NIAAA DIRECTOR'S REPORT ON INSTITUTE ACTIVITIES TO THE 155TH MEETING OF THE NATIONAL ADVISORY COUNCIL ON ALCOHOL ABUSE AND ALCOHOLISM

SEPTEMBER 10, 2020 VIRTUAL MEETING



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Director

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National Institutes of Health

https://www.niaaa.nih.gov/about-niaaa/advisory-council





General Arthur T. Dean Announces Retirement from CADCA



General Arthur T. Dean has announced that he will retire in 2021 after serving CADCA and its coalitions worldwide for 23 years.

General Dean became the Chairman and CEO of CADCA in 1998. His responsibilities in these roles have included providing strategic direction, diversifying and increasing funding, leading the board, serving as the primary spokesman for the organization, and overseeing the operations and personnel of CADCA. He also previously served as a member of the National Advisory Council on Alcohol Abuse and Alcoholism.

In 2016, General Dean was the recipient of NIAAA's Senator Harold Hughes Memorial Award. This award recognizes the contributions of a non-researcher whose work translates research into practice and builds bridges between the alcohol prevention, treatment, and policymaking communities.

In Memoriam Joe L. Martinez, Ph.D.

Dr. Joe Martinez was a professor of psychology at UC Berkeley until his departure as Professor Emeritus in 1995 for UT San Antonio. At UT San Antonio, he founded and directed the Cajal Neuroscience Research Center and held the Ewing Halsell Distinguished Chair. He moved to University of Illinois at Chicago in 2013 to become the chair of the Department of Psychology and retired in 2016. Dr. Martinez previously served as a member of the National Advisory Council on Alcohol Abuse and Alcoholism.



He remained committed to diversity in neuroscience training throughout his career. He directed the APA Diversity Training Program for 25 years and was a co-creator of the Summer Program in Neuroscience, Excellence, and Success (SPINES), a month-long course designed to increase the success of underrepresented doctoral and postdoctoral students in neuroscience.

Dr. Martinez was a great scholar, thinker, mentor, and visionary. NIAAA aspires to build on his legacy of mentoring scientists from all races, ethnicities, and backgrounds to build a research enterprise that benefits from the perspectives of a truly diverse workforce.

Welcome to New NIAAA Staff, con't



Ms. Jayme Gemmell joined the Administrative Services Branch as the Intramural Section Chief. Jayme worked at the National Institute of Allergy and Infectious Diseases (NIAID) for the past eight years, most recently as the Deputy Operations Administrative Manager within the Intramural program.



Dr. Jeremy Luk joined the Office of the Clinical Director as a licensed clinical psychologist with research expertise in alcohol and drug use, mental health, suicide, and health disparities. He obtained his Ph.D. in clinical psychology from the University of Washington and completed postdoctoral training at the University of California San Diego and at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD).



Dr. Laura Manella joined the Communications and Public Liaison Branch as a science writer/editor. Laura earned a Ph.D. in neurobiology from Cornell University, where she studied the effects of stress on rodent sensory memories. Following a postdoctoral teaching fellowship, she served as an AAAS Science and Technology Policy Fellow in the science communication and policy offices at the National Institute on Deafness and Other Communication Disorders (NIDCD).

Welcome to New NIAAA Staff



Ms. Angela Szwec, LATG, was appointed Animal Care and Use Committee (ACUC) Administrator in the Office of Laboratory Science within the Division of Intramural Clinical and Biological Research. Angela received her M.S. in Biomedical and Veterinary Sciences from Virginia-Maryland Regional College of Veterinary Medicine. She is a Certified Professional in IACUC Administration and has 13 years of laboratory animal research experience supporting the intramural research program at the National Institutes of Health.



Ms. Michele-Vera Yonga, RN, joined the Laboratory of Neuroimaging within the Division of Intramural Clinical and Biological Research as a Nurse Practitioner. After earning her B.S. in Nursing from the University of Texas at Arlington, Ms. Yonga obtained her M.S. in Nursing from the University of South Alabama and earned her Post Masters Certificate as a Family Nurse Practitioner from the American Academy of Nurse Practitioners National Certification Board in 2018. She has previous experience in rehabilitation medicine, and in family and urgent care.

Departing Staff

Dr. Joseph Hibbeln, Captain of the Commissioned Corps of the U.S. Public Health Service, retired from government service in June 2020 after 28 years at NIAAA. During this time, he received international recognition for initiating the study of the role of omega-3 fats in depressive and impulsive disorders. His research portfolio covered epidemiological studies on nutritional intake of omega-3 fatty acids, clinical studies on metabolism of nutritional fats, and treatment of mental health conditions by establishing a healthy balance of nutritional fatty acids.

Dr. Soundar Regunathan, Program Officer in the Division of Neuroscience and Behavior (DNB), retired from Federal service in August 2020. During his time at NIAAA, Dr. Regunathan developed robust research programs on alcohol and pain, alcohol and sleep, as well as research on sex differences in alcohol effects. He was the program officer for the Neurobiology of Adolescent Drinking in Adulthood (NADIA) Consortium and contributed significantly to DNB's research program on effects of adolescent drinking on the brain.

Dr. Corinde Wiers, Research Fellow in the Laboratory of Neuroimaging within the Division of Intramural Clinical and Biological Research, has accepted a position at the University of Pennsylvania as a tenure-track Assistant Professor of Psychiatry and Radiology. Her research laboratory will primarily study the effects of metabolic ketosis on alcohol consumption and brain energetics in alcohol use disorder using PET and MRI.

Budget Update

- NIAAA is currently closing out FY 2020.
 - The FY 2020 appropriation for NIAAA provided \$545.4 million. This represents a \$19.8 million (3.8%) increase over the FY 2019 budget level.
 - NIAAA estimates it will support a total of 739
 RPGs in FY 2020.
- FY 2021 budget is under development.

NIAAA Statement on Health Disparities, Diversity, and Structural Racism

At NIAAA, we recognize that diverse research teams broaden the scope of scientific inquiry, bring creative solutions to bear on complex scientific problems, and encourage research relevant to the health care needs of under-served populations.

NIAAA is committed to diversifying the scientific workforce by promoting training, funding opportunities, and success for African Americans and other minorities facing disparities in funding rates and/or opportunities to pursue a successful research career.

Our commitment extends to our intramural and extramural research programs and spans the pipeline from early education to established scientists. We are also committed to significantly expanding health disparities research so that all members of society may benefit from the work that we fund.

Health Disparities, Diversity, and Structural Racism (I)

NIH is considering how best to begin redressing structural racism in the biomedical research enterprise. These steps could include:

- Listening, learning, and self-assessing through engagement with internal and external stakeholders and experts
- Improving diversity and inclusion in the NIH and extramural workforce and changing the culture throughout the biomedical enterprise
- Advancing health disparities research, including how structural racism affects health as well as interventions and implementation
- Communicating findings and tracking results

Health Disparities, Diversity, and Structural Racism (II)

- Eliminate disparities in funding among grantees from underrepresented groups by:
 - Increasing diverse representation in peer review panels
 - Ensuring that diverse perspectives are reflected in post-review funding decisions
 - Increasing outreach to applicants from underrepresented groups
- Enhance training and career development opportunities for researchers from underrepresented groups by:
 - Establishing guidance for NIAAA training and research centers and consortia to expand recruitment, training, mentoring, and significant leadership opportunities to underrepresented scientists
 - Expanding diversity supplement program and career development awards
 - Increasing recruitment and participation of underrepresented individuals in intramural research at all levels
 - Expanding use of existing mechanisms for early training opportunities for underrepresented minorities ("pipeline programs" such as summer research and mentoring programs)

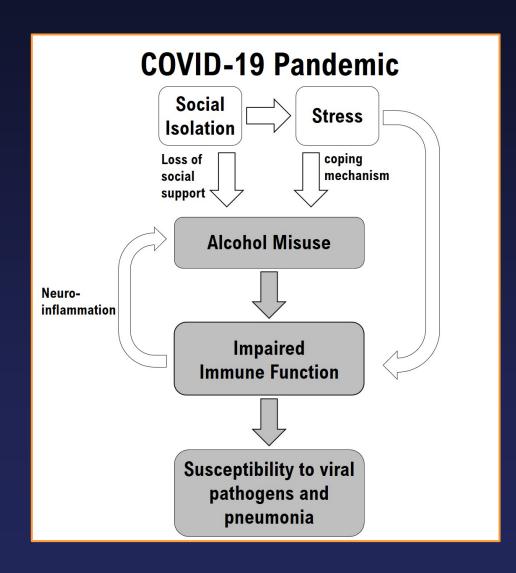
Health Disparities, Diversity, and Structural Racism (III)

Expand health disparities research by:

- Supporting alcohol projects that incorporate analyses of social determinants of health disparities, such as systemic racism, to inform intervention development
- Increasing funding opportunities for research on alcohol-related health disparities
- Applying health disparities research findings towards the development of novel basic research hypotheses in priority areas such as adversity and social variables
- Ensure that our research and outreach benefits underserved communities by:
 - Increasing NIAAA outreach efforts to populations disproportionately affected by alcohol misuse
 - Encouraging similar efforts by NIAAA-funded research centers and consortia

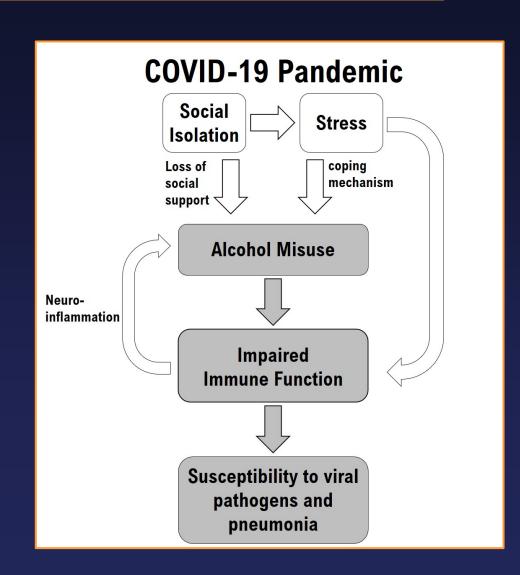
Impact of COVID-19 Pandemic on Alcohol Use and Treatment

- Physical distancing can lead to social isolation or loss of social support, which can lead to stress.
 Stress and uncertainty associated with the pandemic may prompt more people to drink alcohol to cope. For those in recovery, stress related to the pandemic could precipitate relapse.
- Physical distancing poses challenges for treatment and recovery. Face-to-face therapy and in-person mutual support group meetings may not be possible, but telehealth and virtual meetings can be helpful options for individuals seeking treatment or in recovery from AUD.



Impact of Alcohol Use on COVID-19 Pandemic

- The biological effects of alcohol could also exacerbate the pandemic. Alcohol compromises immune function, increasing the risk and severity of lung infections. Chronic alcohol consumption increases the risk for acute respiratory distress syndrome (ARDS), with increased need for mechanical ventilation, prolonged intensive care unit stay, and higher incidence of mortality.
- Alcohol is also known to produce behavioral disinhibition and can promote risky behavior with both friends and strangers.



NIAAA Participation in NIH-wide COVID-19 Activities

NIH Intramural Targeted Anti-COVID-19 (ITAC) program

Drs. Vijay Ramchandani and Nancy Diazgranados were awarded funding for their project "COVID-19 Pandemic Impact on Alcohol (PIA) – A Natural History Study."

NIH Rapid Acceleration of Diagnostics (RADx) Programs
Underrepresented Populations (RADx-UP) – focuses on
underserved and vulnerable populations disproportionately
affected by the pandemic

Radical (RADx-rad) – supports new, non-traditional approaches to address current gaps in COVID-19 testing and surveillance

NIAAA Participation in NIH-wide COVID-19 Activities, con't

Trans-NIH Working Groups

- Social, Behavioral, and Economic Health Impacts of COVID-19
- Pregnant and Lactating Women and Children
- Bringing NIH Clinical Trial Networks Together
- Preclinical Therapeutic Discovery

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)
Initiative - public-private partnership to develop a coordinated research
strategy for prioritizing and speeding development of the most promising
treatments and vaccines

NIH COVID-19 Candidate and Technologies Portal Review Group - performs initial triage for all applications submitted to the Portal for data on diagnostic, therapeutic, vaccine, and other candidates or technologies with near-term potential for testing against COVID-19

NIH-wide COVID-19 Funding Opportunities with NIAAA Participation

- Emergency Awards RADx-rad:
 - Automatic Detection and Tracing of SARS-CoV-2 (U01 Clinical Trial Not Allowed) <u>RFA-OD-20-014</u> (Administered by NIAAA)
 - Novel Biosensing for Screening, Diagnosis and Monitoring of COVID-19
 From Skin and The Oral Cavity (Fast-Track STTR or R44 Clinical Trial Not Allowed)
 RFA-OD-20-021; RFA-OD-20-020
 - Data Coordination Center (U24 Clinical Trial Not Allowed) RFA-OD-20-019
 - Screening for COVID-19 by Electronic-Nose Technology (SCENT) (U18 -Clinical Trial Not Allowed) <u>RFA-OD-20-017</u>
 - Multimodal COVID-19 surveillance methods for high risk clustered populations (R01 - Clinical Trial Optional) <u>RFA-OD-20-016</u>
- Digital Healthcare Interventions to Address the Secondary Health Effects Related to Social, Behavioral, and Economic Impact of COVID-19 (R01 - Clinical Trial Optional) PAR-20-243
- Community Interventions to Address the Consequences of the COVID-19 Pandemic among Health Disparity and Vulnerable Populations (R01 - Clinical Trial Optional) PAR-20-237

COVID-19 NOSIs are listed in the Director's Report.

NIAAA Funding Opportunity Announcements

- Collaborative Partnership between Research Centers in Minority Institutions (RCMI) and Alcohol Research Centers (U54 - Clinical Trial Optional): <u>RFA-AA-20-010</u>
- Alcohol-HIV/AIDS Program Project Comorbidities, Coinfections, and Complications Research: Intervention and Cross-Cutting Foundational Research (P01 - Clinical Trial Optional): <u>RFA-AA-20-009</u>

NOSIs

- Epidemiology and Prevention in Alcohol Research: <u>NOT-AA-20-017</u>
- Secondary Analyses of Existing Alcohol Research Data: NOT-AA-20-018
- Alcohol and Aging: <u>NOT-AA-20-019</u>

NIAAA participation in NIH-wide FOAs

NIAAA is currently participating in over 20 FOAs and NOSIs, including:

- BRAIN Initiative:
 - Data Archives for the BRAIN Initiative (R24 Clinical Trial Optional) <u>RFA-MH-20-600</u>
 - Theories, Models and Methods for Analysis of Complex Data from the Brain (R01 - Clinical Trial Not Allowed) <u>RFA-EB-20-002</u>
 - Proof of Concept Development of Early Stage Next Generation Human Brain Imaging (R01 - Clinical Trial Not Allowed) <u>RFA-EB-20-001</u>
- Mechanism for Time-Sensitive Drug Abuse Research (R21 -Clinical Trial Optional) PAR-19-064

Please refer to the Director's Report for full listing.

What's Ahead?

Mendelson Honorary Lecture (Virtual event)

September 22 at 1:30 p.m. (EDT)

Dr. Sandra A. Brown will present "Discerning Risks and Effects of Alcohol in the Midst of Adolescent Development."

Dr. Brown currently serves as Vice Chancellor for Research and Distinguished Professor of Psychology and Psychiatry at UC San Diego.

View the event at: https://videocast.nih.gov/watch=38535



Roundtable on NIAAA Definition of Recovery (Virtual event)

September 30 from noon to 3 p.m. (EDT)

NIAAA recently developed a definition for recovery from AUD in order to support recovery research and to guide the provision of AUD treatment. Development of NIAAA's definition of recovery will be described, followed by brief presentations by nine recovery experts and a discussion. *Dr. Brett Hagman is the contact for this event.*

Alcohol-Associated Liver Disease and Alcohol Use Disorder (Virtual event)

October 6 at 1:00 p.m. (EDT)

Experts in ALD and AUD will come together to provide insights for improving clinical trial design and recruitment and retention of patients with AUD and/or ALD.

Dr. Svetlana Radaeva is the contact for this event.

More Upcoming Virtual Events

Substance Abuse Prevention for Youth in Indigenous

Communities (Webinar)

October 8 at 1:00 p.m. (EDT)

NIAAA Liaison Meeting (Virtual event) October 13 at 1:00 p.m. (EDT)

NIAAA 50th Anniversary Lecture Series (Virtual event) November 30 and December 1, 2020



Details will be posted on the NIAAA website closer to the dates of these events:

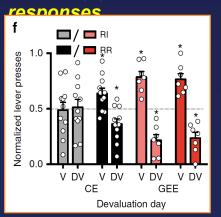
https://www.niaaa.nih.gov/news-events/meetings-events-exhibits

Research Highlights

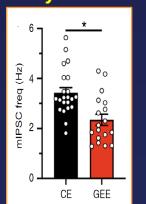
Gestational Alcohol Exposure Disrupts Cognitive Function and Striatal Circuits in Adult Offspring

This study examined the lasting effects of gestational alcohol exposure on disrupted cognitive function (assessed via habit- vs goal-directed behavior) in adult mice. Compared to controls, mice exposed to alcohol during gestation (GEE) were more likely to rely on cognitively demanding goal-directed decision making at the expense of more efficient, habit-guided decision making. This behavior was linked to altered GABAergic and endocannabinoid activity in the dorsolateral striatum (DLS), a brain region involved in learning and habit formation.

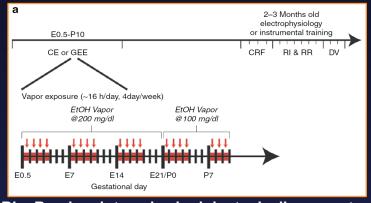
In GEE mice, both RI and RR were sensitive to devaluation, reflecting goal-directed



GEE mice have reduced GABAergic activity in DLS

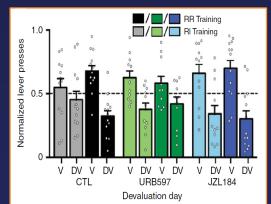


Gestational ethanol exposure paradigm



RI = Random interval schedule: typically promotes habit-guided responses (insensitive to devaluation)
RR = Random ratio schedule: typically promotes goal-directed responses (sensitive to devaluation)

Compounds that increase endocannabinoid concentrations mimic effects of GEE



These results demonstrate a mechanism for GEE-related cognitive deficits and identify a potential target for therapeutic intervention.

Citation: Cuzon Carlson VC, Gremel CM, and Lovinger DM. Nat Commun. 2020 May 22;11(1):2555.

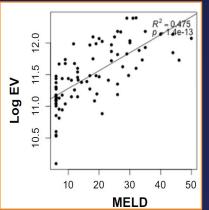
Circulating Extracellular Vesicles Carrying Sphingolipid Cargo for the Diagnosis and Dynamic Risk Profiling of Alcoholic Hepatitis

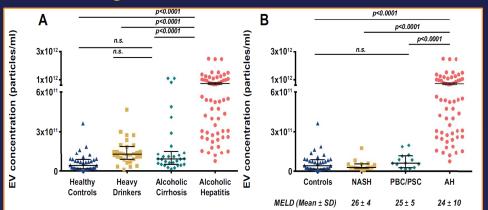
This study demonstrated the utility of plasma extracellular vesicle (EV) concentration and sphingolipid cargo as diagnostic and prognostic biomarkers for alcoholic hepatitis (AH). EVs isolated from plasma samples from healthy controls, heavy drinkers, and patients with other forms of liver disease were compared. EV counts were correlated with disease severity and were significantly higher in AH subjects than heavy drinkers without liver disease, patients with alcoholic cirrhosis, and MELD-matched patients with end-stage liver diseases not attributable to alcohol. Higher EV count was also associated with higher 90-day mortality for AH patients, permitting dynamic risk profiling.

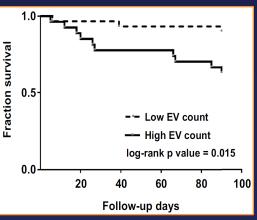
EV counts were correlated with disease severity (MELD scores)

EV counts were higher in AH subjects than (A) heavy drinkers without liver disease and patients with alcoholic cirrhosis, and (B) MELD-matched patients with end-stage liver diseases not attributable to alcohol

90-day survival was lower for AH patients with high EV count







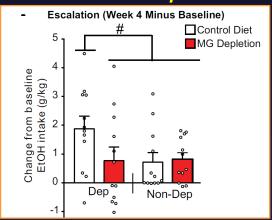
Microglia Control Escalation of Drinking in Alcohol-Dependent Mice: Genomic and Synaptic Drivers

This study investigated the role of microglia, the primary immune cells in the brain, in the development of alcohol dependence using a well-established mouse model of moderate and excessive drinking. Microglia (MG) depletion prevented neuroimmune-induced escalation in drinking, blocked the inflammatory response to alcohol, and decreased anxiety-like behavior during withdrawal.

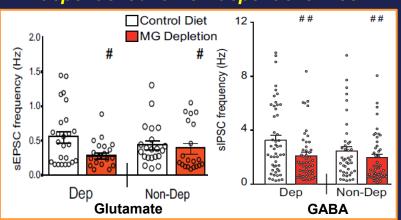
Further analyses demonstrated a link between microglia depletion and reduced GABAergic and glutamatergic transmission in the central nucleus of the amygdala (CeA).

This study suggests that microglia may regulate dependence-induced changes in neuronal function and have a role in the development and progression of alcohol use disorder.

MG depletion prevented escalation of alcohol intake in dependent mice.



MG depletion reduced glutamatergic and GABAergic transmission in CeA of dependent and non-dependent mice.

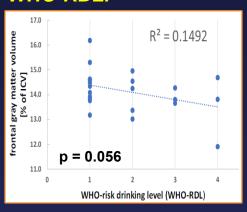


Not All is Lost for Relapsers: Relapsers with Low WHO Risk Drinking Levels and Complete Abstainers have Comparable Regional Gray Matter Volumes

Abstinence following treatment for AUD may not be readily achievable for all individuals. World Health Organization risk drinking levels (WHO-RDL) are proposed as alternative clinical trial endpoints.

Following AUD treatment, cortical and subcortical brain region volumes were assessed among 3 groups of patients: a group who maintained abstinence and two groups who relapsed to drinking (sorted by low vs higher WHO-RDL). Frontal gray matter volume was related to WHO-RDL, and "relapsers" with low WHO-RDL had frontal cortical brain volumes equivalent to those of complete abstainers after the same time period and larger than those of "relapsers" with higher WHO-RDL. These results suggest that WHO-RDL have meaningful structural neuroimaging correlates and that brain regional volumes are objective assessments that may help inform evidence-based criteria for success in AUD treatment or in clinical trials.

Correlation of frontal cortical volume with WHO-RDL.



Abstinent (ABST) and REL-low groups had similar frontal gray matter volumes. The REL-higher group had reduced volume compared to ABST and REL-low.

Table 3. Regional gray matter (GM) volumes by group as % of intracranial volume (F-statistics and follow-up post hoc tests from 3-group ANCOVA with recovery interval as covariate; pairwise comparisons are Bonferroni-corrected)									
Measure	ABST n = 26	REL ^{low} n = 17	REL ^{higher} n = 11	ANCOVA	p REL ^{low} versus REL ^{higher}	p REL ^{low} versus ABST	p REL ^{higher} versus ABST		
Frontal GM	14.8 ± 0.8	14.4 ± 0.7	13.8 ± 0.9	F(2, 51) = 6.97, p = 0.002	0.039	0.152	S 0.001		

Associations Between Medical Conditions and Alcohol Consumption Levels in an Adult Primary Care Population

Electronic health record data from a healthcare system that has integrated alcohol screening into routine primary care were analyzed to identify the associations between common medical conditions and different levels of alcohol use.

Among nearly 900,000 patients who reported alcohol use, those with chronic liver disease, chronic obstructive pulmonary disorder, or hypertension had higher odds for exceeding both daily and weekly alcohol guidelines associated with risk for AUD. These results may aid primary care clinicians in specific disease management strategies targeted at particularly vulnerable patients.

Adjusted associations of prevalent medical conditions with reporting unhealthy alcohol use

Conditionb Exceeding daily limits vs low-risk use Exceeding weekly limits vs low-risk use Exceeding both limits vs low-risk use Arthritis 1.02 (0.95-1.09) 0.98 (0.92-1.05) 0.89 (0.80-0.98) Asthma 1.03 (1.00-1.05) 0.93 (0.90-0.96)° 0.97 (0.93-1.00) Atherosclerosis 0.87 (0.84-0.91)° 1.00 (0.97-1.03) 0.93 (0.88-0.97) Atrial fibrillation 0.80 (0.74-0.87)° 1.12 (1.06-1.18)° 1.00 (0.92-1.09) Cancer 0.91 (0.87-0.95)° 1.06 (1.03-1.10)° 0.92 (0.87-0.97) Cerebrovascular disease 0.81 (0.67-0.97) 0.97 (0.84-1.12) 0.88 (0.70-1.10) Chronic kidney disease 0.91 (0.87-0.96) 0.87 (0.83-0.90)° 0.71 (0.66-0.76)° Chronic liver disease 1.07 (1.01-1.12) 1.09 (1.02-1.17) 1.42 (1.32-1.53)° COPD 1.16 (1.10-1.22)° 1.15 (1.09-1.20)° 1.15 (1.07-1.23)° Chronic pain 0.96 (0.94-0.99) 0.90 (0.86-0.93)° 0.84 (0.80-0.88)° Coronary disease 0.86 (0.82-0.91)° 1.07 (1.03-1.12) 0.85 (0.80-0.92)° Dementia 0.49 (0.32-0.76) 0.67 (0.54-0.83)° 0.45 (0.29-0.70		OR (95% CI) ^{c,d}					
Asthma 1.03 (1.00-1.05) 0.93 (0.90-0.96)° 0.97 (0.93-1.00) Atherosclerosis 0.87 (0.84-0.91)° 1.00 (0.97-1.03) 0.93 (0.88-0.97) Atrial fibrillation 0.80 (0.74-0.87)° 1.12 (1.06-1.18)° 1.00 (0.92-1.09) Cancer 0.91 (0.87-0.95)° 1.06 (1.03-1.10)° 0.92 (0.87-0.97) Cerebrovascular disease 0.81 (0.67-0.97) 0.97 (0.84-1.12) 0.88 (0.70-1.10) Chronic kidney disease 0.91 (0.87-0.96) 0.87 (0.83-0.90)° 0.71 (0.66-0.76)° Chronic liver disease 1.07 (1.01-1.12) 1.09 (1.02-1.17) 1.42 (1.32-1.53)° COPD 1.16 (1.10-1.22)° 1.15 (1.09-1.20)° 1.15 (1.07-1.23)° Chronic pain 0.96 (0.94-0.99) 0.90 (0.86-0.93)° 0.84 (0.80-0.88)° Coronary disease 0.86 (0.82-0.91)° 1.07 (1.03-1.12) 0.85 (0.80-0.92)° Dementia 0.49 (0.32-0.76) 0.67 (0.54-0.83)° 0.45 (0.29-0.70) Diabetes 1.11 (1.08-1.15)° 0.90 (0.86-0.93)° 0.96 (0.92-1.00) Epilepsy 0.94 (0.85-1.04) 1.05 (0.93-1.19) 1.03 (0.89-1.21) Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58)° Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13)° 1.37 (1.34-1.40)° 1.48 (1.44-1.52)° Injury or poisoning 1.06 (1.04-1.07)° 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91)° 0.72 (0.69-0.76)° 0.63 (0.59-0.67)° Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97)° 0.88 (0.84-0.91)° Osteoporosis/osteopenia 0.75 (0.70-0.79)° 0.64 (0.62-0.67)° 0.50 (0.46-0.54)° Parkinson disease/syndrome 0.44 (0.31-0.64)° 0.83 (0.69-1.01) 0.54 (0.37-0.80)	Condition ^b						
Atherosclerosis 0.87 (0.84-0.91)e 1.00 (0.97-1.03) 0.93 (0.88-0.97) Atrial fibrillation 0.80 (0.74-0.87)e 1.12 (1.06-1.18)e 1.00 (0.92-1.09) Cancer 0.91 (0.87-0.95)e 1.06 (1.03-1.10)e 0.92 (0.87-0.97) Cerebrovascular disease 0.81 (0.67-0.97) 0.97 (0.84-1.12) 0.88 (0.70-1.10) Chronic kidney disease 0.91 (0.87-0.96) 0.87 (0.83-0.90)e 0.71 (0.66-0.76)e Chronic liver disease 1.07 (1.01-1.12) 1.09 (1.02-1.17) 1.42 (1.32-1.53)e 0.70 COPD 1.16 (1.10-1.22)e 1.15 (1.09-1.20)e 1.15 (1.07-1.23)e 0.84 (0.80-0.88)e 0.96 (0.94-0.99) 0.90 (0.86-0.93)e 0.84 (0.80-0.88)e 0.86 (0.82-0.91)e 1.07 (1.03-1.12) 0.85 (0.80-0.92)e 0.86 (0.82-0.91)e 1.07 (1.03-1.12) 0.85 (0.80-0.92)e 0.80 Dementia 0.49 (0.32-0.76) 0.67 (0.54-0.83)e 0.45 (0.29-0.70) Diabetes 1.11 (1.08-1.15)e 0.90 (0.86-0.93)e 0.96 (0.92-1.00) Epilepsy 0.94 (0.85-1.04) 1.05 (0.93-1.19) 1.03 (0.89-1.21) Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58)e 0.99 (0.97-1.02) Hypertipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13)e 1.37 (1.34-1.40)e 1.48 (1.44-1.52)e 1.19 (1.09-1.03) 0.99 (0.97-1.02) Migraine 0.88 (0.85-0.91)e 0.72 (0.69-0.76)e 0.63 (0.59-0.67)e 0.50 (0.93-0.98) 0.94 (0.92-0.97)e 0.88 (0.84-0.91)e 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e 0.83 (0.69-1.01) 0.54 (0.37-0.80) 0.99 (0.97-0.01) 0.99 (0.97-0.01) 0.99 (0.97-0.01) 0.99 (0.97-0.01)e 0.54 (0.37-0.80)	Arthritis	1.02 (0.95-1.09)	0.98 (0.92-1.05)	0.89 (0.80-0.98)			
Atrial fibrillation 0.80 (0.74-0.87)° 1.12 (1.06-1.18)° 1.00 (0.92-1.09) Cancer 0.91 (0.87-0.95)° 1.06 (1.03-1.10)° 0.92 (0.87-0.97) Cerebrovascular disease 0.81 (0.67-0.97) 0.97 (0.84-1.12) 0.88 (0.70-1.10) Chronic kidney disease 0.91 (0.87-0.96) 0.87 (0.83-0.90)° 0.71 (0.66-0.76)° Chronic liver disease 1.07 (1.01-1.12) 1.09 (1.02-1.17) 1.42 (1.32-1.53)° COPD 1.16 (1.10-1.22)° 1.15 (1.09-1.20)° 1.15 (1.07-1.23)° Chronic pain 0.96 (0.94-0.99) 0.90 (0.86-0.93)° 0.84 (0.80-0.88)° Coronary disease 0.86 (0.82-0.91)° 1.07 (1.03-1.12) 0.85 (0.80-0.92)° Dementia 0.49 (0.32-0.76) 0.67 (0.54-0.83)° 0.45 (0.29-0.70) Diabetes 1.11 (1.08-1.15)° 0.90 (0.86-0.93)° 0.96 (0.92-1.00) Epilepsy 0.94 (0.85-1.04) 1.05 (0.93-1.19) 1.03 (0.89-1.21) Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58)° Hypertipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13)° 1.37 (1.34-1.40)° 1.48 (1.44-1.52)° Injury or poisoning 1.06 (1.04-1.07)° 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91)° 0.72 (0.69-0.76)° 0.63 (0.59-0.67)° Osteoprosis/osteopenia 0.75 (0.70-0.79)° 0.64 (0.62-0.67)° 0.50 (0.46-0.54)° Parkinson disease/syndrome 0.44 (0.31-0.64)° 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Asthma	1.03 (1.00-1.05)	0.93 (0.90-0.96) ^e	0.97 (0.93-1.00)			
Cancer 0.91 (0.87-0.95)e 1.06 (1.03-1.10)e 0.92 (0.87-0.97) Cerebrovascular disease 0.81 (0.67-0.97) 0.97 (0.84-1.12) 0.88 (0.70-1.10) Chronic kidney disease 0.91 (0.87-0.96) 0.87 (0.83-0.90)e 0.71 (0.66-0.76)e Chronic liver disease 1.07 (1.01-1.12) 1.09 (1.02-1.17) 1.42 (1.32-1.53)e COPD 1.16 (1.10-1.22)e 1.15 (1.09-1.20)e 1.15 (1.07-1.23)e Chronic pain 0.96 (0.94-0.99) 0.90 (0.86-0.93)e 0.84 (0.80-0.88)e Coronary disease 0.86 (0.82-0.91)e 1.07 (1.03-1.12) 0.85 (0.80-0.92)e Dementia 0.49 (0.32-0.76) 0.67 (0.54-0.83)e 0.45 (0.29-0.70) Diabetes 1.11 (1.08-1.15)e 0.90 (0.86-0.93)e 0.96 (0.92-1.00) Epilepsy 0.94 (0.85-1.04) 1.05 (0.93-1.19) 1.03 (0.89-1.21) Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58)e Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13)e 1.37 (1.34-1.40)e 1.48 (1.44-1.52)e Injury or poisoning 1.06 (1.04-1.07)e 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91)e 0.72 (0.69-0.76)e 0.63 (0.59-0.67)e Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97)e 0.88 (0.84-0.91)e Osteoprosis/osteopenia 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e Parkinson disease/syndrome 0.44 (0.31-0.64)e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer	Atherosclerosis	0.87 (0.84-0.91) ^e	1.00 (0.97-1.03)	0.93 (0.88-0.97)			
Cerebrovascular disease 0.81 (0.67-0.97) 0.97 (0.84-1.12) 0.88 (0.70-1.10) Chronic kidney disease 0.91 (0.87-0.96) 0.87 (0.83-0.90)° 0.71 (0.66-0.76)° Chronic liver disease 1.07 (1.01-1.12) 1.09 (1.02-1.17) 1.42 (1.32-1.53)° COPD 1.16 (1.10-1.22)° 1.15 (1.09-1.20)° 1.15 (1.07-1.23)° Chronic pain 0.96 (0.94-0.99) 0.90 (0.86-0.93)° 0.84 (0.80-0.88)° Coronary disease 0.86 (0.82-0.91)° 1.07 (1.03-1.12) 0.85 (0.80-0.92)° Dementia 0.49 (0.32-0.76) 0.67 (0.54-0.83)° 0.45 (0.29-0.70) Diabetes 1.11 (1.08-1.15)° 0.90 (0.86-0.93)° 0.96 (0.92-1.00) Epilepsy 0.94 (0.85-1.04) 1.05 (0.93-1.19) 1.03 (0.89-1.21) Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58)° Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Injury or poisoning	Atrial fibrillation	0.80 (0.74-0.87) ^e	1.12 (1.06-1.18) ^e	1.00 (0.92-1.09)			
Chronic kidney disease 0.91 (0.87-0.96) 0.87 (0.83-0.90)e 0.71 (0.66-0.76)e Chronic liver disease 1.07 (1.01-1.12) 1.09 (1.02-1.17) 1.42 (1.32-1.53)e COPD 1.16 (1.10-1.22)e 1.15 (1.09-1.20)e 1.15 (1.07-1.23)e Chronic pain 0.96 (0.94-0.99) 0.90 (0.86-0.93)e 0.84 (0.80-0.88)e Coronary disease 0.86 (0.82-0.91)e 1.07 (1.03-1.12) 0.85 (0.80-0.92)e Dementia 0.49 (0.32-0.76) 0.67 (0.54-0.83)e 0.45 (0.29-0.70) Diabetes 1.11 (1.08-1.15)e 0.90 (0.86-0.93)e 0.96 (0.92-1.00) Epilepsy 0.94 (0.85-1.04) 1.05 (0.93-1.19) 1.03 (0.89-1.21) Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58)e Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13)e 1.37 (1.34-1.40)e 1.48 (1.44-1.52)e Injury or poisoning 1.06 (1.04-1.07)e 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91)e 0.72 (0.69-0.76)e 0.63 (0.59-0.67)e 0.50 (0.46-0.54)e Osteoprosis/osteopenia 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e Osteoprosis/osteopenia 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e Osteoprosis/osteopenia 0.44 (0.31-0.64)e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer	Cancer	0.91 (0.87-0.95)e	1.06 (1.03-1.10) ^e	0.92 (0.87-0.97)			
Chronic liver disease 1.07 (1.01-1.12) 1.09 (1.02-1.17) 1.42 (1.32-1.53)° COPD 1.16 (1.10-1.22)° 1.15 (1.09-1.20)° 1.15 (1.07-1.23)° Chronic pain 0.96 (0.94-0.99) 0.90 (0.86-0.93)° 0.84 (0.80-0.88)° Coronary disease 0.86 (0.82-0.91)° 1.07 (1.03-1.12) 0.85 (0.80-0.92)° Dementia 0.49 (0.32-0.76) 0.67 (0.54-0.83)° 0.45 (0.29-0.70) Diabetes 1.11 (1.08-1.15)° 0.90 (0.86-0.93)° 0.96 (0.92-1.00) Epilepsy 0.94 (0.85-1.04) 1.05 (0.93-1.19) 1.03 (0.89-1.21) Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58)° Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13)° 1.37 (1.34-1.40)° 1.48 (1.44-1.52)° Injury or poisoning 1.06 (1.04-1.07)° 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.	Cerebrovascular disease	0.81 (0.67-0.97)	0.97 (0.84-1.12)	0.88 (0.70-1.10)			
COPD 1.16 (1.10-1.22)e 1.15 (1.09-1.20)e 1.15 (1.07-1.23)e Chronic pain 0.96 (0.94-0.99) 0.90 (0.86-0.93)e 0.84 (0.80-0.88)e Coronary disease 0.86 (0.82-0.91)e 1.07 (1.03-1.12) 0.85 (0.80-0.92)e Dementia 0.49 (0.32-0.76) 0.67 (0.54-0.83)e 0.45 (0.29-0.70) Diabetes 1.11 (1.08-1.15)e 0.90 (0.86-0.93)e 0.96 (0.92-1.00) Epilepsy 0.94 (0.85-1.04) 1.05 (0.93-1.19) 1.03 (0.89-1.21) Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58)e Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13)e 1.37 (1.34-1.40)e 1.48 (1.44-1.52)e 1.91 (1.09-1.01) Migraine 0.88 (0.85-0.91)e 0.72 (0.69-0.76)e 0.63 (0.59-0.67)e 0.50 (0.94-0.93)e 0.94 (0.92-0.97)e 0.88 (0.84-0.91)e 0.94 (0.92-0.97)e 0.88 (0.84-0.91)e 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e 0.87 (0.95-1.01) Parkinson disease/syndrome 0.44 (0.31-0.64)e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Chronic kidney disease	0.91 (0.87-0.96)	0.87 (0.83-0.90) ^e	0.71 (0.66-0.76) ^e			
Chronic pain 0.96 (0.94-0.99) 0.90 (0.86-0.93)e 0.84 (0.80-0.88)e Coronary disease 0.86 (0.82-0.91)e 1.07 (1.03-1.12) 0.85 (0.80-0.92)e Dementia 0.49 (0.32-0.76) 0.67 (0.54-0.83)e 0.45 (0.29-0.70) Diabetes 1.11 (1.08-1.15)e 0.90 (0.86-0.93)e 0.96 (0.92-1.00) Epilepsy 0.94 (0.85-1.04) 1.05 (0.93-1.19) 1.03 (0.89-1.21) Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58)e Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13)e 1.37 (1.34-1.40)e 1.48 (1.44-1.52)e Injury or poisoning 1.06 (1.04-1.07)e 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91)e 0.72 (0.69-0.76)e 0.63 (0.59-0.67)e Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97)e 0.88 (0.84-0.91)e Osteoporosis/osteopenia 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e Parkinson disease/syndrome 0.44 (0.31-0.64)e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Chronic liver disease	1.07 (1.01-1.12)	1.09 (1.02-1.17)	1.42 (1.32-1.53) ^e			
Coronary disease 0.86 (0.82-0.91)e 1.07 (1.03-1.12) 0.85 (0.80-0.92)e Dementia 0.49 (0.32-0.76) 0.67 (0.54-0.83)e 0.45 (0.29-0.70) Diabetes 1.11 (1.08-1.15)e 0.90 (0.86-0.93)e 0.96 (0.92-1.00) Epilepsy 0.94 (0.85-1.04) 1.05 (0.93-1.19) 1.03 (0.89-1.21) Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58)e Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13)e 1.37 (1.34-1.40)e 1.48 (1.44-1.52)e Injury or poisoning 1.06 (1.04-1.07)e 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91)e 0.72 (0.69-0.76)e 0.63 (0.59-0.67)e Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97)e 0.88 (0.84-0.91)e Osteoporosis/osteopenia 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e Parkinson disease/syndrome <td>COPD</td> <td>1.16 (1.10-1.22)^e</td> <td>1.15 (1.09-1.20)^e</td> <td>1.15 (1.07-1.23)^e</td>	COPD	1.16 (1.10-1.22) ^e	1.15 (1.09-1.20) ^e	1.15 (1.07-1.23) ^e			
Dementia 0.49 (0.32-0.76) 0.67 (0.54-0.83)e 0.45 (0.29-0.70) Diabetes 1.11 (1.08-1.15)e 0.90 (0.86-0.93)e 0.96 (0.92-1.00) Epilepsy 0.94 (0.85-1.04) 1.05 (0.93-1.19) 1.03 (0.89-1.21) Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58)e Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13)e 1.37 (1.34-1.40)e 1.48 (1.44-1.52)e Injury or poisoning 1.06 (1.04-1.07)e 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91)e 0.72 (0.69-0.76)e 0.63 (0.59-0.67)e Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97)e 0.88 (0.84-0.91)e Osteoporosis/osteopenia 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e Parkinson disease/syndrome 0.44 (0.31-0.64)e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer	Chronic pain	0.96 (0.94-0.99)	0.90 (0.86-0.93) ^e	0.84 (0.80-0.88) ^e			
Diabetes 1.11 (1.08-1.15)° 0.90 (0.86-0.93)° 0.96 (0.92-1.00) Epilepsy 0.94 (0.85-1.04) 1.05 (0.93-1.19) 1.03 (0.89-1.21) Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58)° Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13)° 1.37 (1.34-1.40)° 1.48 (1.44-1.52)° Injury or poisoning 1.06 (1.04-1.07)° 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91)° 0.72 (0.69-0.76)° 0.63 (0.59-0.67)° Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97)° 0.88 (0.84-0.91)° Osteoporosis/osteopenia 0.75 (0.70-0.79)° 0.64 (0.62-0.67)° 0.50 (0.46-0.54)° Parkinson disease/syndrome 0.44 (0.31-0.64)° 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Coronary disease	0.86 (0.82-0.91) ^e	1.07 (1.03-1.12)	0.85 (0.80-0.92) ^e			
Epilepsy 0.94 (0.85-1.04) 1.05 (0.93-1.19) 1.03 (0.89-1.21) Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58) ^e Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13) ^e 1.37 (1.34-1.40) ^e 1.48 (1.44-1.52) ^e Injury or poisoning 1.06 (1.04-1.07) ^e 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91) ^e 0.72 (0.69-0.76) ^e 0.63 (0.59-0.67) ^e Osteoparthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97) ^e 0.88 (0.84-0.91) ^e Osteoporosis/osteopenia 0.75 (0.70-0.79) ^e 0.64 (0.62-0.67) ^e 0.50 (0.46-0.54) ^e Parkinson disease/syndrome 0.44 (0.31-0.64) ^e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Dementia	0.49 (0.32-0.76)	0.67 (0.54-0.83) ^e	0.45 (0.29-0.70)			
Gastroesophageal reflux 0.99 (0.97-1.01) 0.99 (0.97-1.02) 0.97 (0.94-1.01) Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58)e Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13)e 1.37 (1.34-1.40)e 1.48 (1.44-1.52)e Injury or poisoning 1.06 (1.04-1.07)e 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91)e 0.72 (0.69-0.76)e 0.63 (0.59-0.67)e Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97)e 0.88 (0.84-0.91)e Osteoporosis/osteopenia 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e Parkinson disease/syndrome 0.44 (0.31-0.64)e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Diabetes	1.11 (1.08-1.15) ^e	0.90 (0.86-0.93) ^e	0.96 (0.92-1.00)			
Heart failure 0.85 (0.76-0.95) 0.99 (0.91-1.07) 0.84 (0.73-0.95) HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58) ^e Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13) ^e 1.37 (1.34-1.40) ^e 1.48 (1.44-1.52) ^e Injury or poisoning 1.06 (1.04-1.07) ^e 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91) ^e 0.72 (0.69-0.76) ^e 0.63 (0.59-0.67) ^e Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97) ^e 0.88 (0.84-0.91) ^e Osteoporosis/osteopenia 0.75 (0.70-0.79) ^e 0.64 (0.62-0.67) ^e 0.50 (0.46-0.54) ^e Parkinson disease/syndrome 0.44 (0.31-0.64) ^e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Epilepsy	0.94 (0.85-1.04)	1.05 (0.93-1.19)	1.03 (0.89-1.21)			
HIV 0.83 (0.74-0.93) 0.72 (0.60-0.87) 0.45 (0.34-0.58) ^e Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13) ^e 1.37 (1.34-1.40) ^e 1.48 (1.44-1.52) ^e Injury or poisoning 1.06 (1.04-1.07) ^e 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91) ^e 0.72 (0.69-0.76) ^e 0.63 (0.59-0.67) ^e Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97) ^e 0.88 (0.84-0.91) ^e Osteoporosis/osteopenia 0.75 (0.70-0.79) ^e 0.64 (0.62-0.67) ^e 0.50 (0.46-0.54) ^e Parkinson disease/syndrome 0.44 (0.31-0.64) ^e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Gastroesophageal reflux	0.99 (0.97-1.01)	0.99 (0.97-1.02)	0.97 (0.94-1.01)			
Hyperlipidemia 1.02 (1.00-1.04) 1.01 (0.99-1.03) 0.99 (0.97-1.02) Hypertension 1.11 (1.09-1.13)e 1.37 (1.34-1.40)e 1.48 (1.44-1.52)e Injury or poisoning 1.06 (1.04-1.07)e 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91)e 0.72 (0.69-0.76)e 0.63 (0.59-0.67)e Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97)e 0.88 (0.84-0.91)e Osteoporosis/osteopenia 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e Parkinson disease/syndrome 0.44 (0.31-0.64)e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Heart failure	0.85 (0.76-0.95)	0.99 (0.91-1.07)	0.84 (0.73-0.95)			
Hypertension 1.11 (1.09-1.13)e 1.37 (1.34-1.40)e 1.48 (1.44-1.52)e Injury or poisoning 1.06 (1.04-1.07)e 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91)e 0.72 (0.69-0.76)e 0.63 (0.59-0.67)e Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97)e 0.88 (0.84-0.91)e Osteoporosis/osteopenia 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e Parkinson disease/syndrome 0.44 (0.31-0.64)e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	HIV	0.83 (0.74-0.93)	0.72 (0.60-0.87)	0.45 (0.34-0.58) ^e			
Injury or poisoning 1.06 (1.04-1.07)e 0.99 (0.97-1.02) 0.98 (0.95-1.01) Migraine 0.88 (0.85-0.91)e 0.72 (0.69-0.76)e 0.63 (0.59-0.67)e Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97)e 0.88 (0.84-0.91)e Osteoporosis/osteopenia 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e Parkinson disease/syndrome 0.44 (0.31-0.64)e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Hyperlipidemia	1.02 (1.00-1.04)	1.01 (0.99-1.03)	0.99 (0.97-1.02)			
Migraine 0.88 (0.85-0.91)e 0.72 (0.69-0.76)e 0.63 (0.59-0.67)e Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97)e 0.88 (0.84-0.91)e Osteoporosis/osteopenia 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e Parkinson disease/syndrome 0.44 (0.31-0.64)e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Hypertension	1.11 (1.09-1.13) ^e	1.37 (1.34-1.40) ^e	1.48 (1.44-1.52) ^e			
Osteoarthritis 0.96 (0.93-0.98) 0.94 (0.92-0.97) ^e 0.88 (0.84-0.91) ^e Osteoporosis/osteopenia 0.75 (0.70-0.79) ^e 0.64 (0.62-0.67) ^e 0.50 (0.46-0.54) ^e Parkinson disease/syndrome 0.44 (0.31-0.64) ^e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Injury or poisoning	1.06 (1.04-1.07) ^e	0.99 (0.97-1.02)	0.98 (0.95-1.01)			
Osteoporosis/osteopenia 0.75 (0.70-0.79)e 0.64 (0.62-0.67)e 0.50 (0.46-0.54)e Parkinson disease/syndrome 0.44 (0.31-0.64)e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Migraine	0.88 (0.85-0.91) ^e	0.72 (0.69-0.76) ^e	0.63 (0.59-0.67) ^e			
Parkinson disease/syndrome 0.44 (0.31-0.64) ^e 0.83 (0.69-1.01) 0.54 (0.37-0.80) Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Osteoarthritis	0.96 (0.93-0.98)	0.94 (0.92-0.97) ^e	0.88 (0.84-0.91) ^e			
Peptic ulcer 1.10 (0.95-1.27) 0.98 (0.84-1.14) 1.03 (0.83-1.27)	Osteoporosis/osteopenia	0.75 (0.70-0.79) ^e	0.64 (0.62-0.67) ^e	0.50 (0.46-0.54) ^e			
	Parkinson disease/syndrome	0.44 (0.31-0.64) ^e	0.83 (0.69-1.01)	0.54 (0.37-0.80)			
Rheumatoid arthritis 0.94 (0.84-1.06) 0.92 (0.82-1.02) 0.77 (0.64-0.91)	Peptic ulcer	1.10 (0.95-1.27)	0.98 (0.84-1.14)	1.03 (0.83-1.27)			
Micandicid at antics 0.54 (0.04-0.51)	Rheumatoid arthritis	0.94 (0.84-1.06)	0.92 (0.82-1.02)	0.77 (0.64-0.91)			

Citation: Sterling SA, Palzes VA, Lu Y, Kline-Simon AH, Parthasarathy S, Ross T, Elson J, Weisner C, Maxim C, and Chi FW. JAMA Netw Open. 2020 May 1;3(5):e204687

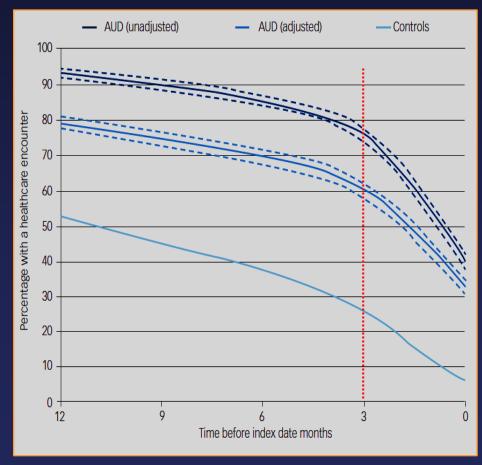
Healthcare Utilisation Prior to Suicide in Persons with Alcohol Use Disorders: National Cohort and Nested Case-Control Study

AUD is one of the strongest reported risk factors for suicidal behavior. This study examined healthcare utilization patterns prior to suicide in persons with AUD in a large population-based cohort followed from 2002 to 2015.

Of the people with AUD who died by suicide, 39.7% had a healthcare encounter within 2 weeks and 75.6% had a healthcare encounter within 3 months prior to death, compared with 6.3% and 25.4% of controls, respectively.

These results indicate that healthcare encounters at primary care and specialty outpatient clinics offer critical opportunities to identify active suicidality and intervene accordingly in patients with AUD.

Backward cumulative prevalence of a healthcare encounter prior to death by suicide



THANK YOU!

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