GERONTOLOGICAL SOCIETY OF AMERICA®

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Meaningful Lives As We Age

Friday, November 22, 2024

Christopher J. Lynch, PhD
Senior Advisor
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

RE: NOT-DK-24-026 Request for Information: Research Strategies for Addressing Obesity Heterogeneity

Via electronic mail:obesityheterogeneity@nih.gov

Dear Dr. Lynch,

On behalf of the Gerontological Society of America (GSA), we appreciate the opportunity to offer input on the request for information regarding research strategies for addressing obesity heterogeneity.

Our mission is to foster excellence, innovation, and collaboration to advance aging research, education, practice, and policy, and our vision is "meaningful lives as we age." GSA's 5,400 members include gerontologists, health professionals, behavioral & social scientists, biologists, demographers, economists, and many other disciplines. These experts study all facets of aging with a life-course orientation. The multidisciplinary nature of the GSA membership is a valued strength, enabling the Society to provide a 360-degree perspective on the issues facing our population as we age.

GSA continues to address the chronic disease of obesity as an opportunity to improve health outcomes across the life course and has worked to develop several resources for the care and management of obesity in older people.

This includes a model for care of older people that provides a useful framework for primary care providers in helping older people with obesity recognize their condition and take action to maintain a healthy weight. The GSA KAER Framework—Kickstart, Assess, Evaluate, and Refer (KAER)—supports primary care teams to better meet the needs of older people with obesity and overweight. Using this Framework with the tools and resources in the GSA Toolkit for the Management of Obesity in Older Adults, care teams can kickstart the discussion of weight with older people and their families; assess the presence of altered body fat amount, distribution, and/ or function; evaluate the individualized care plans developed for older adults with overweight and obesity; and refer patients to community resources.

In 2023, GSA hosted a roundtable discussion in Washington, D.C. with researchers, clinicians, and advocates who were asked to address key questions about obesity as a disease of body weight regulation and how outdated paradigms and perceptions about obesity can be improved among health professionals, policymakers, and the public. That discussion produced valuable information on key aspects of obesity care across the lifespan and particularly in clinical care for older adults. This report, titled "Bringing Obesity Management to the Forefront of Care for Older Adults: Seven Strategies for Success," presents the roundtable's insights, which are discussed in the framework of seven strategies for addressing barriers to quality obesity care for older people.

One of more than 40 Interest Groups, the GSA Obesity and Aging Interest Group is an interdisciplinary group of researchers, academics, clinicians, healthcare providers, program administrators, and policymakers focused on the important issues surrounding obesity and aging. Their goal is to foster collaboration, promote advocacy, and drive innovation around the assessment, treatment, and prevention of obesity in older adults.

We are pleased to offer the following comments and recommendations.

1. How best to study obesity heterogeneity based on scientific opportunity and potential health impact.

A first step would be to understand heterogeneity in tissue depots. Supporting studies in human and non-human primates that link measures of heterogeneity within tissue depots, between tissue depots, and overall patterns of adipose tissue distribution across the body and within other tissue (e.g. fatty infiltration in the muscle) would be helpful. It is important to have longitudinal data to understand when in the life course these patterns first manifest, and how they evolve with age. It is important to understand whether what's happening in other tissues affects adipose and vice-versa--linking different patterns of adipose tissue to gene transcription and tissue physiology in muscle, liver, blood, etc. It is also important to have follow-up data on health outcomes and disease risk correlates of different patterns of disease.

With respect to obesity specifically – it is important to understand the brain's role and to look at differences in brain structure and function (i.e., functional connectivity) to see if there are clusters of patterns within the central nervous system that map to other kinds of phenotypic variability. We suggest examining these patterns both at rest, in response to food cues, while fasting, while satiated, and in response to small doses of signaling molecules such as leptin. It would be important to see the extent to which relationships between social determinants of health and obesity phenotypes are mediated through such central mechanisms.

Also important is the use of different trial designs and precision medicine analytics in understanding the heterogeneity of older adults with obesity. There are a variety of different manners in leveraging heterogeneity (SMART designs, factorials) and data-driven approaches that are being used in other types of diseases and large consortium studies – e.g., Nutrition for Precision Health), and obesity and aging should not be an exception. NIH should offer an additional focus on translational science in thinking about how we can leverage science that is easily conducted, evaluated, and applicable to clinical care.

It would also be helpful to have a more rigorous definition of obesity heterogeneity, whether it is differences in its clinical/phenotypic manifestations, its consequences on health, the various etiologic factors, or its response to treatment, etc.

2. Promising strategies to reveal distinct mechanistic pathways [endotypes] underlying obesity subtypes, and their biomarkers.

We recognize that machine learning as a promising strategy in this area as larger amounts of data are collected from studies (see response to question 3). For example, artificial intelligence (AI) could be used to examine various subgroups of clustered phenotypes. We also encourage using biomarkers of aging to better understand subtypes and phenotypes and to better understand responders/non-responders to the treatment of obesity.

3. How advances in data science, including machine learning and artificial intelligence, can be leveraged to accelerate the development of precision approaches to prevention and treatment of obesity and its associated co-morbidities.

We recommend that study design come before analytic approaches. Machine learning and AI could be powerful tools to develop precision medicine-based approaches. However, there is still a need for large amounts of data that need to be collected from studies that could be intentionally designed to answer such questions. Such methods cannot tell us which patients will benefit from lifestyle modification, medications, or surgical approaches without sufficient common data elements across various high-risk subpopulations. There is a need for appropriate data collected rigorously and with designs that support causal inference. AI could be used to identify subgroups and phenotypes, using large data sources to identify subgroups or using small data sets for detailed phenotyping from biology to clinical details.

4. How can NIH best incorporate the expectation of inter-individual variability during the planning of obesity prevention or treatment trials [e.g., statistical plans for latent class or principal component analyses to capture or refine predictors of response or discover endotypes]?

Depending on what the expectation is, the impact may not be addressable in single studies. This may only be understood after the fact and through meta-analyses or data pooling. If there is a strong expectation that only certain "kinds" of obesity would be responsive to a given intervention, then we encourage recruitment based on risk factors for this subset. Encouraging diversity among study participants in terms of age, gender, ethnicity, and socioeconomic status can help ensure sufficient representation of specific endophenotypes, increasing the likelihood of successful subgroup analyses.

In addition, more advanced machine learning approaches (dynamic treatment responses) relying on heterogeneity capitalize on the importance of diversity rather than depending on homogeneous populations that may not be applicable to real-world populations. Having variety can tease out and make the study population more representative as to what is seen in usual clinical care. As we noted earlier, a stricter definition of obesity heterogeneity would be helpful. This would be helpful in exploring, for example, why some people with body mass index (BMI) of 35 kg/m^2 are otherwise relatively healthy and others are diabetic with significant cardiovascular disease. Quantifying such heterogeneity could be useful in identifying subpopulations of participants most likely to benefit from treatment.

5. Strategies that incorporate community factors, cultural, social, and economic factors, or other social determinants of health into endotypes.

We support an approach that measures these social determinants of health in harmonizable ways across studies. There is a vast need for more trials and data in older people over the age of 65 as there is a clear disparity in such data. We encourage focusing more on high-risk and at-risk populations who lack access to transportation, healthy food, internet access and telemedicine, and basic and modern infrastructure.

6. The potential role of obesity endotypes in discerning susceptibility to or resilience from obesity co-morbidities.

Rather than using the term "obesity co-morbidities," we encourage using the term "obesity-related complications."

Obesity is a chronic disease that leads to complications. Certain subtypes of endotypes (clinical/biological) may lead to specific outcomes, and some subtypes would not. A better understanding of these is needed, and more research (and funding) is critically needed in this regard. A translational geroscience approach would be a promising next step.

Additionally, the potential role of endotypes in determining susceptibility and resilience from obesity-related complications plays a different role in older people. There are many diseases where obesity is a risk factor in middle-aged people and associated as being a less severe disease and having rates of better survival in people 65 and older. It is critical to know if this is because the obesity phenotype differs in middle-aged versus older populations.

Note of specific interest to NIA: We are particularly interested in information on age-related variability in obesity outcomes and treatment response heterogeneity, the role of health disparities and biological mechanisms of obesity in aging, heterogeneity of the impact of obesity on longevity, healthy ageing, intervention refinement and optimization, along with outcome measure validation particularly in ageing.

To address this, additional data is needed in future and existing trials to examine the age-related variability in obesity outcomes and treatment response. Increased data is needed to determine variations and causations in older people who respond to treatment and those who are unresponsive to understand why the treatment is successful or unsuccessful.

Again, we thank you for this opportunity to offer input regarding research strategies in obesity heterogeneity. If you have any questions, please contact Patricia D'Antonio, Vice President of Policy and Professional Affairs at pdantonio@geron.org or 202-587-5880, or Jordan Miles, Director of Policy at jmiles@geron.org or 202-587-5884.

Sincerely,

James C. Appleby, BSPharm, MPH, ScD (Hon)
Chief Executive Officer