

# Brain Health Outcomes in Sexual and Gender Minority Groups

## Results From the All of Us Research Program

Shufan Huo, MD, PhD, Cyprien A. Rivier, MD, MSc, Santiago Clocchiatti-Tuozzo, MD, MHS, Daniela Renedo, MD, N. Abimbola Sunmonu, MD, PhD, Adam de Havenon, MD, MSc, Daniel F. Sarpong, PhD, Nicole Rosendale, MD, Kevin N. Sheth, MD, and Guido J. Falcone, MD

### Correspondence

Dr. Falcone  
guido.falcone@yale.edu

*Neurology*® 2024;103:e209863. doi:10.1212/WNL.0000000000209863

## Abstract

### Background and Objectives

Sexual and gender minority (SGM) groups have been historically underrepresented in neurologic research, and their brain health disparities are unknown. We aim to evaluate whether SGM persons are at higher risk of adverse brain health outcomes compared with cisgender straight (non-SGM) individuals.

### Methods

We conducted a cross-sectional study in the All of Us Research Program, a US population-based study, including all participants with information on gender identity and sexual orientation. We used baseline questionnaires to identify sexual minority (lesbian, gay, bisexual, diverse sexual orientation; nonstraight sexual orientation) and gender minority (gender diverse and transgender; gender identity different from sex assigned at birth) participants. The primary outcome was a composite of stroke, dementia, and late-life depression, assessed using electronic health record data and self-report. Secondly, we evaluated each disease separately. Furthermore, we evaluated all subgroups of gender and sexual minorities stratified by sex assigned at birth. We used multivariable logistic regression (adjusted for age, sex assigned at birth, race/ethnicity, cardiovascular risk factors, other relevant comorbidities, and neighborhood deprivation index) to assess the relationship between SGM groups and the outcomes.

### Results

Of 413,457 US adults enrolled between May 31, 2017, and June 30, 2022, we included 393,041 participants with available information on sexual orientation and gender identity (mean age 51 [SD 17] years), of whom 39,632 (10%) belonged to SGM groups. Of them, 38,528 (97%) belonged to a sexual minority and 4,431 (11%) to a gender minority. Compared with non-SGM, SGM persons had 15% higher odds of the brain health composite outcome (odds ratio [OR] 1.15, 95% CI 1.08–1.22). In secondary analyses, these results persisted across sexual and gender minorities separately (all 95% CIs > 1). Assessing individual diseases, all SGM groups had higher odds of dementia (SGM vs non-SGM: OR 1.14, 95% CI 1.00–1.29) and late-life depression (SGM vs non-SGM: OR 1.27, 95% CI 1.17–1.38) and transgender women had higher odds of stroke (OR 1.68, 95% CI 1.04–2.70).

### Discussion

In a large US population study, SGM persons had higher odds of adverse brain health outcomes. Further research should explore structural causes of inequity to advance inclusive and diverse neurologic care.

From the Department of Neurology (S.H., C.A.R., S.C.-T., D.R., N.A.S., A.d.H., K.N.S., G.J.F.), Yale Center for Brain and Mind Health (S.H., C.A.R., S.C.-T., D.R., A.d.H., K.N.S., G.J.F.), Department of Internal Medicine (S.C.-T.), Department of Neurosurgery (D.R.), and Office of Health Equity Research (D.F.S.), Yale University School of Medicine, New Haven, CT; and Weill Institute for Neurosciences (N.R.), Department of Neurology, University of California San Francisco.

Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Copyright © 2024 American Academy of Neurology

e209863(1)

Copyright © 2024 American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

# Glossary

AAN = American Academy of Neurology; AFAB = assigned female at birth; AMAB = assigned male at birth; EHR = electronic health record; ICD-9 = *International Classification of Diseases, Ninth Revision*; ICD-10 = *International Classification of Diseases, 10th Revision*; non-SGM = cisgender straight; OR = odds ratio; SGM = sexual and gender minority; SNOMED = Systematized Nomenclature of Medicine.

## Introduction

In a world that increasingly recognizes the crucial role of equitable health care, it remains concerning how little is known about the health disparities faced by sexual and gender minority (SGM) groups. Compared with other minoritized communities, this group has only gained attention in neurologic research in recent years, and structured data on the health care disparities of SGM persons remain scarce, including in the realm of brain health.<sup>1,2</sup>

Driven by the concerns of an aging population, brain health has become a critical focus across international and US health organizations.<sup>3-5</sup> The American Academy of Neurology (AAN) defined brain health as “(...) the optimal neurologic function that best supports one’s physical, mental, and social well-being through every stage of life.”<sup>3</sup> Key outcomes related to brain health—such as stroke, dementia, and late-life depression—are the leading cause of disability-adjusted life years and second leading cause of death.<sup>6</sup> However, the intersection of brain health with the health care disparities suffered by SGM persons is not well understood. Existing evidence indicates that SGM persons with stroke may have different risk factors, stroke mechanisms, and an increased recurrent stroke risk compared with cisgender straight (non-SGM) persons.<sup>7</sup> Yet, in a survey led by the AAN, only a minority of neurologists recognized the intersection of SGM identity with neurologic health.<sup>8</sup> This is unsurprising, given that studies investigating SGM health often suffer small sample sizes, lack of granular ascertainment of SGM status, and overemphasis of certain topics such as HIV, hormone use, substance use disorder, and mental health outcomes.<sup>9</sup>

To tackle this knowledge gap, we leveraged the recently introduced All of Us Research Program. We hypothesize that the risk of adverse brain health outcomes differs between SGM persons, including SGM subgroups, and their non-SGM peers.

## Methods

### Study Design, Setting, and Participants

We conducted a cross-sectional study nested within the All of Us Research Program, a large population-based cohort that aims to enroll 1 million Americans.<sup>10</sup> Data collection was performed between May 31, 2017, and June 30, 2022, for US residents aged 18 years or older. On enrollment, baseline health surveys, biospecimen collection, and physical measurements

were conducted and longitudinal health data were accessed using electronic health record (EHR) data. All data sources were harmonized using the standardized Observational Medical Outcomes Partnership Common Data Model version 5.3.1. We included participants with available data on sexual orientation and gender identity. Answers that were excluded were “None,” “Skip,” and “Prefer Not to Answer.” The analytical sample consisted of 393,041 participants.

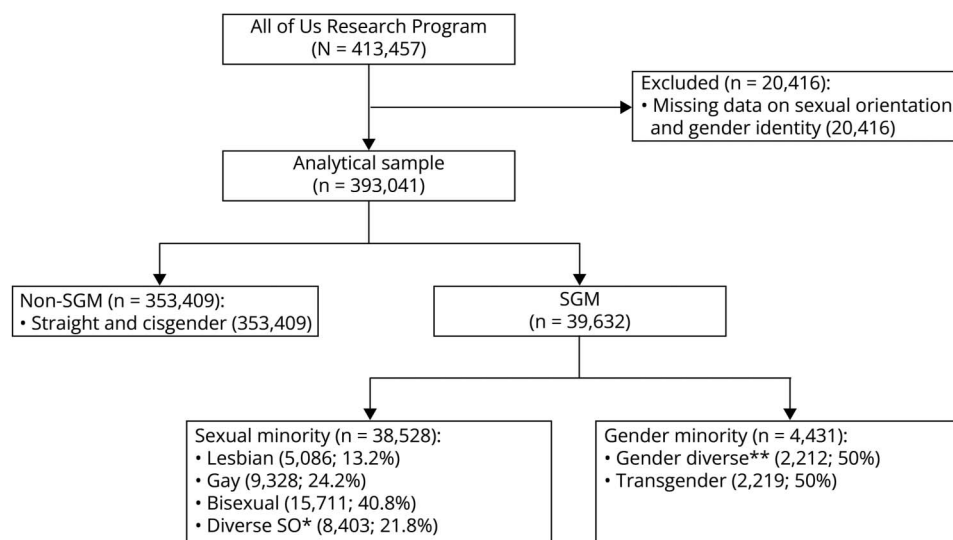
### Exposures

We categorized participants as SGM persons based on self-identified sexual orientation and/or gender identity obtained in baseline questionnaires (Figure 1 for an exhaustive list of questionnaire responses per category). To examine the different risk profiles of subgroups within the larger SGM umbrella, we divided SGM in smaller categorizations. The sexual minority group was defined as anyone who identified as nonstraight. We further divided the sexual minority group into lesbian, gay, bisexual, and diverse sexual orientation subgroups. The gender minority group was defined as anyone who identified as a gender different from the sex assigned at birth (non-cisgender). We further divided the gender minority group into transgender and gender-diverse subgroups (Figure 1).

For the primary analysis, we compared SGM groups with non-SGM groups. Secondary analyses investigated outcomes within SGM groups separately, comparing sexual minority persons with straight persons and gender minority persons with cisgender persons. In the interaction analysis, we then investigated the subgroups of SGM groups stratified by sex assigned at birth to compare with straight and cisgender persons, respectively, of the same sex assigned at birth.

### Outcomes

To cover the most prominent diseases from the neurologic, cognitive, and psychiatric aspects of brain health, the primary brain health outcome was a composite of stroke, dementia, and late-life depression, whichever occurred first. This composite outcome was chosen to capture a holistic view of brain health, acknowledging that these conditions are interrelated and share common risk factors. Late-life depression, defined as depressive episode first diagnosed at or after the age of 60,<sup>11</sup> often co-occurs with dementia and stroke, sharing modifiable risk factors with these conditions.<sup>12</sup> It is furthermore associated with cerebral small vessel disease, supporting the hypothesis of a vascular contribution to late-life depression.<sup>13</sup> The bidirectional relationship between late-life depression and dementia, along with the well-described occurrences of

**Figure 1** Participant Selection and Categorization Flowchart

This figure illustrates the participant selection process from the total sample size of the All of Us Research Program to the respective subcategories of SGM. The categories gender minority and sexual minority are not mutually exclusive because participants could be part of both minority groups. As such, the numbers will not add up to the total number of all SGM persons. \*Diverse sexual orientation groups include queer, polysexual, omnisexual, sapiosexual, pansexual, asexual, two-spirit, have not figured out or in the process, mostly straight but sometimes attracted to people of your own sex, do not use labels, and something else (free text). \*\*Gender identities summarized as gender diverse include genderqueer, genderfluid, gender variant, two-spirit, questioning, or unsure. Non-SGM = cisgender straight; SGM = sexual and gender minority; SO = sexual orientation.

poststroke depression and poststroke dementia, further complicates distinguishing between these conditions.<sup>14</sup> Thus, including them under the umbrella of brain health reflects their interconnected nature. By examining these conditions together, we aim to provide a comprehensive assessment of brain health disparities in SGM populations. In addition, by using the outcome that occurs first, we exclude overlaps, ensuring that each condition is analyzed as an independent event. The secondary outcomes were each disease evaluated independently from the others. Outcomes were assessed using a combination of EHR data and baseline questionnaires. For EHR data, we used *International Classification of Diseases, Ninth Revision (ICD-9)*, *International Classification of Diseases, 10th Revision (ICD-10)*, and *Systematized Nomenclature of Medicine (SNOMED)* codes to define each outcome (eTable 1).

## Covariates

In our multivariable analysis, we used age at baseline, self-identified race/ethnicity (Asian, Black or African American, Hispanic or Latino, Other/Multiethnic, White), prevalent cardiovascular comorbidities (atrial fibrillation, hyperlipidemia, hypertension, type 2 diabetes mellitus), smoking (never, past smoker, current), substance use disorder, HIV infection, and neighborhood deprivation index (continuous). All comorbidities were used as binary variables (yes/no). All variables were assessed at baseline through questionnaires, and for the comorbidities, *ICD-9*, *ICD-10*, and *SNOMED* codes were used (eTable 1). The neighborhood deprivation index is an aggregate variable derived from the American Community Survey data<sup>15</sup> that ascertains income, vacant housing, economic poverty, high school education, health insurance coverage, and assisted income by zip code and is scored continuously between 0 (low) and 1 (high) levels of deprivation.

## Statistical Analysis

We present discrete variables as counts (percentages [%]) and continuous variables as means (SD) or median (interquartile range), as appropriate. We pursued exploratory, post hoc, complete case analyses including study participants without missing data for the data points of interest for each comparison. To identify potential biases, we included a comparison of baseline characteristics between the whole cohort and the complete cases (eTable 2). In our primary analysis, we used multivariable logistic regressions to assess the relationship between SGM status and the composite brain health outcome. We used 3 sequential models of adjustment: model 1 adjusted for age, sex assigned at birth, and race/ethnicity; model 2 further adjusted for cardiovascular comorbidities that are less prevalent in the SGM community (baseline Table 1 and eTable 2 for age-matched characteristics) and the neighborhood deprivation index; and model 3 adjusted for all covariates from models 1 + 2 and added comorbidities more prevalent in the SGM community, namely smoking, substance use disorder, and HIV (Table 1).

In our sensitivity analysis, we assessed whether age was a main confounder in the relationship between SGM status and adverse brain health outcomes. We created an age-matched cohort to control for the confounding effect of age across SGM and non-SGM groups by exact matching. We evaluated the fractions of persons with adverse brain health outcomes for both the unmatched and the matched dataset. Furthermore, we calculated the risk ratios to compare the likelihood of suffering from brain health outcomes between SGM and non-SGM groups.

In our secondary analyses, we evaluated each SGM subgroup and each brain health outcome separately using fully adjusted model 3. We furthermore conducted an interaction analysis using product terms and stratified analyses (multivariable

**Table 1** Baseline Characteristics

	Non-SGM	SGM
<b>Total, n</b>	353,409	39,632
<b>Demographics</b>		
<b>Age, y, mean (SD)</b>	52.0 (16.9)	42.6 (16.3)
<b>Sex assigned at birth<sup>a</sup></b>		
<b>Female</b>	218,671 (61.9)	24,125 (60.9)
<b>Intersex</b>	0 (0)	39 (0.1)
<b>Male</b>	134,738 (38.1)	15,364 (38.8)
<b>Race/ethnicity, n (%)</b>		
<b>Asian</b>	12,093 (3.4)	1,203 (3.0)
<b>Black or African American</b>	65,597 (18.6)	6,926 (17.5)
<b>Hispanic or Latino</b>	63,674 (18.0)	7,085 (17.9)
<b>Other/multiethnic</b>	16,739 (4.7)	2,573 (6.5)
<b>White</b>	195,306 (55.3)	21,845 (55.1)
<b>Vascular risk factors</b>		
<b>Atrial fibrillation, n (%)</b>	11,880 (3.4)	616 (1.6)
<b>Hyperlipidemia, n (%)</b>	81,435 (23.0)	5,554 (14.0)
<b>Hypertension, n (%)</b>	87,354 (24.7)	6,406 (16.2)
<b>Type 2 diabetes mellitus, n (%)</b>	38,293 (10.8)	2,945 (7.4)
<b>Smoking,<sup>a</sup> n (%)</b>		
<b>Never</b>	201,601 (60.4)	20,699 (56.1)
<b>Past smoker</b>	79,462 (23.8)	8,172 (22.2)
<b>Current smoker</b>	52,920 (15.8)	7,994 (21.7)
<b>Relevant medical history</b>		
<b>Substance use disorder, n (%)</b>	18,384 (5.2)	2,876 (7.3)
<b>HIV, n (%)</b>	2,329 (0.7)	1,836 (4.6)
<b>Social determinants of health</b>		
<b>Deprivation index, mean (SD)</b>	0.3 (0.1)	0.3 (0.1)

Abbreviations: non-SGM = cisgender straight; SGM = sexual and gender minority.

This table summarizes the baseline characteristics of the cohort stratified by SGM status. The categories gender minority and sexual minority are not mutually exclusive because participants could be categorized as part of both groups. As such, the numbers will not add up to the total number of all SGM persons.

<sup>a</sup> The percentages are calculated with counting missing values (n = 69 for sex assigned at birth, n = 22,193 for smoking) and thus might not add up to 100%.

logistic regression using model 3) to investigate the influence of sex assigned at birth on the relationship between SGM status and adverse brain health outcomes. We chose this approach to clearly differentiate the effects of sex assigned at birth from the concept of gender identity. Thereby, we ensured that each minority group is compared with nonminority persons of the same sex assigned at birth. This stratification

allows categorization of sexual minority groups into lesbian (assigned female at birth [AFAB]), gay (assigned male at birth [AMAB]), bisexual (AFAB or AMAB), and diverse sexual orientation groups (AFAB or AMAB). Furthermore, this approach separates transgender persons into transgender women (AMAB), transgender men (AFAB), and gender-diverse persons (AFAB or AMAB). Intersex persons were excluded from this stratified analysis because of low numbers (n = 39). Statistical significance was defined as a 95% CI excluding 1 for 2-tailed hypothesis testing. Statistical analyses were performed in R version 4.2.2, and matching was performed using the R package MatchIt version 4.5.5.

**Standard Protocol Approvals, Registrations, and Patient Consents**

The study was approved by the All of Us Institutional Review Board,<sup>16</sup> and all participants or their legal guardians have provided written informed consent.

**Data Availability**

This study used data from the All of Us Research Program's Controlled Tier Dataset C2022Q4R9 and Registered Tier Dataset R2022Q4R9, available to authorized users on the Researcher Workbench through [allofus.nih.gov](https://allofus.nih.gov). All data access and analyses were conducted within a secure informatic workspace provided by the NIH.

**Results**

Of the 413,457 participants included in the All of Us Research Program, 393,041 (95%) had full information on sexual orientation and gender identity and were included in our analysis. Of those, 39,632 participants were categorized as SGM (10%). Within the SGM group, 38,528 participants (97%) were included in the sexual minority group and 4,431 participants (11%) in the gender minority group. Of note, these 2 groups were not mutually exclusive, given that a participant could identify in a way that was categorized as part of both SGM groups. Within the sexual minority group, 5,086 participants (13.2%) were categorized as lesbian, 9,328 (24.2%) as gay, 15,711 (40.8%) as bisexual, and 8,403 (21.8%) as diverse sexual orientations (Figure 1 for a list of these). Within the gender minority group, 2,212 participants (50%) were categorized as gender diverse and 2,219 (50%) as transgender. Baseline characteristics are listed in Table 1. The mean age at baseline was 52 years (SD 16.9) in the non-SGM group and 42.6 years (SD 16.3) for SGM persons. Across all cardiovascular risk factors, prevalence was lower in SGM than in non-SGM persons. By contrast, the prevalence of smoking, substance use disorder, and HIV infection was higher in SGM than in non-SGM persons. When evaluating baseline characteristics of complete cases of all covariates (model 3) only, the distribution of exposures and covariates did not change considerably (eTable 2).

**Primary Analysis**

The prevalence of the composite brain health outcome was 5.4% (n = 21,091), including 11,553 cases of late-life



depression (45.8%), 6,605 cases of stroke (31.3%), and 2,933 cases of dementia (13.9%). In evaluating the combined brain health outcome with fully adjusted model 3, SGM participants showed a 15% higher likelihood of experiencing an adverse outcome (odds ratio [OR] 1.15, 95% CI 1.08–1.22). When comparing results between models 1 and 3, the results for the composite brain health outcome remained significant in all models (all analyses with 95% CI >1, Table 2).

Matched Analysis

In our sensitivity analysis, we evaluated the percentage of participants with prevalent adverse brain health outcomes, comparing those from SGM and non-SGM groups before and after matching by age. Before matching, the mean age of non-SGM persons was 52.0 years (SD 16.9) and 42.6 years (SD 16.3) for SGM persons. After matching, the mean age was harmonized to 43.1 years (SD 16.4) and 43.7 years (SD 16.4), respectively. eTable 3 gives a complete overview of the baseline characteristics of the matched cohort. Even after matching, the prevalence of all cardiovascular comorbidities was higher for non-SGM than for SGM persons, except smoking, which was more common in SGM (21.67% current smokers) than in non-SGM persons (16.71% current smokers). After matching by age, the risk of adverse brain health outcomes changed from 5.55% (95% CI 5.49–5.64) to 3.75% (95% CI 3.68–3.82) for non-SGM participants and from 3.55% (95% CI 3.37–3.73) to 4.71% (95% CI 4.46–5.00) for SGM participants. The higher risk of adverse brain health outcomes in the SGM group after adjusting for age suggests that age was a major confounder in the relationship between adverse brain health outcomes and SGM status.

Secondary Analyses

All results from the primary and secondary analyses are summarized in Figure 2. For all SGM persons, the probability of encountering dementia was increased by 14% (OR 1.14, 95% CI 1.00–1.29) and for late-life depression by 27% (OR 1.27, 95% CI 1.17–1.38). However, the odds of experiencing a stroke were not significantly elevated (OR 0.97, 95% CI 0.87–1.07). These results remained unchanged across all 3 models (Table 2).

When investigating sexual minority groups and gender minority groups independently, we found that sexual minority people compared with straight people had similar odds to those observed in all SGM persons. When comparing gender minority groups with cisgender people, the odds of all outcomes except stroke were increased even more than for sexual minority persons (gender minority persons vs cisgender persons: composite brain health OR 1.48, 95% CI 1.22–1.81; stroke OR 1.22, 95% CI 0.90–1.66; dementia OR 1.44, 95% CI 1.00–2.07; late-life depression OR 1.55, 95% CI 1.17–2.04, Figure 2).

Interaction With Sex at Birth and Stratified Subgroup Analyses

A significant interaction was observed between SGM status and sex assigned at birth (AMAB: OR 1.23, 95% CI 1.08–1.39), meaning that participants AMAB from SGM communities are 23% more likely to suffer adverse brain health outcomes than SGM persons AFAB.

For the subgroups within the sexual minority group, we found that lesbian (OR 1.17, 95% CI 1.00–1.36) and gay (OR 1.17, 95% CI 1.04–1.32) persons had increased odds of the composite brain health outcome (Figure 3). The odds of dementia were increased in lesbian (OR 1.46, 95% CI 1.08–1.96) and bisexual (OR 1.34, 95% CI 1.04–1.74) persons AFAB. The odds of late-life depression were increased in gay persons (OR 1.55, 95% CI 1.33–1.81), bisexual persons (OR 1.35, 95% CI 1.05–1.74), and persons of diverse sexual orientation (OR 1.33, 95% CI 1.00–1.75) AMAB.

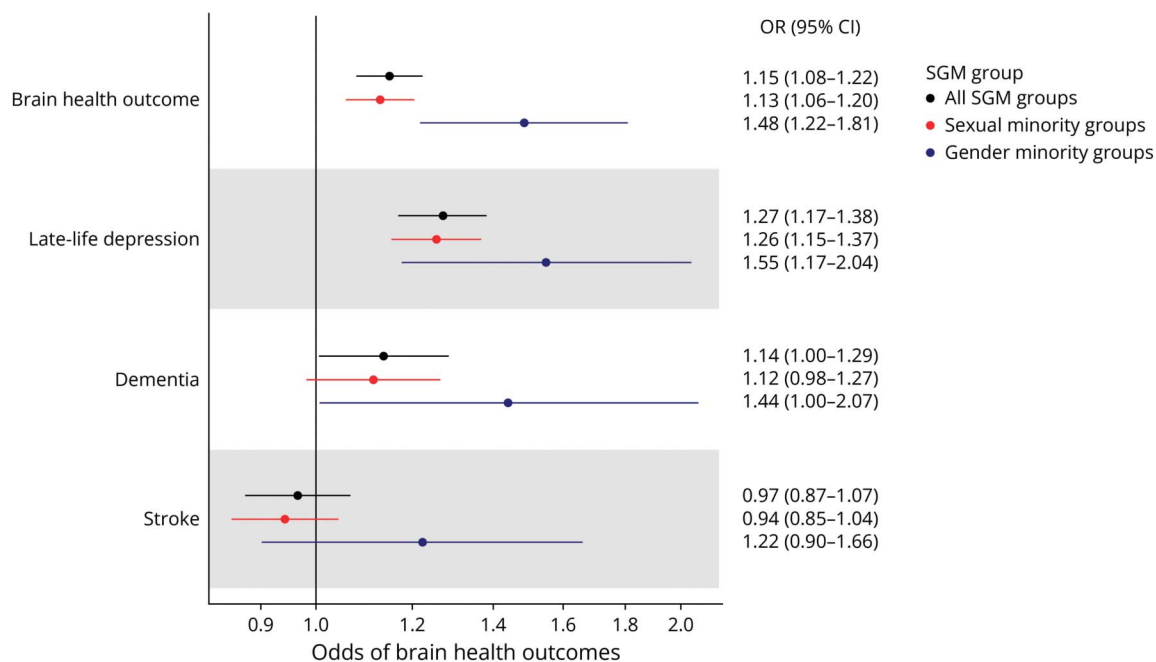
For the subgroups within the gender minority group, the odds of the composite brain health outcome were increased for groups AMAB, including transgender women (OR 1.75, 95% CI 1.25–2.46) and some gender-diverse participants (OR 1.76, 95% CI 1.06–2.98, Figure 4). The odds of dementia were increased for gender-diverse persons (AFAB: OR 1.94, 95% CI 1.06–3.56, AMAB: OR 2.57, 95% CI 1.25–5.30). The odds of late-life depression were increased for transgender women (AMAB: OR 2.19, 95% CI 1.40–3.44). Finally, the odds of stroke were only increased for transgender women (AMAB: OR 1.68, 95% CI 1.04–2.70).

Table 2 Odds of Prevalent Brain Health Outcomes for Sexual and Gender Minority Participants in 3 Different Models

Analysis	Outcome	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Primary	Brain health outcome	1.15 (1.09–1.22)	1.24 (1.17–1.32)	1.15 (1.08–1.23)
Secondary	Late-life depression	1.26 (1.17–1.36)	1.36 (1.26–1.48)	1.27 (1.17–1.38)
	Dementia	1.22 (1.09–1.37)	1.28 (1.14–1.44)	1.14 (1.00–1.29)
	Stroke	0.97 (0.88–1.07)	1.03 (0.94–1.14)	0.97 (0.87–1.07)

Abbreviations: non-SGM = cisgender straight; OR = odds ratio; SGM = sexual and gender minority. This table shows the results of the stepwise-adjusted models for SGM compared with non-SGM participants and brain health outcomes. Model 1 adjusted for age and race/ethnicity; model 2 further adjusted for cardiovascular comorbidities and neighborhood deprivation index; and model 3 further adjusted for smoking, substance use disorder, and HIV.

**Figure 2** SGM Groups and Brain Health Outcomes



This figure summarizes the results investigating the relationship between different SGM groups and brain health outcomes. Results are plotted as OR and 95% CI on a logarithmic scale. The reference group for all SGM groups is non-SGM, the reference group for sexual minority groups is straight individuals, and the reference group for gender minority groups is cisgender individuals. Non-SGM = cisgender straight; OR = odds ratio; SGM = sexual and gender minority.

## Discussion

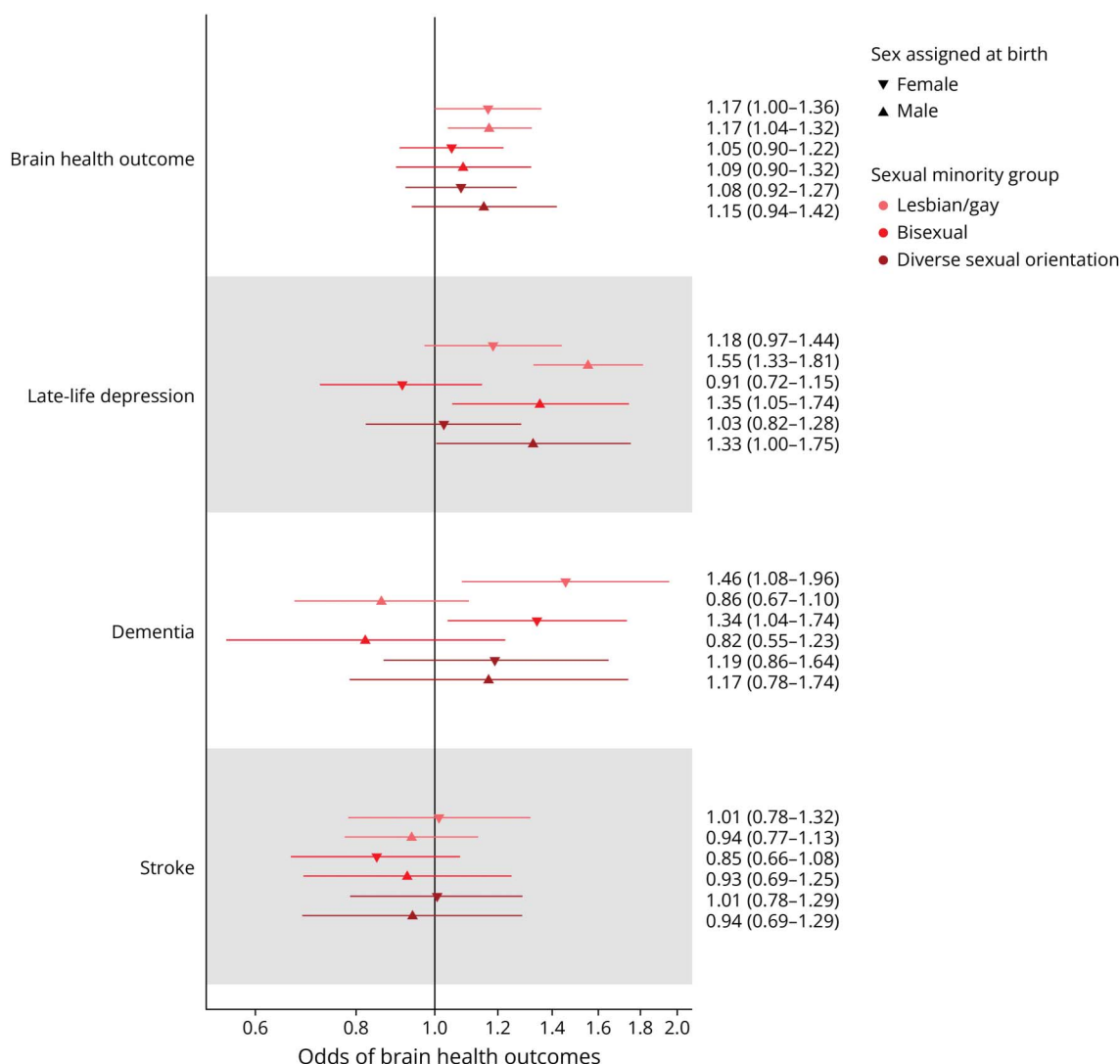
This cross-sectional study showed that SGM persons are at an increased risk of adverse brain health outcomes, both when compared with the non-SGM groups and when investigating several subgroups. We, therefore, address a crucial lack of research about brain health disparities in the SGM community, which to date have not been sufficiently described. A recent review of 348 studies on SGM health in neurology has disclosed the lacking quality of available evidence (58.9% case reports or series), a limited breadth of neurologic pathology (70.9% focused on HIV and its neurologic sequelae), and inclusion of only a portion of the overall SGM community (72.4% including sexual minority cisgender men).<sup>17</sup> A recent cross-sectional study from population-based data indicates that sexual minority individuals have distinct cardiovascular risk profiles compared with straight adults.<sup>15,18</sup> The translation of these findings into concrete implications for brain health, including stroke risk and vascular contribution to cognitive decline, requires further investigation. We, therefore, elucidated risk profiles within distinct subgroups of the SGM community for 3 major diseases impairing brain health.

Our findings indicate elevated risks of late-life depression in all SGM persons and SGM groups separately. Specifically, we have found that sexual minority persons AMAB and transgender women are particularly vulnerable for late-life depression. It is well documented that SGM populations have higher rates of anxiety and depression compared with non-

SGM populations.<sup>19–21</sup> However, late-life depression, which is a known surrogate for brain health in the elderly with distinct neuroanatomical, cognitive, clinical, and genetic profiles,<sup>22</sup> has not been studied in SGM persons yet.

Furthermore, we showed that the risk of dementia is elevated in all SGM persons, with sexual minority persons AFAB and gender-diverse persons being particularly vulnerable. In the existing evidence, some studies suggest a higher susceptibility of SGM persons to subjective cognitive impairment<sup>23</sup> while the disparities in objective cognitive measures and risk of dementia remain underexplored.<sup>24</sup> First data reveal that transgender and nonbinary adults might be at increased risk of developing Alzheimer disease.<sup>25</sup> While we could not confirm these findings for transgender persons, we did find the same increase in risk of dementia in gender-diverse persons. The health disparities unique to this group that cause increased risk of dementia remain to be explored.

Finally, our results show that the risk of stroke is only increased in transgender women. Although existing literature on stroke risk specific to the transgender community is scarce, some studies suggest that increased stroke risk in transgender women might relate to gender-affirming hormone therapy with estrogens while transgender men receiving testosterone lack consistent evidence for increased cerebrovascular disease.<sup>26</sup> These findings are consistent with known stroke risk for oral contraceptives containing estrogens and postmenopausal hormone therapy with estrogens.<sup>27</sup> However,

**Figure 3** Sexual Minority Groups Stratified by Sex Assigned at Birth

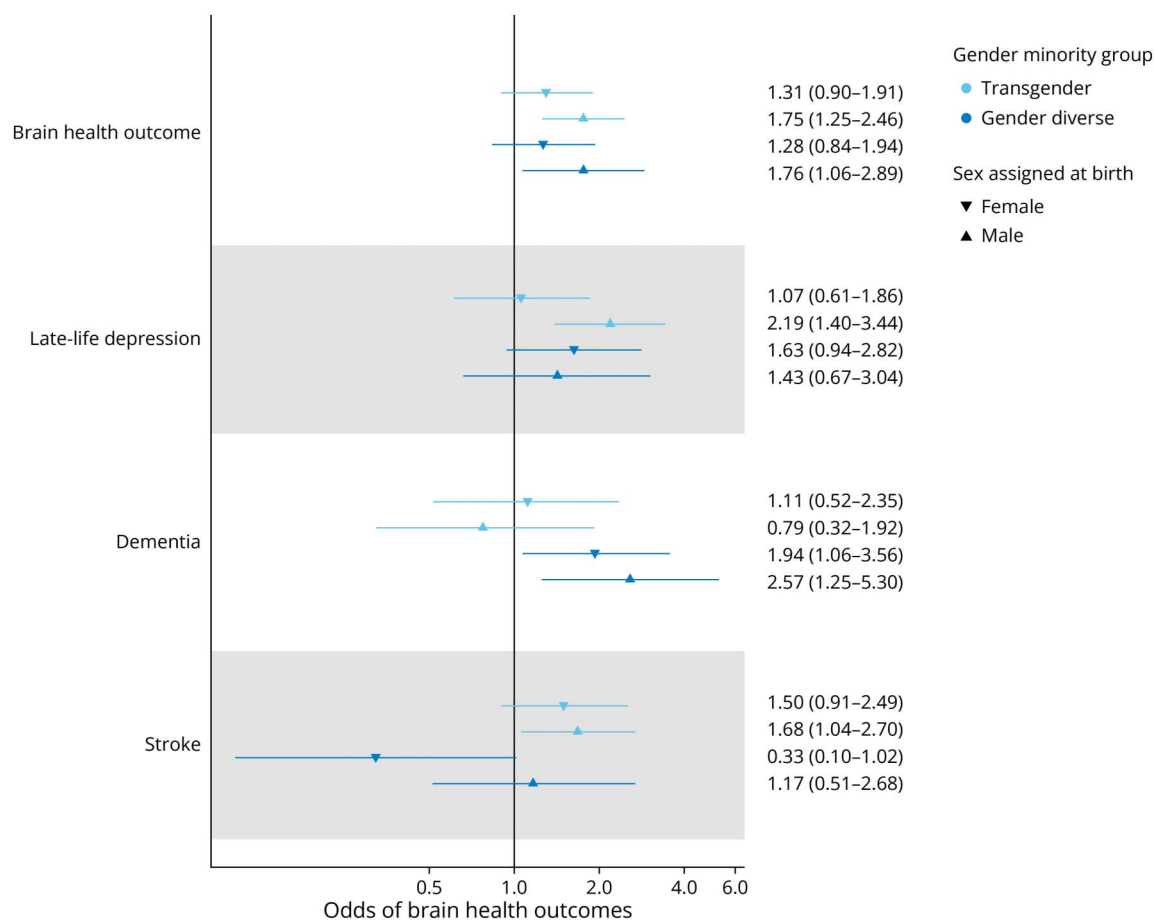
This figure illustrates the relationship between different sexual minority groups and brain health outcomes stratified by sex assigned at birth. Lesbian persons are reflected in the group lesbian/gay and of female sex assigned at birth. Gay persons are reflected in the group lesbian/gay and of male sex assigned at birth. Results are plotted as OR and 95% CI on a logarithmic scale. The reference group for all comparisons is straight individuals (non-sexual minority). OR = odds ratio.

studies investigating other potential mechanisms of stroke risk in transgender women, such as the effect of psychosocial stress, are currently lacking.

Our study contributes to a better understanding of the crucial area of SGM health focused on overall brain health. The reasons for the observed disparities could be due to a variety of contributions from physical (e.g., gender-affirming hormone therapy<sup>26</sup> and violence<sup>28</sup>), psychosocial (e.g., discrimination,<sup>29</sup> stigma,<sup>30</sup> stress,<sup>31</sup> and depression<sup>32</sup>), and systemic (e.g., policy and legal protection<sup>33–35</sup> and health care access<sup>36–38</sup>) factors. These factors can impair brain health in various ways. For instance, chronic stress and trauma from discrimination, stigma, and violence can lead to neuroinflammation and affect brain health.<sup>39,40</sup> Gender-affirming hormone therapy may have complex effects on brain structure and function,

including influences on cerebral volume and vasculature.<sup>41,42</sup> Inadequate health care access and discrimination by health care practitioners can impair primary prevention and delay or prevent treatment of brain health conditions, leading to prolonged burden of associated diseases.<sup>43</sup> Systemic factors, including insufficient policy and legal protections, can exacerbate these issues by creating barriers to adequate care and support.

Furthermore, it is important to recognize the distinct challenges and risk profiles each group encounters, given the scarcity of studies providing a more detailed picture of all SGM groups.<sup>17</sup> For example, stigmatization of bisexual people is often different from that against lesbian or gay people.<sup>44</sup> Moreover, evidence suggests that transgender and gender-diverse persons not only have increased incidence of mental

**Figure 4** Gender Minority Groups Stratified by Sex Assigned at Birth

This figure illustrates the relationship between different gender minority groups and brain health outcomes stratified by sex assigned at birth. Results are plotted as OR and 95% CI on a logarithmic scale. Transgender women are transgender persons AMAB identifying as woman, and transgender men are transgender persons AFAB identifying as man. The reference group for all comparisons is cisgender individuals (non-gender minority). AFAB = assigned female at birth; AMAB = assigned male at birth; OR = odds ratio.

health conditions, but their challenges are more likely not recognized and addressed appropriately by their health care providers.<sup>45</sup> This unmet need can lead to chronic manifestations of psychological distress and psychiatric diseases, which are substantial risk factors of dementia. Despite common obstacles, some studies suggest that gender-diverse persons report worse health outcomes than binary transgender persons, potentially evoked by a phobic culture toward crossing gender binary norms.<sup>46</sup>

Notably, our study found a reduced prevalence of cardiovascular comorbidities among SGM individuals, even after adjusting for age, despite an increased prevalence of smoking and substance use disorder. While smoking and substance use may serve as coping mechanisms for managing everyday minority stress, the observed lower cardiovascular risk profile concerning comorbidities in SGM individuals warrants further investigation. This paradox might be influenced by unmeasured confounders such as socioeconomic status or physical activity levels. The investigation of underlying protective factors can shape interventions in communities with

higher cardiovascular risk. By understanding the brain health disparities suffered by members of the SGM community and its smaller subgroups, even independently from known risk factors, we highlight a crucial need for further research about the causal mechanisms behind our observations.

Our study sets an example for the enormous potential of the All of Us Research Program, one of the most ambitious and expansive research endeavors in US history that lists diversity as one of its core values.<sup>47</sup> By combining multidimensional data sources, this program unveils unprecedented insights into SGM and other health disparities.<sup>48</sup> All of Us has a unique data structure encompassing large-scale information on ethnic<sup>49</sup> and nonethnic minority groups<sup>50</sup> and social determinants of health. Moreover, it incorporates an extensive array of EHR data, physical measurements, biospecimen collection, digital health technology, and genotyping.<sup>10</sup> Therefore, All of Us will offer new avenues for minority research using these multimodal large-scale data to deepen our understanding of health disparities. Our study addresses the current scarcity of publications using All of Us data for SGM research,<sup>51,52</sup>



thereby contributing a pivotal perspective to the relatively underexplored area of brain health.

While providing valuable insights into the brain health status of SGM persons, our study has limitations. First, although we included neighborhood deprivation and race/ethnicity as covariates in our models, our analysis was focused specifically on SGM groups without exploring the specific interactions with these and other social determinants of health.<sup>38</sup> The SGM community encompasses people who experience marginalization due to other experiences (i.e., intersectionality), which we did not fully encapsulate here. Another limitation is the potential presence of unmeasured confounders. Our purely descriptive analysis does not unravel the complex web of causes and mechanisms underpinning the inequities faced by SGM persons, suggesting caution in interpreting these findings. For example, we did not assess gender-affirming hormone therapy in transgender persons, which would have been informative in investigating causes of the increased stroke risks in transgender women. Furthermore, the stratification of lesbian people under AFAB and gay people under AMAB differs from most community definitions that use gender rather than sex assigned at birth. Although methodologically necessary for this investigation and unlikely to affect the overall results, this approach can lead to misclassification of gender minority groups, particularly transgender individuals, and should be acknowledged. Of note, because of low numbers of participants assigned intersex at birth, we could not explore the risks specific to this group in our stratified analysis. Moreover, the All of Us Research Program, from which our data are sourced, purposefully oversamples minoritized groups. While this enhances the representation of SGM persons, it might introduce a sampling bias, potentially skewing the health status of participants relative to the general US population. Despite these limitations, the study leverages data from the All of Us Research Program, the largest cohort of its kind, specifically designed to address disparities in medical research.

In our cross-sectional study, SGM persons had an increased risk of adverse brain health outcomes. Our findings underscore the need for further research focusing on the health care disparities affecting the SGM community. Future research should not only explore further neurologic outcomes but also investigate possible causal factors of disparities. Generating this knowledge will be crucial before implementing interventions and policies to address these issues. Our results highlight the importance of continued investigation into these disparities to ultimately inform future policy decisions toward more inclusive and equitable neurologic health care.

Acknowledgment

The authors gratefully acknowledge All of Us participants for their contributions, without whom this research would not have been possible. The authors also thank the NIH’s All of Us Research Program for making available the participant data examined in this study.

Study Funding

This work was funded by the German Research Foundation (DFG) under the grant number S14143076.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* March 20, 2024. Accepted in final form July 23, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Rebecca Burch, MD.

Appendix Authors

Name	Location	Contribution
Shufan Huo, MD, PhD	Department of Neurology, and Yale Center for Brain and Mind Health, Yale University School of Medicine, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Cyprien A. Rivier, MD, MSc	Department of Neurology, and Yale Center for Brain and Mind Health, Yale University School of Medicine, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Santiago Clocchiatti-Tuozzo, MD, MHS	Department of Neurology, Yale Center for Brain and Mind Health, and Department of Internal Medicine, Yale University School of Medicine, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Daniela Renedo, MD	Department of Neurology, Yale Center for Brain and Mind Health, and Department of Neurosurgery, Yale University School of Medicine, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
N. Abimbola Sunmonu, MD, PhD	Department of Neurology, Yale University School of Medicine, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Adam de Havenon, MD, MSc	Department of Neurology, and Yale Center for Brain and Mind Health, Yale University School of Medicine, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Daniel F. Sarpong, PhD	Office of Health Equity Research, Yale University School of Medicine, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Nicole Rosendale, MD	Weill Institute for Neurosciences, Department of Neurology, University of California San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

Continued

Appendix (continued)

Name	Location	Contribution
Kevin N. Sheth, MD	Department of Neurology, and Yale Center for Brain and Mind Health, Yale University School of Medicine, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
Guido J. Falcone, MD	Department of Neurology, and Yale Center for Brain and Mind Health, Yale University School of Medicine, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

References

1. Byer L, Orozco-Poore C, Rosendale N. Limitations and future directions in sex, sexuality, and gender diverse research in neurology. *Ann Neurol*. 2024;95(3):421-431. doi:10.1002/ana.26863

2. Volpe SG, Ahmad J, Patel RA, Rosendale N. Neurological care for LGBT+ people. *Nat Rev Neurol*. 2024;20(5):288-297. doi:10.1038/s41582-024-00944-0

3. Rost NS, Salinas J, Jordan JT, et al. The brain health imperative in the 21st century: a call to action: the AAN brain health platform and position statement. *Neurology*. 2023; 101(13):570-579. doi:10.1212/WNL.000000000000207739

4. Optimizing brain health across the life course: WHO position paper. Accessed December 12, 2023. who.int/publications-detail-redirect/9789240054561.

5. Caceres BA, Streed CG, Corliss HL, et al. Assessing and addressing cardiovascular health in LGBTQ adults: a scientific statement from the American Heart Association. *Circulation*. 2020;142(19):e321-e332. doi:10.1161/CIR.0000000000000914

6. GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*. 2019;18(5):459-480. doi:10.1016/S1474-4422(18)30499-X

7. Diaz MA, Rosendale N. Exploring stroke risk factors and outcomes in sexual and gender minority people. *Neurol Clin Pract*. 2023;13(1):e200106. doi:10.1212/CPJ.000000000000200106

8. Rosendale N, Ostendorf T, Evans DA, et al. American Academy of Neurology members' preparedness to treat sexual and gender minorities. *Neurology*. 2019;93(4): 159-166. doi:10.1212/WNL.00000000000007829

9. Volpe SG, Zuniga MC, Caunca MR, Rosendale N. Gender and sex equity in stroke research, education, and care. *Stroke*. 2023;54(2):e44-e47. doi:10.1161/STROKEAHA.122.039893

10. All of Us Research Program Investigators, Denny JC, Rutter JL, et al. The "All of Us" research program. *N Engl J Med*. 2019;381(7):668-676. doi:10.1056/nejmr1809937

11. Randall Espinoza MD, Aaron H. Kaufman MD. Diagnosis and treatment of late-life depression. *Psychiatric Times*. 2014;31(10). Accessed January 17, 2024. psychiatrictimes.com/view/diagnosis-and-treatment-late-life-depression.

12. Szymkowicz SM, Gerlach AR, Homiak D, Taylor WD. Biological factors influencing depression in later life: role of aging processes and treatment implications. *Transl Psychiatry*. 2023;13(1):160. doi:10.1038/s41398-023-02464-9

13. Farhat NS, Theiss R, Santini T, Ibrahim TS, Aizenstein HJ. Neuroimaging of small vessel disease in late-life depression. *Adv Exp Med Biol*. 2019;1192:95-115. doi: 10.1007/978-981-32-9721-0\_5

14. Richard E, Reitz C, Honig LH, et al. Late-life depression, mild cognitive impairment, and dementia. *JAMA Neurol*. 2013;70(3):374-382. doi:10.1001/jamaneurol.2013.603

15. Brokamp C, Beck AF, Goyal NK, Ryan P, Greenberg JM, Hall ES. Material community deprivation and hospital utilization during the first year of life: an urban population-based cohort study. *Ann Epidemiol*. 2019;30:37-43. doi:10.1016/j.jannepidem.2018.11.008

16. All of Us Research Program, Institutional Review Board. Accessed February 30, 2024. allfous.nih.gov/about/who-we-are/institutional-review-board-irb-of-all-of-us-research-program.

17. Rosendale N, Wong JO, Flatt JD, Whitaker E. Sexual and gender minority health in neurology: a scoping review. *JAMA Neurol*. 2021;78(6):747-754. doi:10.1001/jamaneurol.2020.5536

18. Caceres BA, Sharma Y, Ravindranath R, et al. Differences in ideal cardiovascular health between sexual minority and heterosexual adults. *JAMA Cardiol*. 2023;8(4):335-346. doi:10.1001/jamacardio.2022.5660

19. Källström M, Nousiainen N, Jern P, Nickell S, Gunst A. Mental health among sexual and gender minorities: a Finnish population-based study of anxiety and depression discrepancies between individuals of diverse sexual orientations and gender minorities and the majority population. *PLoS One*. 2022;17(11):e0276550. doi:10.1371/journal.pone.0276550

20. Wittgens C, Fischer MM, Buspavanich P, Theobald S, Schweizer K, Trautmann S. Mental health in people with minority sexual orientations: a meta-analysis of

population-based studies. *Acta Psychiatr Scand*. 2022;145(4):357-372. doi:10.1111/acps.13405

21. Stacey L, Wislar W. Physical and mental health disparities at the intersection of sexual and gender minority statuses: evidence from population-level data. *Demography*. 2023;60(3):731-760. doi:10.1215/00703370-10708592

22. Wen J, Fu CHY, Tosun D, et al. Characterizing heterogeneity in neuroimaging, cognition, clinical symptoms, and genetics among patients with late-life depression. *JAMA Psychiatry*. 2022;79(5):464-474. doi:10.1001/jamapsychiatry.2022.0020

23. Brown MJ, Patterson R. Subjective cognitive decline among sexual and gender minorities: results from a US population-based sample. *J Alzheimers Dis*. 2020;73(2): 477-487. doi:10.3233/JAD-190869

24. Romanelli RJ, Rosenblatt AS, Marcum ZA, Flatt JD. Cognitive impairment in sexual and gender minority groups: a scoping review of the literature. *LGBT Health*. 2024; 11(3):178-192. doi:10.1089/lgbt.2023.0095

25. Brady B, Zheng L, Kootar S, Anstey KJ. Sex and gender differences in risk scores for dementia and Alzheimer's disease among cisgender, transgender, and non-binary adults. *Alzheimers Dement*. 2024;20(1):5-15. doi:10.1002/alz.13317

26. Connelly PJ, Marie Freely E, Perry C, et al. Gender-affirming hormone therapy, vascular health and cardiovascular disease in transgender adults. *Hypertension*. 2019; 74(6):1266-1274. doi:10.1161/HYPERTENSIONAHA.119.13080

27. Demel SL, Kittner S, Ley SH, McDermott M, Rexrode KM. Stroke risk factors unique to women. *Stroke*. 2018;49(3):518-523. doi:10.1161/STROKEAHA.117.018415

28. Inwards-Breland DJ, Johns NE, Raj A. Sexual violence associated with sexual identity and gender among California adults reporting their experiences as adolescents and young adults. *JAMA Netw Open*. 2022;5(1):e2144266. doi:10.1001/jamanetworkopen.2021.44266

29. Ayhan CHB, Bilgin H, Uluhan OT, Sukut O, Yilmaz S, Buzlu S. A systematic review of the discrimination against sexual and gender minority in health care settings. *Int J Health Serv*. 2020;50(1):44-61. doi:10.1177/0020731419885093

30. Hatzenbuehler ML, Lattanner MR, McKetta S, Pachankis JE. Structural stigma and LGBTQ+ health: a narrative review of quantitative studies. *Lancet Public Health*. 2024; 9(2):e109-e127. doi:10.1016/S2468-2667(23)00312-2

31. Cook SH, Slopen N, Scarimbolo L, et al. Discrimination is associated with C-reactive protein among young sexual minority men. *J Behav Med*. 2022;45(4):649-657. doi: 10.1007/s10865-022-00307-4

32. Thoma BC, Hone E, Roig A, et al. Risk for suicidal behavior after psychiatric hospitalization among sexual and gender minority patients. *JAMA Netw Open*. 2023;6(9): e2333060. doi:10.1001/jamanetworkopen.2023.33060

33. Cahill S, Miller AS, Keuroghlian AS. Sexual and gender minority health equity in the Biden Administration. *JAMA Health Forum*. 2022;3(2):e214868. doi:10.1001/jamahealthforum.2021.4868

34. Mallory C, Chin MG, Lee JC. Legal penalties for physicians providing gender-affirming care. *JAMA*. 2023;329(21):1821-1822. doi:10.1001/jama.2023.8232

35. McDowell A, Raifman J, Progovac AM, Rose S. Association of nondiscrimination policies with mental health among gender minority individuals. *JAMA Psychiatry*. 2020;77(9):952-958. doi:10.1001/jamapsychiatry.2020.0770

36. Meléndez García CE, Coulter RWS. Someone like me: the importance of visible sexual and gender minority health care professionals. *JAMA Pediatr*. 2023;177(7): 657-658. doi:10.1001/jamapediatrics.2023.1053

37. Medina-Martínez J, Saus-Ortega C, Sánchez-Lorente MM, Sosa-Palanca EM, García-Martínez P, Mármol-López ML. Health inequities in LGBT people and nursing interventions to reduce them: a systematic review. *Int J Environ Res Public Health*. 2021; 18(22):11801. doi:10.3390/ijerph182211801

38. Trinh MH, Agénor M, Austin SB, Jackson CL. Health and healthcare disparities among U.S. women and men at the intersection of sexual orientation and race/ethnicity: a nationally representative cross-sectional study. *BMC Public Health*. 2017; 17(1):964. doi:10.1186/s12889-017-4937-9

39. Diamond LM, Dehlin AJ, Alley J. Systemic inflammation as a driver of health disparities among sexually-diverse and gender-diverse individuals. *Psychoneuroendocrinology*. 2021;129:105215. doi:10.1016/j.psypneuen.2021.105215

40. Huebner DM, McGarrity LA, Perry NS, Spivey LA, Smith TW. Cardiovascular and cortisol responses to experimentally-induced minority stress. *Health Psychol*. 2021; 40(5):316-325. doi:10.1037/hea0001067

41. Konadu ME, Reed MB, Kaufmann U, et al. Changes to hypothalamic volume and associated subunits during gender-affirming hormone therapy. *J Psychiatry Neurosci*. 2023;48(5):E369-E375. doi:10.1503/jpn.230017

42. Wright ME, Murphy K. A mini-review of the evidence for cerebrovascular changes following gender-affirming hormone replacement therapy and a call for increased focus on cerebrovascular transgender health. *Front Hum Neurosci*. 2023;17:1303871. doi:10.3389/fnhum.2023.1303871

43. Salcedo-Betancourt JD, Farouk SS, Reddy YNV. Ensuring health equity for sexual and/or gender minority individuals. *Nat Rev Nephrol*. 2022;18(6):341-342. doi: 10.1038/s41581-022-00572-1

44. Dodge B, Herbenick D, Friedman MR, et al. Attitudes toward bisexual men and women among a nationally representative probability sample of adults in the United States. *PLoS One*. 2016;11(10):e0164430. doi:10.1371/journal.pone.0164430

45. Health TLP. Addressing health inequalities in gender diverse people. *Lancet Public Health*. 2024;9(2):e68. doi:10.1016/S2468-2667(24)00006-9

46. Burgwal A, Gvianishvili N, Hård V, et al. Health disparities between binary and non binary trans people: a community-driven survey. *Int J Transgenderism*. 2019;20(2-3): 218-229. doi:10.1080/15532739.2019.1629370

47. All of Us Research Program, Core Values. Accessed February 7, 2024. [allofus.nih.gov/about/core-values](https://allofus.nih.gov/about/core-values).
48. Mapes BM, Foster CS, Kusnoor SV, et al. Diversity and inclusion for the All of Us research program: a scoping review. *PLoS One*. 2020;15(7):e0234962. doi:10.1371/journal.pone.0234962
49. Acosta JN, Leasure AC, Both CP, et al. Cardiovascular health disparities in racial and other underrepresented groups: initial results from the All of Us Research Program. *J Am Heart Assoc*. 2021;10(17):e021724. doi:10.1161/JAHA.121.021724
50. Leasure AC, Acosta JN, Both C, et al. Stroke disparities among nonracial minorities in the All of Us Research Program. *Stroke*. 2021;52(8):E488-E490. doi:10.1161/STROKEAHA.121.034903
51. Tran NK, Lunn MR, Schulkey CE, et al. Prevalence of 12 common health conditions in sexual and gender minority participants in the All of Us Research Program. *JAMA Netw Open*. 2023;6(7):e2324969. doi:10.1001/jamanetworkopen.2023.24969
52. Wong CN, Wilczek MP, Smith LH, et al. Frailty among sexual and gender minority older adults: the All of Us Database. *J Gerontol A Biol Sci Med Sci*. 2023;78(11):2111-2118. doi:10.1093/gerona/glad149