that prevalence of diseases or disorders change throughout the course of individual's life. For instance, earlier in life and mid-life ages, men are more prone to suffer from heart disease than women. However, later in life, older post-menopausal women are similarly susceptible to heart diseases as men, due to lack of oestrogen protection.

Integrating sex and gender in medical and biological research: challenges, and opportunities

Incorporating both sexes and different identity types and simultaneously examining sex or gender differences is essential in medical and biological research. It offers valuable insights into the causes, development, and management of various diseases and conditions. For instance, it is known that conditions such as autism spectrum disorders and Parkinson's disease are more prevalent in males, while major depressive disorder, anxiety disorders, autoimmune diseases, and multiple sclerosis are more commonly diagnosed in females. Additionally, sex differences regarding disease onset are also common, affecting the course of symptoms manifestation. These distinctions in disease patterns provide important insights into the underlying mechanisms and potential treatments. It's crucial to ensure that research studies are adequately powered to detect interaction effects between sex or gender and treatment. By assuming that the same sample size can be used for both sexes may limit our understanding of disease processes and treatment efficacy. Failing to consider sex differences may result in missed opportunities to tailor treatments for specific subpopulations effectively.

In 2016, the National Institutes of Health (NIH) in the United States issued a requirement stating that all preclinical research must incorporate sex as a biological variable (SABV), unless there is a compelling justification. Despite this mandate, the integration of sex and gender dimensions in current studies still remains a significant challenge. Unfortunately, many studies funded by the NIH and other institutions still fail to adequately analyse and report outcomes by sex. A recent analysis revealed that only a minority of NIH-sponsored studies in 2015 included sex as a variable in their statistical analysis, and even among those that did, many used sex as a covariate, a statistical method that significantly lessen its influence. This failure to comply with the NIH mandate significantly obstructs the progress in understanding how diseases and treatments differ between sexes and genders. Until these practices become standard, the research community will continue to encounter difficulties in using the potential of considering sex and gender to advance medical and biological knowledge effectively (Galea, Choleris, Albert, McCarthy, & Sohrabji, 2020). Other meta-analysis and reports on the matter, further underline the notion that the omission of sex and gender considerations in research have several detrimental consequences. Such omissions, can lead to the abandonment of promising treatment options for one sex or the other, as illustrated by the case of progesterone as a treatment for traumatic brain injury, where the phase 3 clinical trial failed potentially due to the inclusion of both sexes. Additionally, a lack of statistical power to detect sex differences may result in incomplete or inconclusive findings. In summary, overlooking the integration of sex and gender dimensions in research can hinder scientific progress, limit the effectiveness of treatments, and perpetuate health disparities. Hence, researchers should adopt an approach that considers diverse types of sex or gender differences, and eventually ensures that research outcomes are reported and analysed with sex as a critical variable, aiming to overcome these challenges effectively (Wright et al., 2014).

An example of ineffective intervention is the approval of numerous drugs for Clinical trials I and II only to fail in Clinical trials III, due to the lack of sex or gender inclusion in preclinical and clinical previous studies. This highlights the critical consequences of neglecting sex and gender dimensions in research, and simultaneously emphasizing the importance of integrating sex and gender considerations at all stages of research to avoid such setbacks.

Such failures not only result in wasted resources but also delay the development of treatments. Gender bias in pharmaceutical research and clinical trials, where many approved treatments are primarily tested on male subjects, raises significant concerns regarding potential adverse effects in women. This bias has led to a limited understanding of how treatments may affect women differently from men, potentially resulting in a higher incidence of adverse effects, reduced treatment efficacy, or suboptimal dosing. A commentary by Carey and colleagues, sheds light on drugs and devices intended for women that have caused significant morbidity and mortality, underscoring the ongoing challenges in research policy and drug/device approval processes. Historically, women have been underrepresented in clinical trials, a situation that can be traced back to policies initially designed to protect them during pregnancy. Notable examples like thalidomide and diethylstilbestrol (DES) prompted legislative changes, ultimately empowering the FDA to demand safety and efficacy data before drug approval. Efforts by women's health advocates led to policy changes and the establishment of entities such as the NIH Office of Research on Women's Health and the Women's Health Initiative. Despite these advancements, gender disparities persisted, with insufficient representation and analysis of sex and gender differences in drug trials. In 1993, the FDA lifted restrictions on the inclusion of women of childbearing potential in early clinical trials and reinforced expectations for sex and gender analysis. Recent legislation, including the [Research for All Act of 2015](#), continues to promote gender equality in research. Nevertheless, women still face elevated risks from unsafe medications and devices designed for their use (Carey et al., 2017). This issue underscores the critical importance of incorporating sex and gender dimensions in research projects. By including both sexes and considering potential sex-based differences in drug responses, researchers can uncover valuable insights that not only enhance treatment effectiveness but also minimize the risk of adverse effects in specific subpopulations. Addressing this gender bias is not only a matter of scientific rigor but also an ethical imperative to ensure that medical treatments are safe and effective for everyone.

Finally, a concerning issue within healthcare is the gender bias exhibited by clinicians when examining patients. In many cases, clinicians may attribute the expressed distress or pain observed in women to their sex or gender, rather than basing their assessments on actual clinical insights. This bias can manifest as a stereotype, assuming that women tend to be more emotional or occasionally overreacting to symptoms (Samulowitz, Gremyr, Eriksson, & Hensing, 2018). Such assumptions can lead to delayed or inadequate medical interventions, as well as misdiagnoses, posing serious risks to patient well-being. Addressing and rectifying this gender bias in clinical practice is imperative. Healthcare professionals should strive for an unbiased and evidence-based approach to patient care, recognizing that individuals, regardless of their sex or gender, may experience pain, distress, or symptoms that warrant thorough evaluation and appropriate medical attention. By fostering a healthcare environment that values equity and inclusivity, clinicians can contribute to improved patient outcomes and a healthcare system that serves everyone equally and effectively.

EU Guidelines Relating to the Integration of the Gender or Sex Dimension in Research Projects

The EU has identified that gender and sex play significant roles in influencing research outcomes. In fields like health, ignoring these factors can lead to skewed results,

misinterpretations, or even ineffective interventions. Recognizing the potential impact on the validity and relevance of research, the EU has actively broadcasted the inclusion of a gender or sex analysis in its research framework. Therefore, the [Horizon Europe](#) framework, in the context of the [Health cluster](#), mandates the integration of the gender or sex dimension in research and innovation content when it is relevant to the topic addressed. This is not just about gender equality in research teams, but rather about ensuring that the research itself systematically considers gendered implications and outcomes in health and disease ([Work Programme 2023-2024](#)).

Specific Guidelines ([Horizon Europe Programme Guide](#)):

1. *Research Design and Methodology*: Proposals under Horizon Europe are urged to demonstrate a clear understanding of when, why, and how the gender or sex dimension is relevant in the research context. This means, from the onset, considering if there are potential differences between genders of sexes in both clinical and preclinical studies (Mason, 2020).
2. *Data Collection and Analysis*: When gathering and evaluating data, research projects are advised to disaggregate data by sex and gender, ensuring that potential differences or trends can be identified and assessed (Dalla et al., 2023).
3. *Interdisciplinary Approaches*: Given that the gender or sex dimension can intersect with other socio-economic categories (like age, ethnicity, socio-economic status), research projects are encouraged to employ interdisciplinary approaches that consider these interplays.
4. *Dissemination and Exploitation*: The results, conclusions, and any subsequent applications or innovations derived from research should consider and reflect the gendered insights. This ensures that any products, solutions, or knowledge generated are relevant and effective for all genders.
5. *Support and Resources*: Recognizing the need for expertise and guidance in this area, the EU has facilitated various resources and training materials for researchers. Notably, the [Gendered Innovations project](#), funded by the European Commission, offers tools, methods, and best practices to integrate the gender dimension into research and innovation. Briefly, the European Commission has been at the forefront of promoting the integration of the gender dimension into research and innovation policies. Despite significant efforts, there is still room for improvement, as highlighted by findings from the She Figures 2018 report. To address these challenges, the European Commission established the Gendered Innovations Expert Group, building on previous work, to strengthen the integration of sex and gender analysis into research and innovation (R & I). This integration is seen as essential for maintaining Europe's leadership in science and technology and supporting inclusive growth. It is a priority within Horizon Europe, with implications for various aspects of the R & I cycle. Integrating sex and gender analysis adds value to research, questions gender norms and stereotypes, enhances societal relevance, and contributes to the production of goods and services suited to new markets.

The [policy report](#) presents the work of the Gendered Innovations 2 Expert Group, including case studies, terms, methods, and policy recommendations. These materials address global challenges, targeted impacts, and key orientations of Horizon Europe's

clusters and mission areas. They also align with the United Nations Sustainable Development Goals. The 15 interdisciplinary case studies illustrate how sex and gender analysis can lead to new insights and innovations, often considering intersections with other social categories like ethnicity and age. The case studies cover various fields, such as health sciences, smart mobility, energy solutions, waste management, urban spaces, aquaculture, information technology, taxation, economics, and the impact of sex and gender in the COVID-19 pandemic. These studies demonstrate the broad applicability and significance of sex and gender analysis in research and innovation.

These guidelines not only improve the quality and relevance of research but also promote more inclusive and innovative solutions that cater to the entire population's needs.

Examples of sex and gender analysis in health research

Integrating the sex and gender dimension into interdisciplinary research is paramount for producing nuanced, comprehensive, and effective results. Below are selected case studies from international and national research literature that serve as exemplary models for the integration of the sex/gender dimension in interdisciplinary research relevant to the Health Cluster of Horizon Europe. These studies, conducted by esteemed researchers in their respective field, underscore the significance of studying sex differences in the most prevalent diseases and disorders, providing clear insights into how sex and gender should be integrated into research efforts.

Gender and sex dimensions have become pivotal in research on numerous diseases and disorders, with a clear understanding that they deeply influence prevalence, symptomatology, and treatment responses. For instance, in mental health disorders, major depression and anxiety disorders are often more prevalent in women, while neurodevelopmental disorders like autism and ADHD are more common in men. Acknowledging this, clinical and preclinical research has shifted towards a more integrated view of sex and gender. For instance, guidelines, policies, and equality plans now emphasize incorporating both sex and gender in research, recognizing them as distinct yet interrelated. This is vital in the development of inclusive psychopharmacological treatments where traditionally, a 'one-size-fits-all' approach was taken. Advances in neuropsychopharmacology now account for sex and gender, with preclinical studies recommended to involve both male and female cohorts. However, many clinical trials lack adequate representation, hindering their ability to detect sex and gender differences. The move towards sex and gender specificity in mental health research has led to calls for increased, targeted funding, especially from bodies like the European Commission and the National Institutes of Health. Foundations like the European Brain Foundation exemplify this shift, advocating for research that reduces the burden of brain disorders for all through inclusivity and collaboration (Christina Dalla, 2023). Such strides in interdisciplinary research are pertinent to the Health Cluster of the Horizon, showcasing a comprehensive integration of the gender dimension.

It is imperative to recognize the gender-specific nuances in cardiovascular disease (CVD), which continue to be a significant concern for women's health. Unlike men, women typically develop CVD 7 to 10 years later in life but remain vulnerable, particularly after the age of 65. Unfortunately, the risk of heart disease in women is often underestimated, perpetuating a

dangerous misconception that they are "protected" from CVD. Recent data underscores a troubling trend of increasing myocardial infarctions among midlife women while declining rates among similarly aged men. This alarming discrepancy extends to clinical practices, where women are less likely to be referred for essential testing and interventions, resulting in less aggressive treatment approaches. Understanding these gender-specific issues is pivotal in the context of our report, as we delve into the gender-specific facets of coronary heart disease (CHD) affecting women. Epidemiologically, it's crucial to consider the impact of endogenous oestrogens before menopause, which appear to delay the onset of atherosclerosis in women. However, early menopause, occurring before the age of 40, is associated with a two-year reduction in life expectancy. Smoking, a classic risk factor, exerts a more detrimental effect on young women, emphasizing the need for gender-specific intervention strategies. Additionally, postmenopausal women experience changes in body weight and fat distribution, which increase the prevalence of obesity and type 2 diabetes, contributing to elevated CHD risk. Blood pressure patterns also change, potentially linked to declining oestrogen levels during menopause. Female-specific risk factors warrant special attention. Conditions like polycystic ovary syndrome (PCOS) have been associated with an increased risk of atherosclerosis, metabolic syndrome, and type 2 diabetes in women. Furthermore, women with a history of hypertensive disorders during pregnancy face an elevated risk of developing hypertension and experiencing premature cardiovascular disease (Maas & Appelman, 2010).

Interdisciplinary research has increasingly incorporated sex and gender analysis in the context of Alzheimer's Disease (AD), recognizing its significant impact on the quality of life and economic burdens faced by many. Epidemiological studies have consistently shown disparities in AD based on sex. For instance, European data reveals a higher incidence of AD in women compared to age-matched men, especially those aged 65 and above, whereas in Brazil, women consistently face a higher annual mortality rate from AD than men, possibly because women outlive men. This trend is not only seen in human studies but also in rodent models, further underlining the importance of addressing sex differences in AD pathophysiology. It's crucial to differentiate between "sex", a biological variable, and "gender", a complex interplay of psychological, social, political, and cultural elements. Factors such as genetic predispositions, developmental changes linked to hormones, and broader societal factors all intertwine to influence AD susceptibility and vulnerability differently in males and females. The nuances between susceptibility and vulnerability have been highlighted, suggesting females might be more susceptible to AD, while males may be more vulnerable, especially in the advanced stages. This differentiation is further complicated by factors like age, which affects the timing and accuracy of AD diagnoses (Medeiros & Silva, 2019). Moreover, low education has been correlated with AD and so far is reported to have a similar harmful effect in both men and women, however, historically low education status is more common in women (Rocca, Mielke, Vemuri, & Miller, 2014). Lastly, regarding disease progression stress have been reported to exacerbate disease symptomatology (Justice, 2018), and it is known that the prevalence of stress-related disorders and anxiety disorders is higher in women than men. Overall, understanding these intricacies can guide tailored interventions and treatments, emphasizing the importance of integrating both the sex and gender dimension in research relevant to the Health Horizon Cluster.

Similarly, the gender/sex dimension has played a pivotal role, especially in understanding neuropsychiatric disorders and antidepressant responses. Women, being more frequently affected by depression and anxiety disorders than men, have shown distinct responses to antidepressants, as elucidated by both human and animal model studies. Data from EU population indicate that women have a higher neuropsychiatric disorder burden, being more susceptible to ailments like dementia, PTSD, and major depression. Historically, women's representation in clinical trials was limited until the 1990s, but post that period, there's been a concerted effort to include them. Still, results on sex differences in drug responses remain mixed. Moreover, females exhibit different stress vulnerability, coping strategies, and hormonal impacts on mood and behaviour, emphasizing the need to adjust behavioural indices in research according to gender. Additionally, biological markers, such as the serotonergic system, show pronounced sex differentiation. Interestingly, despite some inconsistencies in clinical trials, preclinical research has underscored the importance of recognizing sex differences to improve clinical research quality and develop gender-specific treatments (Kokras & Dalla, 2017). Notably, distinctions between male and female responses to medications, specifically antidepressants, have been highlighted. For instance, the pharmacokinetics and pharmacodynamics of antidepressants showcase differences in absorption, distribution, metabolism, excretion, and efficacy based on sex. Women, for example, exhibit differences in gastric acid secretion, drug bioavailability, body fat distribution of lipophilic molecules, and hormonal fluctuations impacting drug absorption during menstrual cycles. Men and women also respond differently to specific antidepressants influenced by factors such as age and hormonal status. Hormonal replacement therapy and oestrogens have shown potential to enhance antidepressant effects, particularly in menopausal women. Furthermore, preclinical studies in animals have revealed behavioural and drug response differences between male and female subjects. Recognizing the importance of these differences, prominent institutions like the NIH and the European Union commission emphasize the inclusion of both sexes in preclinical research, aiming for more accurate investigations and improved treatment outcomes. This interdisciplinary approach is not only pivotal for a comprehensive understanding of disease mechanisms but also for the development of effective treatment regimens tailored to individual needs based on sex and gender (Pavlidis, Kokras, & Dalla, 2023).

Depression, a leading cause of disability worldwide, manifests differently between genders, with women being twice as likely as men to be diagnosed. The aetiology of depression is complex, with various theories pointing to neurotransmitter system dysfunctions, stress responses, and even gut microbiota. Sex differences are particularly notable in areas like depression-related transcriptional patterns, neuroanatomy changes, and immune signatures. For instance, anatomical abnormalities in limbic regions, especially the hippocampus, often appear in people with depression. These reductions in hippocampal volume seem more pronounced in men, suggesting distinct vulnerabilities between genders. On a neurogenesis front, stress exposure, particularly chronic stress, induces varied effects in the hippocampus of male and female rats. Such differences hint at the influence of sex hormones, with androgens being vital for men and oestrogens for women. Men with conditions like hypogonadism, characterized by reduced testosterone production, exhibit a heightened association with depression. On the other hand, women face increased depression risks during times of significant ovarian hormone fluctuations, like the postpartum period. Both human and animal studies emphasize the protective role of gonadal hormones against

depression and their potential to enhance treatment efficacy. Given these complexities, future research should prioritize the differentiation of biological sex from socio-cultural gender constructs and emphasize the importance of integrating gender/sex dimensions to foster a more comprehensive understanding of depression and its treatments (Eid, Gobinath, & Galea, 2019).

Practical suggestions for inclusion of gender and sex in preclinical and clinical research

To strengthen the integration of gender in the design of research projects, one must first be clear in formulating the aims of the research. The inclusion of both sexes is not just an ethical imperative but a scientific necessity, given the inherent biological differences which can influence outcomes. For example, in the realm of genomics and neuro-omics, it's evident that both X and Y chromosomes, previously overlooked in many studies, play a pivotal role in understanding sex differences in diseases and traits. As we know, roughly 1500 genes on the X chromosome are expressed in the brain, making them prime candidates for studying neurological differences. Therefore, the aims should emphasize understanding such foundational differences and their implications in disease and health outcomes. When raising research questions, it's essential to probe deeply into areas that have either been traditionally ignored or have shown considerable potential for varied outcomes based on sex (Dalla et al., 2023). For instance, one might ask how genes on the X and Y chromosomes influence neurological differences or what role they play in specific psychiatric disorders. Given that both human and rodent studies reveal pronounced differences in gene expression patterns between sexes in response to stress, it would be pertinent to investigate how these differences culminate in varied psychiatric manifestations between males and females. The drug development process, which is already extensive and expensive, provides another avenue for inquiry. How can this process be optimized to address and incorporate sex-specific effects right from the early stages? Considering known sex differences, particularly in the metabolism of drugs and the involvement of the cytochrome P450 enzyme superfamily, how can drug efficacy and safety be ensured for both sexes? In terms of statistics, it's not just about quantity but quality. The data collected should be comprehensive, aiming to capture the nuances of sex differences. This means tracking and analysing gene expression patterns related to both X and Y chromosomes across sexes, monitoring male and female responses to stress, especially focusing on neural and hormonal changes, and documenting any sex-based discrepancies in how drugs are metabolized and eliminated from the body. Furthermore, given the paramount role of sex hormones in drug pharmacology, researchers should be vigilant in collecting statistics that allow for the delineation of dose-response relationships for both sexes, ensuring that drug dosages are effective and safe. Finally, it is important to monitor the bilateral interplay of hormonal fluctuations with antidepressants in both women and men (Dalla et al., 2023). Numerous international and national research teams have implemented essential measures to incorporate sex as a biological variable effectively. They achieve this by including both sexes in animal cohorts, utilizing sex as a statistical factor, and closely monitoring the oestrous cycle in female rodents. These data acquisition approaches enable the inclusion of hormonal fluctuations and oestrous cycle phases as variables in statistical analyses. The goal is to gain insights into how crucial hormonal differences between sexes influence the development and treatment of various diseases and disorders (Dalla et al., 2023).

Enhancing sex and gender integration in research funding institutions: key strategies

Funding institutions hold a position of significant influence when it comes to shaping the trajectory and priorities of research efforts. To effectively advance the cause of rigorous gender integration in research, these institutions must take decisive steps to ensure that gender considerations are not just a checkbox but an integral aspect of every research proposal. This begins with establishing a clear mandate that places the onus on researchers to elucidate how they intend to incorporate sex/gender dimension in their study design. In cases where gender may be deemed irrelevant on the surface, requiring a comprehensive justification serves as a safeguard against overlooking potential gender-related nuances that could impact research outcomes. This requirement encourages researchers to critically assess the relevance of gender in their work, promoting a culture of conscientiousness. Beyond the proposal stage, the composition of grant review panels plays a pivotal role in shaping research priorities. By proactively including gender specialists within these panels, funding institutions can ensure that projects with a robust and nuanced gender-centric approach receive the attention they deserve. These specialists can provide invaluable insights and guidance, helping to identify proposals that align most closely with the gender integration goals. However, elevating the quality of gender-inclusive research goes beyond selection processes; it necessitates ongoing capacity building. Regular training sessions and workshops, spanning diverse fields such as genomics and drug development, can empower researchers with the knowledge and tools needed to navigate the complexities of integrating gender effectively. Emphasizing the significance of data collection methodologies cannot be overstated, particularly in areas like clinical trials. Encouraging research methodologies that strive to equally represent both sexes ensures that research outcomes are not only representative but also robust. Furthermore, recognizing the urgent need to address gender disparities in various fields, institutions should consider designating special funding or grants explicitly dedicated to such research. These financial incentives not only attract researchers but also underscore the institutional commitment to gender-inclusive research. However, the research journey extends far beyond data collection. The dissemination of research results holds immense sway over the broader research community and the public. Institutions should actively advocate for the publication of results that not only include gender-based analyses but also emphasize their significance. This practice promotes a culture where gender is not an afterthought but a fundamental aspect of research worth highlighting. Feedback loops are vital for continuous growth and improvement. By establishing mechanisms that allow researchers to share their experiences, challenges, and insights related to gender integration in their projects, funding institutions can iteratively refine their policies and support structures. This iterative approach fosters a learning environment where best practices evolve, ultimately driving more effective gender integration in research. Transparency and stakeholder engagement serve as cornerstones for building trust in the research community. Funding decisions, particularly those concerning gender considerations, should be transparent, leaving no room for ambiguity. Engaging with a diverse array of stakeholders, ranging from gender activists to community leaders, enriches the perspectives of institutions and helps ensure alignment with the actual needs of the community being served. Incorporating gender into research is not merely about improving the quality of outcomes; it's about fostering inclusivity to ensure that research serves and genuinely reflects the diverse populations it aims to benefit.

Links:

- Research of All Act of 2015: <https://www.govinfo.gov/app/details/BILLS-114hr2101ih>
- Horizon Europe: https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe_en
- Health Cluster: https://research-and-innovation.ec.europa.eu/funding/funding-opportunities/funding-programmes-and-open-calls/horizon-europe/cluster-1-health_en
- Work Programme 2023-2024: https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/wp-call/2023-2024/wp-4-health_horizon-2023-2024_en.pdf
- Horizon Europe Programme Guide: https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/guidance/programme-guide_horizon_en.pdf
- Gendered Innovations project: https://research-and-innovation.ec.europa.eu/news/all-research-and-innovation-news/gendered-innovations-2-2020-11-24_en

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