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Commentary

Reimagining obesity analyses: the need for new approaches to study obesity-related multimorbidity and event cascades

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Obesity is an urgent and major global public health challenge. Recent data from the Non-communicable Disease Risk Factor Collaboration estimates that over 880 million adults are living with obesity worldwide in 2022 [1]. In the United States, the prevalence of obesity reached 42.8% according to the 2017–2018 NHANES survey [2]. Projections indicate that obesity rates are expected to continue rising in the coming decades [3]. Obesity adversely affects both individual and population health and contributes substantially to global healthcare costs [4].

A comprehensive understanding of obesity is essential for managing its extensive impacts. Obesity stems from a blend of genetic, environmental, behavioral, and psychosocial factors [5]. Beyond the visible accumulation of excess fat and its physical burden, obesity disrupts the body through hormonal imbalances and metabolic dysfunction, driving a wide range of chronic diseases across multiple systems, such as type 2 diabetes (T2DM), hypertension, cardiovascular disease (CVD), chronic kidney disease (CKD), obstructive sleep apnea, nonalcoholic fatty liver disease, osteoarthritis, and certain cancers [6,7]. In addition to these chronic conditions, obesity also impairs overall well-being and quality of life [8]. While the health impacts of obesity are well recognized and extensively studied, most research has focused on its association with individual conditions, either cross-sectionally or over a defined follow-up period. This approach highlights the specific disease risks associated with obesity but overlooks its central role in driving a complex web of interconnected health outcomes. Obesity commonly triggers a cascade of conditions over time, underscoring the need for a framework that addresses multimorbidity and disease progression. A revamped approach to obesity research and analysis would better capture its full impact and more accurately predict the net health benefit of individual and population-wide obesity reduction.

1. The limitations of traditional approaches

Traditional research on obesity-related outcomes has largely centered around the time-to-first-event approach. While this methodology has been instrumental in identifying obesity as a major risk factor for a variety of diseases, it pays little attention to the complexity involved, as it fails to acknowledge the intricate relationships beneath the surface or recognize obesity as a "root cause" of various consecutive conditions.

The problem with focusing on time-to-first event is that it assumes a linear, isolated relationship between obesity and each condition, ignoring the fact that many individuals develop multiple chronic diseases concurrently or in a dependent sequence. For instance, an individual with obesity might develop hypertension first, followed by T2DM and then CKD. Similarly, another individual might progress from obesity to obstructive sleep apnea, then develop heart failure (HF), and eventually atrial fibrillation. These complex, multimorbid trajectories are not adequately captured in studies that only assess the risk of a single disease outcome, leading to an incomplete understanding of obesity's true cumulative impact on overall health.

Given the unique nature of obesity as an upstream and pervasive risk factor that influences multiple stages of disease progression, several analytical approaches have emerged. For instance, additive and interaction models have been used to explore how obesity, in combination with already prevalent conditions like T2DM, can significantly elevate cardiovascular risk or alter its effects depending on diabetes status. However, these approaches often treat obesity as one of many contributing factors, rather than acknowledging its central role in driving complex health trajectories.

The emerging concept of cardiovascular-kidney-metabolic (CKM) syndrome has helped to unify risk factors and conditions with shared underlying mechanisms, emphasizing a staged approach based on disease severity [9]. While the CKM syndrome provides a valuable clinical framework that stages related diseases—with obesity positioned as an earlier health condition—it does not fully reflect the cumulative or progressive nature of obesity-related risk over time. In particular, the model lacks the integration of temporal sequencing of comorbidities. Future iterations of the CKM construct may benefit from incorporating

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dynamic risk modeling to enhance its utility for research and population-level surveillance.

2. The rise of multimorbidity research

The existing multimorbidity research typically employs either cross-sectional or longitudinal approaches. The cross-sectional approach examines the prevalence and patterns of multiple diseases at a single point, providing insights into disease burdens and clustering within specific populations. By capturing the total number of conditions, this approach may highlight the greater burden of adverse health outcomes among individuals with obesity. Clustering analyses can further identify common patterns of co-occurring conditions such as T2DM, hypertension, and osteoarthritis. However, while cross-sectional studies offer a valuable snapshot of disease burden, they do not capture the dynamic progression or the sequence of those conditions over time.

Longitudinal approaches, on the other hand, allow for the tracking of disease development over time, offering a more complete picture of how obesity-related multimorbidity evolves. This methodology usually uses survival analysis, where the time to development of multiple diseases is tracked in a cohort. This allows for the identification of patterns in disease accumulation, such as which conditions tend to develop first and how they influence the risk of subsequent diseases. For example, the onset of hypertension in individuals with obesity may increase the risk of developing heart disease, which in turn may increase the likelihood of CKD. By mapping these trajectories, longitudinal multimorbidity studies can help identify critical points for intervention to prevent the cascade of disease progression.

Despite these advances, there is no universally accepted methodology for multimorbidity research [10]. Studies have used varying definitions of multimorbidity, applied different statistical methods, and examined diverse combinations of chronic conditions. This lack of standardization makes it difficult to compare findings across studies and limits the generalizability of results, while directly undervaluing obesity as a central risk factor.

3. Event cascades: a frontier format to study multimorbidity in obesity research

Event cascades map a sequence of health events unfolding over time, typically triggered by a single root condition—in this case, obesity. We believe that people with obesity follow distinct pathways in disease development, where each step's risk can be quantified through cascade analyses.

Event cascade analyses can reveal critical points for intervention. By mapping the progression from obesity to severe health outcomes, clinicians can pinpoint critical stages within the cascade where interventions yield the greatest clinical benefit, allowing for targeted strategies to halt or slow disease progression and maximize health outcomes. Informing these cascading risks is also critical for estimating the long-term burden of obesity, offering patients and health systems a more comprehensive understanding of their health trajectory and guiding long-term management strategies.

Compared to traditional multimorbidity research or multistate modeling, the event cascade framework offers a more clinically intuitive and temporally structured approach to understanding disease progression. While multistate models estimate transitions between predefined disease states and can account for competing risks or recurrent events, they often lack the capacity to fully characterize the directionality, conditional dependencies, and cumulative nature of sequential disease burdens. Time-varying survival analysis, though useful for capturing changes in exposures or covariates over time, generally remains anchored to a single endpoint and fails to model the interlinked progression from one disease to another. In contrast, event cascade analysis explicitly models the sequential unfolding of related health events, offering insight into both individual and population-level trajectories.

Studying event cascades is more challenging than traditional multimorbidity research, as it requires large datasets, long follow-up, and precise information on the timing and sequence of health events. The goal is not merely to identify which diseases cluster together, but to trace their exact development sequence and understand the accumulated risks of the factor of interest. Cascade nodes will be anchored to the first documented occurrence of specific obesity-related conditions, determined through standardized diagnostic codes or validated clinical definitions. The cascade can be followed until the end of a defined follow-up period, throughout the individual's lifespan, or until a hard endpoint such as HF or atherosclerotic CVD, depending on the exact research question. For instance, if the goal is to examine the 10-year downstream impact of obesity, an individual with obesity may be followed using electronic health records, documenting a progression from metabolic syndrome to T2DM and ultimately to HF by the end of the follow-up period. Cascade analysis allows for a comprehensive assessment of obesity's adverse effects and estimates the risk of developing subsequent conditions based on an individual's prior diagnoses, using approaches such as sequential Cox models or stratified survival analysis. By modeling these cascade pathways, we can gain insight into disease dynamics and inform more targeted prevention strategies.

In addition to the large sample sizes required, a major challenge in studying event cascades lies in selecting the appropriate diseases and determining their order of analysis. We recommend basing these decisions on two key factors: hypotheses about underlying pathophysiological mechanisms and insights derived from multimorbidity cluster analyses. A detailed approach is essential, as the sequence in which relevant conditions emerge may vary by factors such as age, sex, and genetics, requiring flexibility in event cascade studies across subgroups. Furthermore, the extensive datasets needed for cascade analyses are not always accessible, and even when available, their complexity can present significant analytical challenges.

4. A call to action

To truly understand the burden of obesity and identify effective interventions, we must go beyond conventional analytic approaches such as time-to-first-event, interaction, and additive analyses (Fig. 1).

We now have effective treatments for obesity. However, critical questions remain*: In whom should we intervene, and when?* Given that it is neither feasible nor cost-effective to treat everyone, there is an urgent need for modeling approaches that can identify high-risk individuals and determine the most effective and cost-efficient timing for intervention. These insights are vital not only for guiding clinical decision-making but also for informing policies that could profoundly impact healthcare spending, economic productivity, and public health on a large scale.

We call for coordinated efforts across disciplines to advance understanding of obesity-related multimorbidity and disease cascades, aiming to inform more precise, timely, and impactful prevention and treatment strategies. For researchers, there is a pressing need to leverage large-scale longitudinal datasets with sufficient detail on timing, sequencing, and clinical outcomes, such as the All of Us Research Program or the UK Biobank. Funding priorities should support the development and validation of cascade modeling approaches across diverse populations. For clinicians, cascade-based risk models could support more personalized care planning by identifying high-risk trajectories and informing when to initiate pharmacologic or behavioral interventions based on a patient's current health profile and disease stage. For policymakers, integrating cascade frameworks into cost-effectiveness analyses and predictive modeling can help prioritize prevention strategies, allocate resources more efficiently, and shape policies that address the long-term economic and societal burden of obesity.

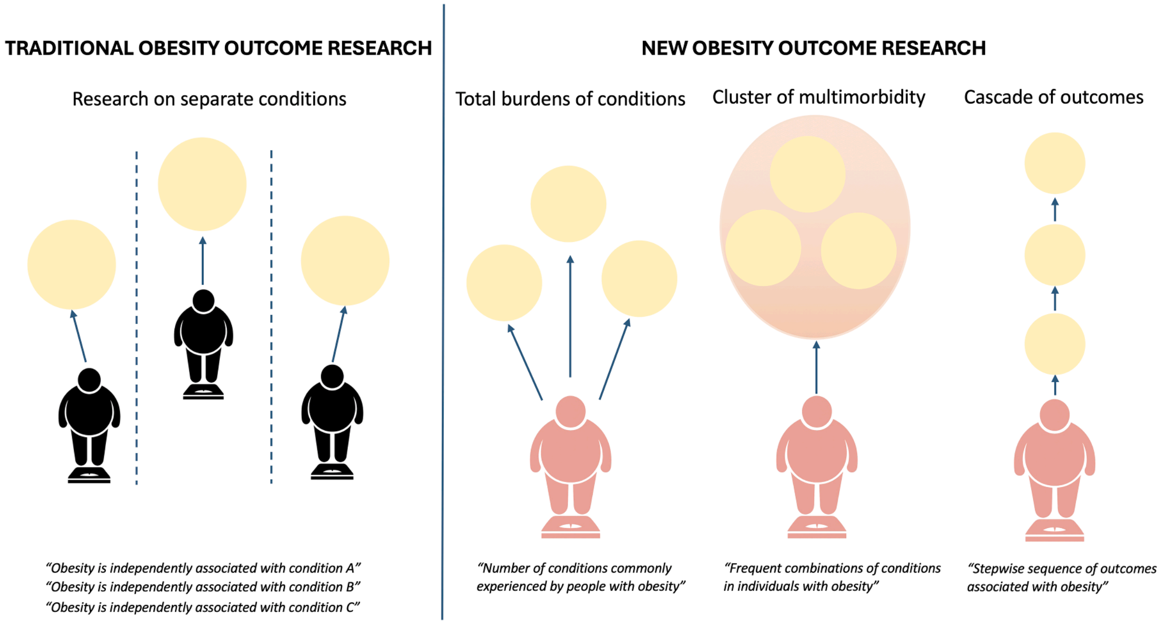

Fig. 1. Conceptual illustration of traditional vs. emerging approaches in obesity outcomes research.

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Declaration of competing interest

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