Unlocking the broad health benefits and risks of GLP-1 receptor agonist drugs

This study systematically analyzed 175 health outcomes in 2 million people using glucagon-like peptide-1 receptor agonists (GLP-1RAs) or other antihyperglycemics. GLP-1RAs reduce risks of neurocognitive, substance use, cardiovascular and respiratory disorders, but increase risks of gastrointestinal issues, hypotension and pancreatitis. The study provides important insights for clinical practice and future research.

This is a summary of:
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The question

GLP-1RAs have revolutionized the management of diabetes and obesity. Initially developed as antihyperglycemic agents, they have shown remarkable effectiveness in reducing body weight[1] and improving cardiometabolic health[2,3], driving a massive increase in usage[4]. However, emerging evidence has hinted at broader effects beyond those currently recognized[5]. These observations underscore the need for a systematic evaluation of GLP-1RAs across all possible health outcomes to comprehensively map their effectiveness and risks.

Here, we leveraged the breadth and depth of the healthcare databases of the US Department of Veterans Affairs (which operates the largest integrated health-care network in the USA) to comprehensively map the associations of GLP-1RAs with 175 health conditions, addressing an urgent societal and clinical need to better understand the broad effects of these widely used drugs. By doing so, the study addresses a critical knowledge gap, offering insights to improve clinical care, enhance adverse event monitoring, and advance mechanistic and clinical research to explore broadening therapeutic applications.

The Solution

This investigation used a discovery-based approach, analyzing a large cohort from the US Department of Veterans Affairs health-care databases. The study compared 215,970 individuals initiating GLP-1RAs with multiple control groups of nearly 2 million individuals, including users of other antihyperglycemic drugs (sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium–glucose cotransporter 2 inhibitors) and those continuing usual care without GLP-1RAs. By evaluating associations with 175 health outcomes, the study applied inverse probability weighting and statistical corrections for multiple comparisons to ensure robustness. This comprehensive design was well-suited to map both established and previously unrecognized benefits and risks of GLP-1RAs, providing a broad understanding of their pleiotropic effects across various health domains.

The study revealed that GLP-1RA use is associated with reduced risks of neurocognitive disorders, substance use disorders, cardiovascular and renal outcomes, and respiratory illnesses (Fig. 1). However, it also highlighted increased risks of gastrointestinal issues, hypotension, syncope, interstitial nephritis, and drug-induced pancreatitis. These findings underscore the broad health effects of GLP-1RAs, extending beyond their known benefits in diabetes and weight management. The results offer crucial insights into the potential clinical applications and safety considerations for GLP-1RAs, guiding both pharmacovigilance efforts and future research on their mechanisms and broader therapeutic potential.

The implications

The findings have broad implications for understanding the pleiotropic effects of GLP-1RAs beyond their established role in managing diabetes and obesity. They suggest potential applications in reducing risks of neurocognitive disorders, substance use disorders, and respiratory illnesses. This opens avenues for their use in preventive care and treatment of multimorbidity, particularly in conditions with overlapping metabolic or inflammatory pathways. The insights also highlight the need for targeted clinical trials to explore these emerging benefits and their underlying mechanisms further.

This research has some limitations. For example, the study did not assess variations within different GLP-1RA agents; it might have missed detecting weaker signals that require a larger cohort. The study also did not evaluate effectiveness and risks in specific subpopulations.

Future research should focus on evaluating the effects of GLP-1RAs in various populations and exploring their mechanisms of action across different conditions. Clinical trials targeting specific outcomes, such as neurocognitive or respiratory benefits, will help strengthen evidence. Understanding intra-class variability among GLP-1RAs and durability of health benefits should also be a priority.

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EXPERT OPINION

"This is an interesting study that uses a discovery approach to compare incident GLP-1RA users with a control group of incident users of other antihyperglycemics on the effectiveness and risks for a range of clinical outcomes. The paper is original in that few studies have looked at such a vast range of clinical outcomes, extending to respiratory conditions and thromboembolic events." **An anonymous reviewer.**

FIGURE

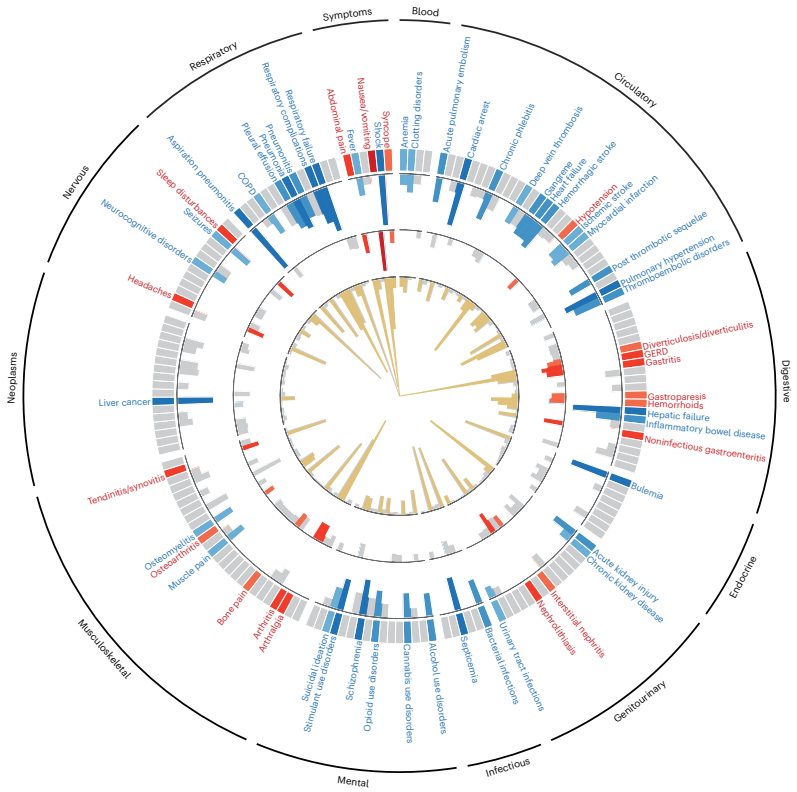

Fig. 1 | Broad health effects of GLP-1RAs across multiple organ systems. This circos plot shows an atlas of associations between GLP-1RAs and 175 health outcomes across 12 outcome categories. From outermost to innermost ring: (1) 12 outcome categories, (2) outcome names with decreased risks (blue), increased risks (red), and nonsignificant associations (grey), (3) heatmap of risk magnitudes, (4) reduced risk magnitudes, (5) increased risk magnitudes, and (6) statistical significance (negative log-transformed *P* values; yellow = significant, gray = nonsignificant). The figure highlights the systemic effects of GLP-1RAs — revealing decreased risks for many health conditions and increased risks for several adverse outcomes. © 2025, Xie, Y. et al.

BEHIND THE PAPER

Shortly after the first GLP-1RAs were approved in 2016, we started thinking about how effective they were compared with older antihyperglycemic agents. This led to a grant application in 2018 to investigate this issue. The grant was funded in 2020 around the time the COVID-19 pandemic was unfolding — to which we responded by swiftly shifting our focus to addressing the urgent public health questions related to COVID-19. All the while, we were witnessing an explosion in utilization of GLP-1RAs, as well as the emergence of studies hinting at broad health effects beyond diabetes and obesity. In late 2023, we embarked on this study to comprehensively evaluate the effectiveness and risks of GLP-1RAs on all health outcomes. The eureka moment came with the discovery of benefits for neurocognitive and addiction disorders, which points to a neurotropic effect of GLP-1RAs. **Z.A.-A.**

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FROM THE EDITOR

"While GLP-1RAs are now commercially available worldwide, the extent of their broad range of health effects are not known. By comprehensively reporting the health benefits and harms associated with GLP-1RA use, this study informs the potential for future clinical research and clinical indications for the right patients living with multiple long-term conditions." **Editorial Team, *Nature Medicine*.**