Volume 1, Issue 1, (2025)
1st January, 2025
DOI.org/10.71079/ASIDE.IM.1.1

ASIDE HEALTHCARE INTERNAL MEDICINE

www.ASIDEjournals.com

PUBLISHED BY
AMERICAN SOCIETY FOR INCLUSION, DIVERSITY, AND EQUITY IN HEALTHCARE (ASIDE)

ISSN (Print) 3065-9671
ISSN (Online) 3065-968X

ISSN 3065-9671
9 773065 967106

ASIDE Internal Medicine

ISSN (Print) 3065-9671, ISSN (Online) 3065-968X – see front matter
https://doi.org/10.71079/ASIDE.IM.1.1
Journal homepage: https://asidejournals.com/index.php/internal-medicine

ASIDE

ASIDE Internal Medicine

ASIDE INTERNAL MEDICINE

Table of Contents

ISSN (Print) 3065-9671, ISSN (Online) 3065-968X – see front matter
https://doi.org/10.71079/ASIDE.IM.1.1
Journal homepage: https://asidejournals.com/index.php/internal-medicine

ASIDE Internal Medicine

Original Article

The Impact of Idiopathic Intracranial Hypertension on Cardiovascular Disease Risk Among UK Women: An Obesity-Adjusted Analysis

Ahmed Y. Azzam[1, 2, 3#], Mahmoud M. Morsy[1, 4#], Mohamed Hatem Ellabban[5], Ahmed M. Morsy[6], Adham Adel Zahran[6], Mahmoud Nassar[7, 8], Omar S. Elsayed[1], Adam Elswedy[1], Osman Elamin[9], Ahmed Saad Al Zomia[10], Hana J. Abukhadijah[11], Hammam A. Alotaibi[12], Oday Atallah[13], Mohammed A. Azab[14], Muhammed Amir Essibayi[2, 15], Adam A. Dmytriw[16, 17], Mohamed D. Morsy[18], David J. Altschul[2, 15]*

1- Faculty of Medicine, October 6 University, 6th of October City, Giza, Egypt.
2- Montefiore-Einstein Cerebrovascular Research Lab, Albert Einstein College of Medicine, Bronx, NY, USA.
3- Director of Clinical Research and Clinical Artificial Intelligence, American Society for Inclusion, Diversity, and Health Equity (ASIDE), Delaware, USA.
4- Clinical Research Fellow, American Society for Inclusion, Diversity, and Health Equity (ASIDE), Delaware, USA.
5- Faculty of Medicine, Al-Azhar University, Cairo, Egypt.
6- Kasr Alainy Faculty of Medicine, Cairo University Hospitals, Cairo University, Cairo, Egypt.
7- Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, New York, USA.
8- Founder, American Society for Inclusion, Diversity, and Health Equity (ASIDE), Delaware, USA.
9- Department of Neurosurgery, Jordan Hospital, Amman, Jordan.
10- College of Medicine, King Khalid University, Abha, Saudi Arabia
11- Medical Research Center, Hamad Medical Corporation, Doha, Qatar.
12- Ophthalmology Department, Prince Sultan Military Medical City, Riyadh, Saudi Arabia.
13- Department of Neurosurgery, Hannover Medical School, Hannover, Germany.
14- Department of Neurosurgery, Cleveland Clinic Foundation, Cleveland, OH, USA.
15- Department of Neurological Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA.
16- Neuroendovascular Program, Massachusetts General Hospital & Brigham and Women's Hospital, Harvard University, Boston, MA, USA
17- Neurovascular Centre, Divisions of Therapeutic Neuroradiology & Neurosurgery, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada.
18- College of Medicine, King Khalid University, Abha, Saudi Arabia.

 # Denotes Equal Contribution as First Author

**** Corresponding author:** Ahmed Y. Azzam, MD, MEng, Montefiore-Einstein Cerebrovascular Research Lab, Albert Einstein College of Medicine, Bronx, NY, USA. Email Address: ahmedyazzam@gmail.com*

ISSN (Print) 3065-9671, ISSN (Online) 3065-968X – see front matter

Citation: Azzam AY, Morsy MM, Ellabban MH, et al. Idiopathic Intracranial Hypertension and Cardiovascular Diseases Risk in the United Kingdom Women: An Obesity-Adjusted Risk Analysis Using Indirect Standardization. ASIDE Int Med. 2024;1(1). doi:10.71079/h1fr8h68

https://doi.org/10.71079/h1fr8h68
Journal homepage: https://asidejournals.com/index.php/internal-medicine

ARTICLE INFO

Article history:
Received 28 Oct. 2024
Received in revised form 15 Nov. 2024
Accepted 17 Nov. 2024

Keywords:
Idiopathic Intracranial Hypertension
Pseudotumor Cerebri
Stroke
Ischemic Stroke
Cardiovascular Disease

ABSTRACT

Introduction: Idiopathic intracranial hypertension (IIH) is known to elevate cardiovascular disease (CVD) risk, but the extent to which obesity and IIH-specific factors contribute to this risk is not well understood. WE aim to separate the effects of obesity from IIH-specific factors on the risk of stroke and CVD, building on previous findings that indicate a two-fold increase in cardiovascular events in women with IIH compared to BMI-matched controls.

Methods: An obesity-adjusted risk analysis was conducted using Indirect Standardization based on data from a cohort study by Adderley et al., which included 2,760 women with IIH and 27,125 matched healthy controls from The Health Improvement Network (THIN). Advanced statistical models were employed to adjust for confounding effects of obesity and determine the risk contributions of IIH to ischemic stroke and CVD, independent of obesity. Four distinct models explored the interactions between IIH, obesity, and CVD risk.

Results: The analysis showed that IIH independently contributes to increased cardiovascular risk beyond obesity alone. Risk ratios for cardiovascular outcomes were significantly higher in IIH patients compared to controls within similar obesity categories. Notably, a synergistic effect was observed in obese IIH patients, with a composite CVD risk ratio of 6.19 (95% CI: 4.58-8.36, $p<0.001$) compared to non-obese controls.

Conclusions: This study underscores a significant, independent cardiovascular risk from IIH beyond obesity. The findings advocate for a shift in managing IIH to include comprehensive cardiovascular risk assessment and mitigation. Further research is required to understand the mechanisms and develop specific interventions for this group.

1. Introduction

Idiopathic intracranial hypertension (IIH) is a condition characterized by elevated intracranial pressure of unknown etiology, typically manifesting as papilledema with associated risks of visual loss and chronic disabling headache [1]. The incidence and economic burden of IIH are rising in parallel with global obesity trends [2]. While obesity is a well-established risk factor for IIH, with over 90% of patients being obese [3], the relationship between IIH and cardiovascular disease (CVD) risk remains poorly understood.

In the United States, studies indicate an incidence increase from 1.6 to 2.4 per 100,000 person-years in the general population, rising dramatically to 15-19 per 100,000 in women of childbearing age [4]. This rising disease burden encompasses both economic impacts, with annual costs exceeding millions of dollars in the US [5], and significant quality of life deterioration, including chronic pain, vision problems, and psychological distress [6].

Adderley et al. conducted a retrospective case-control population-based matched controlled cohort study using 28 years of data from The Health Improvement Network (THIN) database in the United Kingdom, THIN database is a longitudinal primary care database containing anonymized electronic health records from over 17 million patients in the United Kingdom, provides researchers with comprehensive clinical data for epidemiological studies and healthcare research. [7]. Their study suggested that women with IIH have a two-fold increased risk of cardiovascular events compared to BMI-matched controls. However, the mechanisms underlying this elevated risk and the relative contributions of obesity versus IIH-specific factors remained unclear.

The relationship between IIH and CVD risk involves multiple pathophysiological mechanisms beyond adiposity alone. Neuroendocrine dysfunction in IIH is characterized by elevated endogenous testosterone and androstenedione levels [8], distinct from exogenous supplementation or polycystic ovary syndrome (PCOS). This hormonal dysregulation may affect both cerebrospinal fluid (CSF) dynamics and cardiovascular function [9]. Additionally, the current literature studies demonstrate elevated levels of pro-inflammatory cytokines in IIH patients, potentially contributing to both intracranial pressure elevation and vascular dysfunction [9]. IIH patients exhibit distinct metabolic profiles, including altered glucose homeostasis and lipid metabolism, which may independently contribute to cardiovascular risk [9, 10]. Several additional risk factors may contribute to both IIH and CVD, including hormonal contraceptive use, vitamin A metabolism, sleep apnea, and chronic kidney disease [10-12].

Building upon Adderley et al.'s [7] findings, our study aims to disentangle the effects of obesity and IIH on stroke risk specifically. Obesity is a known independent risk factor for stroke, with an average hazard ratio (HR) of 2.29 reported in large-scale evidence [13]. By adjusting for this obesity-related risk, we seek to isolate the potential contribution of IIH itself to stroke incidence.

Our study employs an established methodological approach adapted from epidemiological research in obesity [14, 15] to simulate predicted ischemic stroke and CVD events in both IIH and control groups under normative weight conditions. This approach has been previously used in obesity literature [16, 17].

Understanding the relationship between IIH and their associated risks, independent of obesity, has important clinical implications. If IIH itself confers additional cardiovascular risk, it may warrant more aggressive management of modifiable risk factors and earlier implementation of preventive strategies in this patient population. Furthermore, elucidating the mechanisms underlying this potential association could reveal new therapeutic targets for reducing cardiovascular morbidity in IIH. Our study aims to build upon the foundational work of Adderley et al. [7] to further

investigate the complex interplay between IIH, obesity, and the associated risks. By employing innovative statistical methods to adjust for the confounding effects of obesity, we aim to provide crucial insights into the cardiovascular implications of IIH and inform evidence-based management strategies for this increasingly prevalent condition.

2. Methods

Building upon the foundational work of Adderley et al. [7], we conducted a retrospective analysis using data from their paper which was originally obtained through THIN, a large UK primary care database. Our study focused on women with IIH and matched controls, aiming to elucidate the independent effect of IIH on stroke and cardiovascular risks, distinct from the influence of obesity. Patients were excluded from the Adderley et al. [7], study if they had different diagnostic or clinical codes for conditions that could mimic IIH, specifically hydrocephalus or cerebral venous thrombosis, or any other cause of elevated intracranial pressure (ICP).

Additionally, in the baseline cohort selection, female patients were excluded if they did not have at least one-year of registration with an eligible general practice before cohort entry, to ensure adequate documentation of baseline covariates. For the analysis of individual CVD outcomes, patients with a record of the specific outcome of interest at baseline were excluded from the corresponding analysis, for composite CVD analysis, patients with any CVD at baseline were excluded; for type 2 diabetes analysis, patients with either type 1 diabetes or type 2 diabetes at baseline were excluded. For sensitivity analyses, additional exclusions were applied, including excluding women diagnosed with IIH after age 60 years, since IIH is rare among older adults and there may be potential misclassification errors in this age group.

2.1. Study Population and Data Source:

We utilized the cohort established by Adderley et al. [7], comprising 2,760 women with IIH and 27,125 matched controls. Participants were identified from THIN database records spanning January 1, 1990, to January 17, 2018. Controls were matched to IIH patients based on age, body mass index (BMI), and sex, with up to 10 controls per IIH case.

2.2. *Outcome Measures:*

Our primary outcome of interest was the incidence of composite CVD, heart failure, ischemic heart disease (IHD), ischemic stroke, transient ischemic attack (TIA), hypertension, and type 2 diabetes mellitus. We extracted the relevant data from the corresponding paper, following the coding and identification methods described by Adderley et al [7].

2.3. *Statistical Analysis:*

We extended the original analysis to estimate the independent effect of IIH on stroke and cardiovascular risks, accounting for the confounding effect of obesity. Our approach involved indirect standardization and adjustment with the application of a standardized morbidity ratio (SMR) approach [18-22], adapted to account for obesity as a confounding variable in relationship with IIH in women around the UK. To estimate the incidence of events in both the IIH and control cohorts under a hypothetical scenario of normal weight, we employed an adjustment method based on the average HR for obesity contributing to the event risk in women compared to healthy weight women in 13-year interval from the literature. This approach operates under the assumption that the HR remains constant throughout the 13-year study period and that the impact of obesity on the estimated events is independent of IIH status. We utilized Python 3.12 and its' associated statistical libraries to perform our statistical analysis. Initially, we calculated the observed HR for each event in the IIH group compared to the control group. Subsequently, we adjusted this observed HR by obesity HR to estimate the HR for IIH independent of obesity. Based on the current evidence, the average estimated HR of obesity contributing to composite CVD is 2.89 [23-29]. For obesity, ischemic stroke, and TIA risk, it is estimated around HR= 1.72 [23, 26, 30-36]. For obesity and heart failure risk, it is estimated around HR= 2.61 [37-43]. For obesity and hypertension risk, it is estimated around HR= 2.09 [44-50]. For obesity and IHD risk, it is estimated around HR= 1.8 [23, 24, 26, 28, 30, 51, 52]. And for obesity and type 2 diabetes mellitus risk, it is estimated to be around HR= 4.0 [53-60].

We calculated the HR for each event in the IIH group compared to the control group through the following equation:

$$HR = (IIH\ events\ /\ IIH\ total)\ /\ (Control\ events\ /\ Control\ total)$$

We then adjusted this observed HR by the established HR for obesity in association with the potential risk to estimate the HR for IIH independent of obesity:

$$Adjusted\ HR = Observed\ HR\ /\ Obesity\ HR$$

Using this adjusted HR, we predicted the number of events in both groups under normative weight conditions:
For the IIH group:

$$Predicted\ IIH\ events = (Adjusted\ HR \times Control\ events \times IIH\ total)\ /\ Control\ total$$

For the control group:

$$Predicted\ Control\ events = Control\ events\ /\ Obesity\ HR$$

Using this adjusted HR, we then calculated the predicted number of events in both the IIH and control groups under the assumption of normal weight. This was accomplished by applying the adjusted HR to the control group event rate and scaling for the respective group sizes. For the control group, we divided the observed events by obesity HR to estimate events under normal weight conditions.

This method allows for a comparative analysis of events risk between IIH and control populations, while attempting to control the confounding effect of obesity. It provides insight into the potential independent risk associated with IIH and allows for estimation of event rates under hypothetical normal weight conditions.

2.4. *Ethical Considerations:*

This study adhered to the ethical approval obtained by Adderley et al. [7] from the NHS South-East Multicenter Research Ethics Committee. We did not involve direct analysis of the dataset rather than building customized statistical modelling based on the provided data and metrics from Adderley et al. research paper [7].

3. Results

3.1. Baseline Characteristics:

The original retrospective cohort study by Adderley et al. [7] encompassed 29,885 participants, stratified into 2,760 (9.2%) women with IIH and 27,125 (90.8%) controls. The incident cohort comprised 48.2% and 46.7% of the IIH and control groups, respectively. Both cohorts were predominantly under 60 years of age (98.1% IIH, 95.2% control), with identical median ages of 32.1 years (IQR: 25.62-42.00 IIH, 25.71-42.06 control). Socioeconomic status, assessed via Townsend Deprivation Quintiles, showed a comparable distribution between groups, with a slight overrepresentation of controls in the least deprived quintiles. Smoking habits differed significantly: the IIH cohort exhibited higher rates of current smoking (30.8% vs 22.6%) and lower rates of non-smoking (46.5% vs 55.5%).

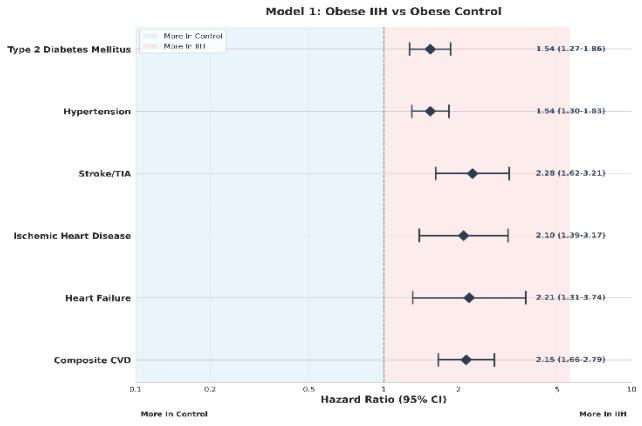


Figure 1: Model 1 – Obese IIH vs Obese Control Forest Plot.

Anthropometric data revealed marginally higher median BMI in the IIH group (34.80, IQR: 29.30-40.30) compared to controls (34.30, IQR: 29.00-39.70). Notably, both groups demonstrated a high prevalence of obesity (BMI >30), affecting 62.6% and 60.9% of the IIH and control cohorts, respectively. Comorbidity profiles and pharmacological interventions showed distinct patterns. The IIH cohort demonstrated a higher prevalence of migraine (21.0% vs. 11.9%), hypertension (13.8% vs. 9.2%), and marginally increased rates of lipid-lowering medication use (6.5% vs. 5.8%). Furthermore, baseline cardiovascular morbidity was more pronounced in the IIH group, with elevated rates of ischemic heart disease (1.3% vs. 0.9%) and ischemic stroke/TIA (1.7% vs 0.7%). Interestingly, type 2 diabetes mellitus prevalence was slightly lower in the IIH cohort (4.7% vs. 5.2%) (**Table 1**).

3.2. Statistical Analysis:

In this analysis, we employed four distinct statistical models to elucidate the complex interrelationships between IIH, obesity, and CVD risk. These models were strategically designed to disentangle the individual and combined effects of IIH and obesity on CVD outcomes.

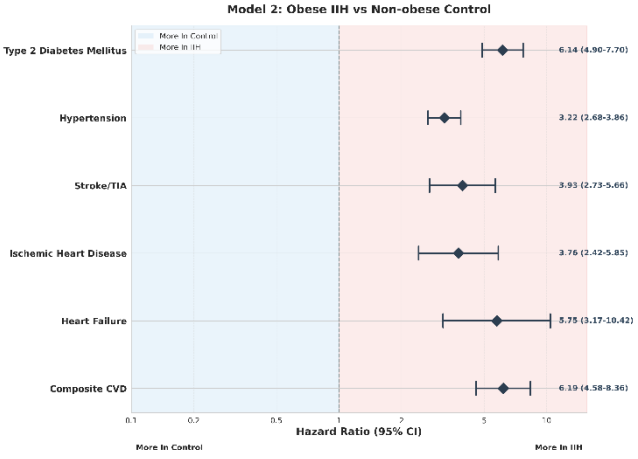
Model 1 (Obese IIH vs Obese Control) was constructed to isolate the effect of IIH within an obese population, effectively controlling for the confounding factor of adiposity. Model 2 (Obese IIH vs Non-obese Control) provided a comprehensive view of the combined impact of IIH and obesity compared to individuals without either condition. Model 3 (Non-obese IIH vs Obese Control) offered a unique perspective, juxtaposing the cardiovascular risks associated with IIH in non-obese individuals against those attributed to obesity alone. Model 4 (Non-obese IIH vs. Non-obese Control) isolated the impact of IIH in a non-obese population, providing critical insights into the condition's effects independent of obesity (**Table 2**).

Table 1: Baseline Characteristics of the Included Individuals in the Original Study.

Variable	Number, (%)	
	Women With IIH (Exposed Group)	**Women Without IIH (Control Group)**
Population	2760 (9.2)	27 125 (90.8)
Incident Cohort	1331 (48.2)	12 679 (46.7)
Population Aged < 60 y	2709 (98.1)	25 811 (95.2)
Age, Median (IQR), y	32.1 (25.62-42.00)	32.1 (25.71-42.06)
Townsend Deprivation Quintile		
1 (Least deprived)	361 (13.1)	4268 (15.7)
2	381 (13.8)	4397 (16.2)
3	532 (19.3)	5174 (19.1)
4	538 (19.5)	5122 (18.9)
5 (Most deprived)	454 (16.5)	4134 (15.2)
Missing data	494 (17.9)	4030 (14.9)
Smoking Status		
Nonsmoker	1284 (46.5)	15 058 (55.5)
Ex-smoker	502 (18.2)	4573 (16.9)
Smoker	849 (30.8)	6134 (22.6)
Missing data	125 (4.5)	1360 (5.0)
BMI, median (IQR)	34.80 (29.30-40.30)	34.30 (29.00-39.70)
Body Mass Index (BMI)		
<25	246 (8.9)	2561 (9.4)
25-30	416 (15.1)	4203 (15.5)
>30	1728 (62.6)	16 514 (60.9)
Missing data	370 (13.4)	3847 (14.2)
Current lipid prescription	180 (6.5)	1572 (5.8)
Migraine	580 (21.0)	3247 (11.9)
Outcomes at Baseline		
Heart Failure	8 (0.3)	58 (0.2)
IHD	35 (1.3)	245 (0.9)
Ischemic Stroke / TIA	46 (1.7)	189 (0.7)
Hypertension	380 (13.8)	2500 (9.2)
Type 2 Diabetes Mellitus	130 (4.7)	1425 (5.2)

Abbreviations: IIH= Idiopathic Intracranial Hypertension; IQR= Interquartile Range; BMI= Body Mass Index; IHD= Ischemic Heart Disease; TIA= Transient Ischemic Attack

Figure 2: Model 2 – Obese IIH vs Non-Obese Control Forest Plot.



Our findings revealed a nuanced and clinically significant relationship between IIH, obesity, and cardiovascular risk. In Model 1 **Figure 1**, IIH was consistently associated with elevated risks across all measured outcomes. The risk ratios (RR) ranged from 1.54 (95% CI: 1.27-1.86, p<0.001) for type 2 diabetes mellitus to 2.28 (95% CI: 1.62-3.21, p<0.001) for stroke/TIA. This uniform pattern of risk elevation suggests that IIH

confers additional cardiovascular risk beyond that attributed to obesity alone, a finding of relevance in clinical risk stratification.

Model 2, **Figure 2** demonstrated even more pronounced risk elevations, with the composite CVD risk reaching a striking RR of 6.19 (95% CI: 4.58-8.36, p<0.001). This marked increase suggests a potential synergistic effect between IIH and obesity on cardiovascular health, which may have significant implications for patient management and therapeutic interventions. Notably, the risk for heart failure in this model was particularly elevated (RR 5.75, 95% CI: 3.17-10.42, p<0.001), highlighting the need for vigilant cardiac monitoring in obese IIH patients.

Interestingly, Model 3, **Figure 3**, presented a more complex picture. The non-significant risk ratios for most outcomes in this model suggest that non-obese individuals with IIH may not have significantly different CVD risks compared to obese individuals without IIH. This finding underscores the profound impact of obesity on cardiovascular health, potentially rivaling or even overshadowing the effects of IIH in certain contexts. Of note in this model was the significantly reduced risk of type 2 diabetes mellitus in non-obese IIH patients compared to obese controls (RR 0.40, 95% CI: 0.28-0.57, p<0.001). This intriguing paradox may offer valuable insights into the underlying pathophysiology of both conditions and warrants further mechanistic investigation.

Model 4, **Figure 4** provided robust corroboration of IIH as an independent risk factor, with significant risk elevations observed across all outcomes in non-obese IIH patients compared to non-obese controls. The composite CVD risk in this model (RR 2.18, 95% CI: 1.41-3.39, p<0.001) closely mirrored that observed in Model 1, further supporting the notion that IIH confers cardiovascular risk independent of obesity status. This finding has important implications for the management of non-obese IIH patients, who may be at underappreciated cardiovascular risk.

Ranking the CVD risks for IIH patients based on our data reveals the highest risk ratios in Model 2, with the following hierarchy: composite CVD (RR 6.19) > heart failure (RR 5.75) > stroke/TIA (RR 3.93) > ischemic heart disease (RR 3.76). This stratification underscores the critical importance of addressing both IIH and obesity in our highest-risk patients and may inform the development of targeted screening and intervention protocols. The data on type 2 diabetes mellitus warrant special consideration. The 6.14-fold increased risk (95% CI: 4.90-7.70, p<0.001) observed in obese IIH patients compared to non-obese controls (Model 2) is particularly striking. This marked elevation, coupled with the paradoxical risk reduction in non-obese IIH patients (Model 3), suggests a complex interplay between IIH, obesity, and metabolic dysfunction. These findings raise intriguing questions about potential shared pathophysiological mechanisms and may open new avenues for research into the neuroendocrine aspects of IIH. Hypertension, a known risk factor for both CVD and IIH progression, showed a consistent pattern of elevated risk across Models 1, 2, and 4. However, the reduced risk observed in Model 3 (RR 0.77, 95% CI: 0.61-0.97, p=0.03) adds another layer of complexity to our understanding of the relationship between IIH, obesity, and blood pressure regulation.

Table 2: Risk Contribution Calculations According to Different Hazard Regression Models.

Outcome	Women With IIH (Exposed Group)	Women Without IIH (Control Group)	P-value
Composite CVD			
Population, No.	2613	26 356	NA
Outcome events, No. (%)	68 (2.5)	328 (1.2)	NA
Person-years	12 809	132 930	NA
Crude incidence rate per 1000 person-years	5.31	2.47	NA
Follow-up, median (IQR), y	3.50 (1.34-7.11)	3.72 (1.51-7.39)	NA
Adjusted HR (95% CI)			
Model 1	2.15 [1.66 - 2.79]	NA	<.001**
Model 2	6.19 [4.58 - 8.36]	NA	<.001 **
Model 3	0.76 [0.50 - 1.15]	NA	0.2
Model 4	2.18 [1.41 - 3.39]	NA	<.001 **
Heart Failure			
Population, No.	2735	26 989	NA
Outcome events, No. (%)	17 (0.6)	78 (0.3)	NA
Person-years	13 445	136 357	NA
Crude incidence rate per 1000 person-years	1.26	0.57	NA
Follow-up, median (IQR), y	3.58 (1.38-7.26)	3.77 (1.52-7.50)	NA
Adjusted HR (95% CI)			
Model 1	2.21 [1.31 - 3.74]	NA	<.001**
Model 2	5.75 [3.17 - 10.42]	NA	<.001**
Model 3	0.91 [0.42 - 1.97]	NA	0.81
Model 4	2.37 [1.04 - 5.39]	NA	0.04*
IHD			
Population, No.	2698	26 749	NA
Outcome events, No. (%)	27 (0.9)	131 (0.5)	NA
Person-years	13 216	134 521	NA
Crude incidence rate per 1000 person-years	2.04	0.97	NA
Follow-up, median (IQR), y	3.56 (1.37-7.20)	3.73 (1.51-7.42)	NA
Adjusted HR (95% CI)			
Model 1	2.10 [1.39 - 3.17]	NA	<.001**
Model 2	3.76 [2.42 - 5.85]	NA	<.001**
Model 3	1.17 [0.68 - 1.99]	NA	0.57
Model 4	2.09 [1.20 - 3.65]	NA	<.01*
Stroke/TIA			
Population, No.	2674	26 755	NA
Outcome events, No. (%)	40 (1.5)	181 (0.7)	NA
Person-years	13 115	135 271	NA
Crude incidence rate per 1000 person-years	3.05	1.34	NA
Follow-up, median (IQR), y	3.51 (1.34-7.17)	3.76 (1.52-7.47)	NA
Adjusted HR (95% CI)			
Model 1	2.28 [1.62 - 3.21]	NA	<.001**
Model 2	3.93 [2.73 - 5.66]	NA	<.001**
Model 3	1.37 [0.89 - 2.09]	NA	0.15
Model 4	2.36 [1.51 - 3.67]	NA	<.001 **
Hypertension			
Population, No.	2232	23 566	NA
Outcome events, No. (%)	148 (6.2)	1059 (4.3)	NA
Person-years	10 505	115 800	NA
Crude incidence rate per 1000 person-years	14.09	9.15	NA
Follow-up, median (IQR), y	3.20 (1.26-6.40)	3.48 (1.43-6.94)	NA
Adjusted HR (95% CI)			
Model 1	1.54 [1.30 - 1.83]	NA	<.001**
Model 2	3.22 [2.68 - 3.86]	NA	<.001**
Model 3	0.77 [0.61 - 0.97]	NA	0.03*
Model 4	1.61 [1.26 - 2.05]	NA	<.001**
Type 2 Diabetes			
Population, No.	2510	24 901	NA
Outcome events, No. (%)	120 (4.6)	799 (3.1)	NA
Person-years	12 300	125 947	NA
Crude incidence rate per 1000 person-years	9.76	6.34	NA
Follow-up, median (IQR), y	3.49 (1.34-6.94)	3.62 (1.47-7.27)	NA
Adjusted HR (95% CI)			
Model 1	1.54 [1.27 - 1.86]	NA	<.001**
Model 2	6.14 [4.90 - 7.70]	NA	<.001**
Model 3	0.40 [0.28 - 0.57]	NA	<.001**
Model 4	1.59 [1.09 - 2.32]	NA	0.02*

* Denotes statistical significance, ** Denotes high statistical significance

Abbreviations: IIH= Idiopathic Intracranial Hypertension; CVD= Cardiovascular Disease; IQR= Interquartile Range; IHD= Ischemic Heart Disease; CI= Confidence Interval.

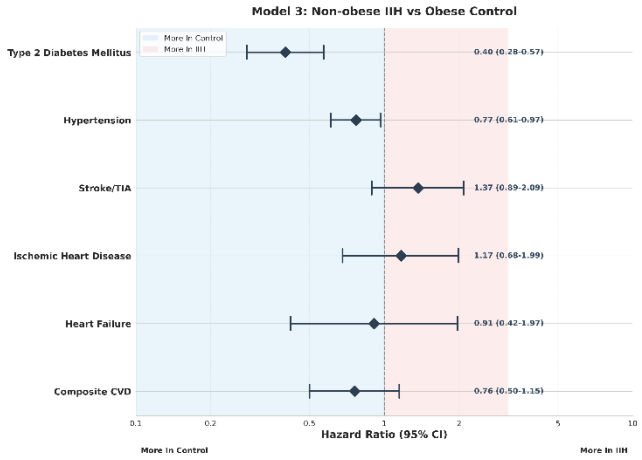


Figure 3: Model 3 – Non-Obese IIH vs Obese Control Forest Plot.

4. Discussion

In our obesity-adjusted analysis, we have uncovered several significant findings that advance our understanding of how IIH influences CVD outcomes. Our primary analysis demonstrated that IIH independently raises CVD risk, as we observed consistent risk elevations (RR= 1.54 to 2.28) across CVD outcomes in our obesity-matched cohorts. Perhaps our most striking finding was the synergistic interaction between IIH and obesity, we found a 6.19-fold increased risk of composite CVD events (95% CI: 4.58-8.36, p<0.001) in obese IIH patients compared to non-obese controls. Through our modelling, we also discovered a metabolic relationship: non-obese IIH patients showed CVD risks comparable to obese controls which is significantly higher than non-obese controls (RR 2.18, 95% CI: 1.41-3.39, p<0.001). We were particularly intrigued by the paradoxical relationship we observed with type 2 diabetes risk which was elevated in obese IIH patients but reduced in non-obese IIH patients compared to obese controls, suggesting more complex metabolic mechanisms than previously recognized (**Figure 5**).

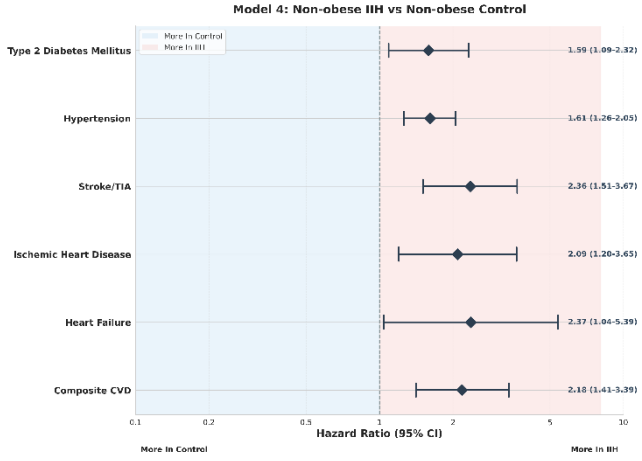


Figure 4: Model 4 – Non-Obese IIH vs Non-Obese Control Forest Plot.

The consistent elevation of risk ratios across Models 1 and 4, which compare IIH patients to controls within the same obesity strata, strongly suggests a distinct pathophysiological process intrinsic to IIH that exacerbates cardiovascular vulnerability. This finding aligns with emerging research on the neuroendocrine and metabolic perturbations in IIH. Recent metabolomic profiling by O'Reilly MW et al [8]. revealed a unique signature of altered androgen metabolism in CSF of IIH patients, characterized by elevated levels of testosterone and androstenedione. This androgen excess may represent a crucial link between IIH and cardiovascular risk through multiple mechanisms, including vascular dysfunction, inflammatory modulation, and metabolic dysregulation. Duckles and Miller [61] demonstrated that testosterone could induce vasoconstriction through both genomic and non-genomic pathways, potentially contributing to hypertension and altered cerebrovascular autoregulation in IIH.

The chronic elevation of in ICP is a characteristic of IIH may have direct and indirect effects on cardiovascular functions. Recent work by Wardlaw et al. [62] on the glymphatic system and intracranial fluid dynamics suggests that altered CSF flow and clearance in IIH may impair the removal of metabolic waste products from the brain. This accumulation of potentially toxic metabolites could exacerbate oxidative stress and vascular inflammation, contributing to the observed CVD risk.

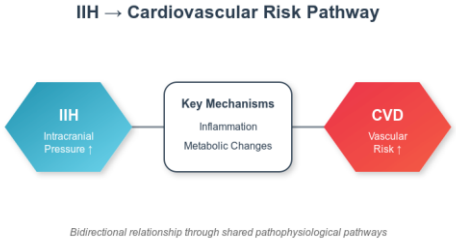


Figure 5: IIH and CVD Risk Pathway.

The striking risk elevations observed in Model 2 (Obese IIH vs Non-obese Control) reveal a synergistic interaction between IIH and obesity that amplifies CVD risk beyond the sum of their individual effects. This synergy likely arises from the convergence of multiple pathophysiological processes, including adipokine dysregulation, neuroendocrine activation, and hemodynamic alterations. Recent work by Hornby et al. [63] demonstrates that IIH patients exhibit a distinct adipokine signature, with particularly elevated CSF leptin levels. The combination of systemic and central adipokine dysregulation may create a uniquely pro-inflammatory and pro-thrombotic state. Moreover, the evidence by Markey K et al. [64] suggests that IIH patients may have altered cortisol metabolism, potentially exacerbating the metabolic and CVD consequences of obesity-related hypothalamic-pituitary-adrenal axis dysfunction.

The paradoxical findings regarding type 2 diabetes risk in our study—elevated in obese IIH patients but reduced in non-obese IIH patients compared to obese controls—challenge our current understanding of metabolic risk in IIH. This observation may be explained by the concept of "metabolic flexibility" proposed by Goodpaster and Sparks [65]. In non-obese IIH patients, the altered androgen metabolism and potential changes in adipose tissue function may confer a degree of metabolic protection. The evidence by Mariniello et al. [66] on androgen effects on adipose tissue suggests that certain androgen profiles can enhance insulin sensitivity and improve glucose uptake in adipocytes. The specific androgen milieu in IIH may thus have differential effects depending on the overall metabolic context. Conversely, in obese IIH patients, this potential metabolic benefit

may be overwhelmed by the profound insulin resistance and chronic inflammation associated with obesity. The interaction between obesity-related metabolic dysfunction and IIH-specific neuroendocrine perturbations may create a "perfect storm" for accelerated progression to type 2 diabetes [66].

Our findings necessitate a paradigm shift in the approach to cardiovascular risk management in IIH patients. We propose a multi-tiered strategy that includes enhanced risk stratification, targeted interventions, personalized metabolic management, and neuroendocrine modulation. The development of IIH-specific CVD risk calculators that incorporate novel biomarkers such as CSF androgen levels, adipokine profiles, and measures of intracranial pressure dynamics could significantly improve risk assessment in this population. Exploration of IIH-specific pharmacological interventions that address the unique pathophysiology of CVD risk in this population is warranted. For example, the potential use of selective androgen receptor modulators (SARMs) to mitigate the adverse cardiovascular effects of androgen excess while preserving potential metabolic benefits merits investigation.

Future research directions should include longitudinal studies employing advanced imaging techniques to elucidate the temporal relationship between IIH onset, progression, and cardiovascular remodelling. Multi-omics approaches integrating genomics, transcriptomics, and metabolomics could unravel the molecular mechanisms underlying the observed synergy between IIH and obesity in cardiovascular risk.

Interventional trials exploring the cardiovascular impact of IIH-specific treatments, including the potential cardioprotective effects of CSF diversion procedures or novel pharmacological agents targeting ICP regulation, are crucial. Additionally, investigation of sex-specific aspects of cardiovascular risk in IIH is essential, given the strong female predominance of the condition and the potential interaction with sex hormones.

The findings from our study reveal a complex, multifaceted relationship between IIH, obesity, and CVD risk that challenges existing paradigms and opens new frontiers in personalized medicine. The independent risk conferred by IIH, the synergistic effects with obesity, and the paradoxical metabolic findings underscore the need for a nuanced, mechanism-based approach to cardiovascular risk management in this unique patient population. As we continue to unravel the intricate pathophysiology of IIH, we move closer to developing targeted interventions that may not only alleviate the neurological symptoms of the condition but also mitigate its long-term cardiovascular consequences. The implications of our findings extend beyond IIH, offering potential insights into the broader interplay between neuroendocrine function, metabolic regulation, and cardiovascular health. The methodology of our paper has several limitations, at first the approach assumes that the HR and the values provided from the original data and the HR for obesity remains constant over the 13-year period and its applicable to both the IIH group and control group.

Secondly, it assumes that the effect of obesity on the events is independent of IIH status in each patient. Thirdly, the predicted events are based on the average HR for obesity from the current literature, which may not be fully representative of the study population in larger populations or another cohort. Also, the adjusted for IIH independent from obesity should be interpreted with caution, as it is an estimation based on the available data and assumptions. To further validate the findings, it would be better to perform tailored individual-level data analysis based on BMI subgroup analysis and sensitivity tests for IIH patients and counting for other potential cofounding variables in the cohort. Additionally, conducting a prospective study that directly compares IIH patients with normal weight controls would provide more comprehensive evidence for the independent effect of IIH on the proposed events.

5. Conclusions

Through our findings, we have established compelling evidence that IIH independently contributes to CVD risk beyond obesity alone. Our statistical modelling has revealed that IIH operates through both independent and obesity-synergistic pathways to elevate CVD risk. We consistently observed elevated risks across our obesity-stratified models, leading us to believe that IIH involves an intrinsic pathophysiological process that worsens CVD outcomes vulnerability. These findings align with emerging research on neuroendocrine dysregulation in IIH. Based on our results, we strongly advocate for a fundamental shift in IIH management to include comprehensive CVD risk assessment and mitigation. We believe developing IIH-specific CVD risk assessment tools and targeted interventions should be a priority. While we acknowledge the limitations of our study, including our assumptions about hazard ratio consistency and obesity effects, we have established a crucial foundation for future studies. We recommend prospective studies comparing IIH patients with normal-weight controls and deeper investigation of underlying mechanisms through multi-omics approaches. Our findings have significant implications for both clinical practice and future research in IIH management.

Conflicts of Interest:

N/A.

Institutional Review Board (IRB) Approval:

N/A.

Funding Source:

The project described was supported by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through CTSA award number: UM1TR004400. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Authors Contribution Statement:

A.Y.A. and M.M.M. contributed equally to this work and were responsible for study conceptualization, data collection, analysis, and manuscript writing. M.H.E., A.M.M., A.A.Z., O.S.E., and A.E. assisted with data collection and analysis. O.E., A.S.A., H.J.A., H.A.A., O.A., and M.A.A. provided methodological and technical support. M.A.E., A.A.D., and M.D.M. contributed clinical expertise and critical review. M.N. assisted with project administration. D.J.A. and A.A.D. supervised the project. All authors reviewed and approved the final version of the manuscript. A.Y.A. serves as the corresponding author and is responsible for all communication regarding this work.

Data Availability Statement:

N/A.

REFERENCES

1. *Mollan SP, Davies B, Silver NC, Shaw S, Mallucci CL, Wakerley BR, Krishnan A, Chavda SV, Ramalingam S, Edwards JJJoN, Neurosurgery, Psychiatry. Idiopathic intracranial hypertension: consensus guidelines on management2018: 1088*
2. *Mollan SP, Aguiar M, Evison F, Frew E, Sinclair AJ. The expanding burden of idiopathic intracranial hypertension. Eye (London, England). 2019: 478 [PMID: 30356129 10.1038/s41433-018-0238-5: 10.1038/s41433-018-0238-5]*
3. *Daniels AB, Liu GT, Volpe NJ, Galetta SL, Moster ML, Newman NJ, Biousse V, Lee AG, Wall M, Kardon R, Acierno MD, Corbett JJ, Maguire MG, Balcer LJ. Profiles of obesity, weight gain, and quality of life in idiopathic intracranial hypertension (pseudotumor cerebri). American journal of ophthalmology. 2007: 635 [PMID: 17386271 10.1016/j.ajo.2006.12.040: 10.1016/j.ajo.2006.12.040]*
4. *Kilgore KP, Lee MS, Leavitt JA, Mokri B, Hodge DO, Frank RD, Chen JJJO. Re-evaluating the incidence of idiopathic intracranial hypertension in an era of increasing obesity2017: 697*
5. *Wall M, McDermott MP, Kieburtz KD, Corbett JJ, Feldon SE, Friedman DI, Katz DM, Keltner JL, Schron EB, Kupersmith MJJJ. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial2014: 1641*
6. *Kalyvas AV, Hughes M, Koutsarnakis C, Moris D, Liakos F, Sakas DE, Stranjalis G, Fouyas IJAn. Efficacy, complications and cost of surgical interventions for idiopathic intracranial hypertension: a systematic review of the literature2017: 33*
7. *Adderley NJ, Subramanian A, Nirantharakumar K, Yiangou A, Gokhale KM, Mollan SP, Sinclair AJ. Association Between Idiopathic Intracranial Hypertension and Risk of Cardiovascular Diseases in Women in the United Kingdom. JAMA neurology. 2019: 1088 [PMID: 31282950 10.1001/jamaneurol.2019.1812: 10.1001/jamaneurol.2019.1812]*
8. *O'Reilly MW, Westgate CS, Hornby C, Botfield H, Taylor AE, Markey K, Mitchell JL, Scotton WJ, Mollan SP, Yiangou A, Jenkinson C, Gilligan LC, Sherlock M, Gibney J, Tomlinson JW, Lavery GG, Hodson DJ, Arlt W, Sinclair AJ. A unique androgen excess signature in idiopathic intracranial hypertension is linked to cerebrospinal fluid dynamics. JCI insight. 2019: [PMID: 30753168 10.1172/jci.insight.125348: 10.1172/jci.insight.125348]*
9. *Colman BD, Boonstra F, Nguyen MN, Raviskanthan S, Sumithran P, White O, Hutton EJ, Fielding J, van der Walt AJJoN, Neurosurgery, Psychiatry. Understanding the pathophysiology of idiopathic intracranial hypertension (IIH): a review of recent developments2024: 375*
10. *Yiangou A, Mollan SP, Sinclair AJJNRN. Idiopathic intracranial hypertension: a step change in understanding the disease mechanisms2023: 769*
11. *Libien J, Kupersmith M, Blaner W, McDermott M, Gao S, Liu Y, Corbett J, Wall M, sciences NIIHSGJJotn. Role of vitamin A metabolism in IIH: Results from the idiopathic intracranial hypertension treatment trial2017: 78*
12. *Alimajstorovic Z, Mollan SP, Grech O, Mitchell JL, Yiangou A, Thaller M, Lyons H, Sassani M, Seneviratne S, Hancox T, Jankevics A, Najdekr L, Dunn W, Sinclair AJ. Dysregulation of Amino Acid, Lipid, and Acylpyruvate Metabolism in Idiopathic Intracranial Hypertension: A Non-targeted Case Control and Longitudinal Metabolomic Study. Journal of proteome research. 2023: 1127 [PMID: 36534069 10.1021/acs.jproteome.2c00449: 10.1021/acs.jproteome.2c00449]*
13. *Strazzullo P, D'Elia L, Cairella G, Garbagnati F, Cappuccio FP, Scalfi L. Excess body weight and incidence of stroke: meta-analysis of prospective studies with 2 million participants. Stroke. 2010: e418 [PMID: 20299666 10.1161/strokeaha.109.576967: 10.1161/strokeaha.109.576967]*
14. *Greenland S, Morgenstern HJAroph. Confounding in health research2001: 189*
15. *Hernán MA, Robins JMJAjoe. Using big data to emulate a target trial when a randomized trial is not available2016: 758*
16. *Lu Y, Hajifathalian K, Ezzati M, Woodward M, Rimm EB, Danaei G, D'Este C. Metabolic mediators of the eff ects of body-mass index, overweight, and obesity on coronary heart disease and stroke: a pooled analysis of 97 prospective cohorts with 1.8 million participants2014:*
17. *Preston SH, Mehta NK, Stokes AJE. Modeling obesity histories in cohort analyses of health and mortality2013: 158*
18. *Fleiss JL, Levin B, Paik MC. Statistical methods for rates and proportions: john wiley & sons; 2013.*
19. *Greenland SJE. Quantifying biases in causal models: classical confounding vs collider-stratification bias2003: 300*
20. *Schneeweiss SJP, safety d. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics2006: 291*
21. *Hernan M, Robins J. Causal inference: What if. boca raton: Chapman & hill/crc2020:*
22. *Lin DY, Psaty BM, Kronmal RAJB. Assessing the sensitivity of regression results to unmeasured confounders in observational studies1998: 948*
23. *Schmiegelow MD, Andersson C, Køber L, Andersen SS, Olesen JB, Jensen TB, Azimi A, Nielsen MB, Gislason G, Torp-Pedersen C. Prepregnancy obesity and associations with stroke and myocardial infarction in women in the years after childbirth: a nationwide cohort study. Circulation. 2014: 330 [PMID: 24146252 10.1161/circulationaha.113.003142: 10.1161/circulationaha.113.003142]*
24. *Li TY, Rana JS, Manson JE, Willett WC, Stampfer MJ, Colditz GA, Rexrode KM, Hu FB. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. Circulation. 2006: 499 [PMID: 16449729 10.1161/circulationaha.105.574087: 10.1161/circulationaha.105.574087]*

25. *Song X, Tabák AG, Zethelius B, Yudkin JS, Söderberg S, Laatikainen T, Stehouwer CD, Dankner R, Jousilahti P, Onat A, Nilsson PM, Satman I, Vaccaro O, Tuomilehto J, Qiao Q. Obesity attenuates gender differences in cardiovascular mortality. Cardiovascular diabetology. 2014: 144 [PMID: 25928355 10.1186/s12933-014-0144-5: 10.1186/s12933-014-0144-5]*
26. *Dikaiou P, Björck L, Adiels M, Lundberg CE, Mandalenakis Z, Manhem K, Rosengren A. Obesity, overweight and risk for cardiovascular disease and mortality in young women. European journal of preventive cardiology. 2021: 1351 [PMID: 34647583 10.1177/2047487320908983: 10.1177/2047487320908983]*
27. *Medina-Inojosa JR, Batsis JA, Supervia M, Somers VK, Thomas RJ, Jenkins S, Grimes C, Lopez-Jimenez F. Relation of Waist-Hip Ratio to Long-Term Cardiovascular Events in Patients With Coronary Artery Disease. The American journal of cardiology. 2018: 903 [PMID: 29482851 10.1016/j.amjcard.2017.12.038: 10.1016/j.amjcard.2017.12.038]*
28. *Kip KE, Marroquin OC, Kelley DE, Johnson BD, Kelsey SF, Shaw LJ, Rogers WJ, Reis SE. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. Circulation. 2004: 706 [PMID: 14970104 10.1161/01.Cir.0000115514.44135.A8: 10.1161/01.Cir.0000115514.44135.A8]*
29. *Czernichow S, Kengne AP, Stamatakis E, Hamer M, Batty GD. Body mass index, waist circumference and waist-hip ratio: which is the better discriminator of cardiovascular disease mortality risk?: evidence from an individual-participant meta-analysis of 82 864 participants from nine cohort studies. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2011: 680 [PMID: 21521449 10.1111/j.1467-789X.2011.00879.x: 10.1111/j.1467-789X.2011.00879.x]*
30. *Kurth T, Gaziano JM, Rexrode KM, Kase CS, Cook NR, Manson JE, Buring JE. Prospective study of body mass index and risk of stroke in apparently healthy women. Circulation. 2005: 1992 [PMID: 15837954 10.1161/01.Cir.0000161822.83163.B6: 10.1161/01.Cir.0000161822.83163.B6]*
31. *Sánchez-Iñigo L, Navarro-González D, Fernández-Montero A, Pastrana-Delgado J, Martínez JA. Risk of incident ischemic stroke according to the metabolic health and obesity states in the Vascular-Metabolic CUN cohort. International journal of stroke : official journal of the International Stroke Society. 2017: 187 [PMID: 28134052 10.1177/1747493016672083: 10.1177/1747493016672083]*
32. *Zahn K, Linseisen J, Heier M, Peters A, Thorand B, Nairz F, Meisinger C. Body fat distribution and risk of incident ischemic stroke in men and women aged 50 to 74 years from the general population. The KORA Augsburg cohort study. PloS one. 2018: e0191630 [PMID: 29401461 10.1371/journal.pone.0191630: 10.1371/journal.pone.0191630]*
33. *Chen MQ, Shi WR, Wang HY, Sun YX. Sex Differences of Combined Effects Between Hypertension and General or Central Obesity on Ischemic Stroke in a Middle-Aged and Elderly Population. Clinical epidemiology. 2021: 197 [PMID: 33732027 10.2147/clep.S295989: 10.2147/clep.S295989]*
34. *Chaudhary D, Khan A, Gupta M, Hu Y, Li J, Abedi V, Zand R. Obesity and mortality after the first ischemic stroke: Is obesity paradox real? PloS one. 2021: e0246877 [PMID: 33566870 10.1371/journal.pone.0246877: 10.1371/journal.pone.0246877]*
35. *Horn JW, Feng T, Mørkedal B, Strand LB, Horn J, Mukamal K, Janszky I. Obesity and Risk for First Ischemic Stroke Depends on Metabolic Syndrome: The HUNT Study. Stroke. 2021: 3555 [PMID: 34281375 10.1161/strokeaha.120.033016: 10.1161/strokeaha.120.033016]*
36. *Yatsuya H, Toyoshima H, Yamagishi K, Tamakoshi K, Taguri M, Harada A, Ohashi Y, Kita Y, Naito Y, Yamada M, Tanabe N, Iso H, Ueshima H. Body mass index and risk of stroke and myocardial infarction in a relatively lean population: meta-analysis of 16 Japanese cohorts using individual data. Circulation Cardiovascular quality and outcomes. 2010: 498 [PMID: 20699444 10.1161/circoutcomes.109.908517: 10.1161/circoutcomes.109.908517]*
37. *Cordola Hsu AR, Xie B, Peterson DV, LaMonte MJ, Garcia L, Eaton CB, Going SB, Phillips LS, Manson JE, Anton-Culver H, Wong ND. Metabolically Healthy/Unhealthy Overweight/Obesity Associations With Incident Heart Failure in Postmenopausal Women: The Women's Health Initiative. Circulation Heart failure. 2021: e007297 [PMID: 33775111 10.1161/circheartfailure.120.007297: 10.1161/circheartfailure.120.007297]*
38. *Padwal R, McAlister FA, McMurray JJ, Cowie MR, Rich M, Pocock S, Swedberg K, Maggioni A, Gamble G, Ariti C, Earle N, Whalley G, Poppe KK, Doughty RN, Bayes-Genis A. The obesity paradox in heart failure patients with preserved versus reduced ejection fraction: a meta-analysis of individual patient data. International journal of obesity (2005). 2014: 1110 [PMID: 24173404 10.1038/ijo.2013.203: 10.1038/ijo.2013.203]*
39. *Halldin AK, Schaufelberger M, Lernfelt B, Björck L, Rosengren A, Lissner L, Björkelund C. Obesity in Middle Age Increases Risk of Later Heart Failure in Women-Results From the Prospective Population Study of Women and H70 Studies in Gothenburg, Sweden. Journal of cardiac failure. 2017: 363 [PMID: 27940334 10.1016/j.cardfail.2016.12.003: 10.1016/j.cardfail.2016.12.003]*
40. *Mørkedal B, Vatten LJ, Romundstad PR, Laugsand LE, Janszky I. Risk of myocardial infarction and heart failure among metabolically healthy but obese individuals: HUNT (Nord-Trøndelag Health Study), Norway. Journal of the American College of Cardiology. 2014: 1071 [PMID: 24345592 10.1016/j.jacc.2013.11.035: 10.1016/j.jacc.2013.11.035]*
41. *Kawada T. Metabolically healthy obesity and cardiovascular events: A risk of obesity. Diabetes, obesity & metabolism. 2022: 763 [PMID: 34927325 10.1111/dom.14628: 10.1111/dom.14628]*
42. *Chandramouli C, Tay WT, Bamadhaj NS, Tromp J, Teng TK, Yap JJL, MacDonald MR, Hung CL, Streng K, Naik A, Wander GS, Sawhney J, Ling LH, Richards AM, Anand I, Voors AA, Lam CSP.*

Association of obesity with heart failure outcomes in 11 Asian regions: A cohort study. PLoS medicine. 2019: e1002916 [PMID: 31550265 10.1371/journal.pmed.1002916: 10.1371/journal.pmed.1002916]

43. *Kenchaiah S, Ding J, Carr JJ, Allison MA, Budoff MJ, Tracy RP, Burke GL, McClelland RL, Arai AE, Bluemke DA. Pericardial Fat and the Risk of Heart Failure. Journal of the American College of Cardiology. 2021: 2638 [PMID: 34045020 10.1016/j.jacc.2021.04.003: 10.1016/j.jacc.2021.04.003]*
44. *Lee SK, Kim SH, Cho GY, Baik I, Lim HE, Park CG, Lee JB, Kim YH, Lim SY, Kim H, Shin C. Obesity phenotype and incident hypertension: a prospective community-based cohort study. Journal of hypertension. 2013: 145 [PMID: 23079679 10.1097/HJH.0b013e32835a3637: 10.1097/HJH.0b013e32835a3637]*
45. *Kabootari M, Akbarpour S, Azizi F, Hadaegh F. Sex specific impact of different obesity phenotypes on the risk of incident hypertension: Tehran lipid and glucose study. Nutrition & metabolism. 2019: 16 [PMID: 30858870 10.1186/s12986-019-0340-0: 10.1186/s12986-019-0340-0]*
46. *Lewandowska M, Więckowska B, Sajdak S. Pre-Pregnancy Obesity, Excessive Gestational Weight Gain, and the Risk of Pregnancy-Induced Hypertension and Gestational Diabetes Mellitus. Journal of clinical medicine. 2020: [PMID: 32599847 10.3390/jcm9061980: 10.3390/jcm9061980]*
47. *Nurdiantami Y, Watanabe K, Tanaka E, Pradono J, Anme T. Association of general and central obesity with hypertension. Clinical nutrition (Edinburgh, Scotland). 2018: 1259 [PMID: 28583324 10.1016/j.clnu.2017.05.012: 10.1016/j.clnu.2017.05.012]*
48. *Curhan GC, Chertow GM, Willett WC, Spiegelman D, Colditz GA, Manson JE, Speizer FE, Stampfer MJ. Birth weight and adult hypertension and obesity in women. Circulation. 1996: 1310 [PMID: 8822985 10.1161/01.cir.94.6.1310: 10.1161/01.cir.94.6.1310]*
49. *Gus M, Fuchs SC, Moreira LB, Moraes RS, Wiehe M, Silva AF, Albers F, Fuchs FD. Association between different measurements of obesity and the incidence of hypertension. American journal of hypertension. 2004: 50 [PMID: 14700512 10.1016/j.amjhyper.2003.08.010: 10.1016/j.amjhyper.2003.08.010]*
50. *Behboudi-Gandevani S, Ramezani Tehrani F, Hosseinpanah F, Khalili D, Cheraghi L, Kazemijaliseh H, Azizi F. Cardiometabolic risks in polycystic ovary syndrome: long-term population-based follow-up study. Fertility and sterility. 2018: 1377 [PMID: 30503137 10.1016/j.fertnstert.2018.08.046: 10.1016/j.fertnstert.2018.08.046]*
51. *Freedman DS, Williamson DF, Croft JB, Ballew C, Byers T. Relation of body fat distribution to ischemic heart disease. The National Health and Nutrition Examination Survey I (NHANES I) Epidemiologic Follow-up Study. American journal of epidemiology. 1995: 53 [PMID: 7785674 10.1093/oxfordjournals.aje.a117545: 10.1093/oxfordjournals.aje.a117545]*
52. *Quesada O, Lauzon M, Buttle R, Wei J, Suppogu N, Kelsey SF, Reis SE, Shaw LJ, Sopko G, Handberg E, Pepine CJ, Bairey Merz CN. Body weight and physical fitness in women with ischaemic heart disease: does physical fitness contribute to our understanding of the obesity paradox in women? European journal of preventive cardiology. 2022: 1608 [PMID: 35244151 10.1093/eurjpc/zwac046: 10.1093/eurjpc/zwac046]*
53. *Okamura T, Hashimoto Y, Hamaguchi M, Obora A, Kojima T, Fukui M. Ectopic fat obesity presents the greatest risk for incident type 2 diabetes: a population-based longitudinal study. International journal of obesity (2005). 2019: 139 [PMID: 29717276 10.1038/s41366-018-0076-3: 10.1038/s41366-018-0076-3]*
54. *Lee DH, Keum N, Hu FB, Orav EJ, Rimm EB, Willett WC, Giovannucci EL. Comparison of the association of predicted fat mass, body mass index, and other obesity indicators with type 2 diabetes risk: two large prospective studies in US men and women. European journal of epidemiology. 2018: 1113 [PMID: 30117031 10.1007/s10654-018-0433-5: 10.1007/s10654-018-0433-5]*
55. *Park SK, Ryoo JH, Oh CM, Choi JM, Jung JY. Longitudinally evaluated the relationship between body fat percentage and the risk for type 2 diabetes mellitus: Korean Genome and Epidemiology Study (KoGES). European journal of endocrinology. 2018: 513 [PMID: 29523634 10.1530/eje-17-0868: 10.1530/eje-17-0868]*
56. *Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA, Speizer FE, Manson JE. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. American journal of epidemiology. 1997: 614 [PMID: 9098178 10.1093/oxfordjournals.aje.a009158: 10.1093/oxfordjournals.aje.a009158]*
57. *Anagnostis P, Paparodis RD, Bosdou JK, Bothou C, Macut D, Goulis DG, Livadas S. Risk of type 2 diabetes mellitus in polycystic ovary syndrome is associated with obesity: a meta-analysis of observational studies. Endocrine. 2021: 245 [PMID: 34176074 10.1007/s12020-021-02801-2: 10.1007/s12020-021-02801-2]*
58. *Sluik D, Boeing H, Montonen J, Pischon T, Kaaks R, Teucher B, Tjønneland A, Halkjaer J, Berentzen TL, Overvad K, Arriola L, Ardanaz E, Bendinelli B, Grioni S, Tumino R, Sacerdote C, Mattiello A, Spijkerman AM, van der AD, Beulens JW, van der Schouw YT, Nilsson PM, Hedblad B, Rolandsson O, Franks PW, Nöthlings U. Associations between general and abdominal adiposity and mortality in individuals with diabetes mellitus. American journal of epidemiology. 2011: 22 [PMID: 21616928 10.1093/aje/kwr048: 10.1093/aje/kwr048]*
59. *Yang J, Qian F, Chavarro JE, Ley SH, Tobias DK, Yeung E, Hinkle SN, Bao W, Li M, Liu A, Mills JL, Sun Q, Willett WC, Hu FB, Zhang C. Modifiable risk factors and long term risk of type 2 diabetes among individuals with a history of gestational diabetes mellitus: prospective cohort study. BMJ (Clinical research ed). 2022: e070312 [PMID: 36130782 10.1136/bmj-2022-070312: 10.1136/bmj-2022-070312]*
60. *Hong S, Park JH, Han K, Lee CB, Kim DS, Yu SH. Association Between Obesity and Cardiovascular Disease in Elderly Patients*

With Diabetes: A Retrospective Cohort Study. The Journal of clinical endocrinology and metabolism. 2022: e515 [PMID: 34597374 10.1210/clinem/dgab714: 10.1210/clinem/dgab714]

61. *Duckles SP, Miller VM. Hormonal modulation of endothelial NO production. Pflugers Archiv : European journal of physiology. 2010: 841 [PMID: 20213497 10.1007/s00424-010-0797-1: 10.1007/s00424-010-0797-1]*
62. *Wardlaw JM, Benveniste H, Nedergaard M, Zlokovic BV, Mestre H, Lee H, Doubal FN, Brown R, Ramirez J, MacIntosh BJ, Tannenbaum A, Ballerini L, Rungta RL, Boido D, Sweeney M, Montagne A, Charpak S, Joutel A, Smith KJ, Black SE. Perivascular spaces in the brain: anatomy, physiology and pathology. Nature reviews Neurology. 2020: 137 [PMID: 32094487 10.1038/s41582-020-0312-z: 10.1038/s41582-020-0312-z]*
63. *Hornby C, Mollan SP, Botfield H, O'Reilly MW, Sinclair AJ. Metabolic Concepts in Idiopathic Intracranial Hypertension and Their Potential for Therapeutic Intervention. Journal of neuro-ophthalmology : the official journal of the North American Neuro-Ophthalmology Society. 2018: 522 [PMID: 29985799 10.1097/wno.0000000000000684: 10.1097/wno.0000000000000684]*
64. *Markey K, Mitchell J, Botfield H, Ottridge RS, Matthews T, Krishnan A, Woolley R, Westgate C, Yiangou A, Alimajstorovic Z, Shah P, Rick C, Ives N, Taylor AE, Gilligan LC, Jenkinson C, Arlt W, Scotton W, Fairclough RJ, Singhal R, Stewart PM, Tomlinson JW, Lavery GG, Mollan SP, Sinclair AJ. 11β-Hydroxysteroid dehydrogenase type 1 inhibition in idiopathic intracranial hypertension: a double-blind randomized controlled trial. Brain communications. 2020: fcz050 [PMID: 32954315 10.1093/braincomms/fcz050: 10.1093/braincomms/fcz050]*
65. *Goodpaster BH, Sparks LM. Metabolic Flexibility in Health and Disease. Cell metabolism. 2017: 1027 [PMID: 28467922 10.1016/j.cmet.2017.04.015: 10.1016/j.cmet.2017.04.015]*
66. *Mariniello B, Ronconi V, Rilli S, Bernante P, Boscaro M, Mantero F, Giacchetti G. Adipose tissue 11beta-hydroxysteroid dehydrogenase type 1 expression in obesity and Cushing's syndrome. European journal of endocrinology. 2006: 435 [PMID: 16914598 10.1530/eje.1.02228: 10.1530/eje.1.02228]*

ASIDE Internal Medicine

Original Article

Safety and Efficacy of Metformin for Idiopathic Intracranial Hypertension. A U.S-Based Real-World Data Retrospective Multicenter Cohort Study.

Ahmed Y. Azzam[1], Mahmoud Nassar[2], Ahmed Saad Al Zomia[3], Adam Elswedy[4], Mahmoud M. Morsy[4], Adham A. Mohamed[5], Osman Elamin[6], Omar S. Elsayed[4], Mohammed A. Azab[7], Muhammed Amir Essibayi[1, 8], Jin Wu[9], Adam A. Dmytirw[10, 11], David J. Altschul[1, 8]*

1- Montefiore-Einstein Cerebrovascular Research Lab, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA.
2- Department of Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, New York, USA.
3- College of Medicine, King Khalid University, Abha, Saudi Arabia.
4- Faculty of Medicine, October 6 University, Giza, Egypt.
5- Cairo University Hospitals, Cairo University, Cairo, Egypt.
6- Department of Neurosurgery, Jordan Hospital, Amman, Jordan.
7- Department of Neurosurgery, Cleveland Clinic Foundation, Cleveland, OH, USA.
8- Department of Neurological Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA.
9- National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA.
10- Neuroendovascular Program, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.
11- Neurovascular Centre, Divisions of Therapeutic Neuroradiology & Neurosurgery, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada.

*** Corresponding author:** *Mahmoud Nassar, MD, PhD, MSc, MHA, MPA, CPHQ, SSBB., Department of Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, New York, USA. Email Address: mailto:Dr.Nassar@aucegypt.edu*

ISSN (Print) 3065-9671, ISSN (Online) 3065-968X – see front matter

Citation: Azzam AY, Nassar M, Al Zomia AS, et al. Safety and Efficacy of Metformin for Idiopathic Intracranial Hypertension. A U.S-Based Real-World Data Retrospective Multicenter Cohort Study. ASIDE Int Med. 2024;1(1). doi:10.71079/2024001001

https://doi.org/10.71079/2024001001
Journal homepage: https://asidejournals.com/index.php/internal-medicine

ARTICLE INFO

Article history:
Received 19 Oct. 2024
Received in revised form 23 Nov. 2024
Accepted 25 Nov. 2024

Keywords:
Idiopathic Intracranial Hypertension
Pseudotumor Cerebri
Metformin
Metabolic Syndrome

ABSTRACT

Introduction: Managing idiopathic intracranial hypertension (IIH) is challenging due to limited treatment options. This study evaluates metformin as a potential therapy for IIH, examining its impact on disease outcomes and safety.

Methods: We performed a retrospective cohort study using the TriNetX database, covering data from 2009 to August 2024. The study included IIH patients, excluding those with other causes of raised intracranial pressure or pre-existing diabetes. Propensity score matching adjusted for age, sex, race, ethnicity, Hemoglobin A1C, and baseline BMI at metformin initiation. We assessed outcomes up to 24 months.

Results: Initially, 1,268 patients received metformin and 49,262 served as controls, showing disparities in various parameters. After matching, both groups consisted of 1,267 patients each. Metformin users had significantly lower risks of papilledema, headache, and refractory IIH at all follow-ups ($p<0.0001$). They also had fewer spinal punctures and reduced acetazolamide use. BMI reductions were more significant in the metformin group from 6 months onward ($p<0.0001$), with benefits persisting regardless of BMI changes. Metformin's safety profile was comparable to the control group.

Conclusions: The study indicates metformin's potential as a disease-modifying treatment in IIH, with improvements across multiple outcomes independent of weight loss. This suggests complex mechanisms at play, supporting further research through prospective clinical trials to confirm metformin's role in IIH management and its mechanisms of action.

1. Introduction

The current standard of care for idiopathic intracranial hypertension (IIH) focuses on reducing intracranial pressure (ICP) and preserving visual function [1, 2]. Weight loss remains the cornerstone of therapy, with studies demonstrating significant improvements in ICP and clinical outcomes following a 5-10% reduction in body weight [3, 4]. The Idiopathic Intracranial Hypertension Weight Trial (IIH: WT) provided Class I evidence that bariatric surgery is superior to community weight management programs in reducing ICP and improving quality of life [5]. Pharmacological management primarily involves acetazolamide, a carbonic anhydrase inhibitor that decreases cerebrospinal fluid (CSF) production. The landmark Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) established acetazolamide's efficacy in improving visual field function and reducing ICP when combined with a low-sodium weight reduction diet [6]. Other therapeutic approaches include topiramate, which offers the dual benefit of ICP reduction and migraine prophylaxis, and surgical interventions such as CSF diversion procedures or optic nerve sheath fenestration for medically refractory cases [7].

Despite these interventions, the management of IIH remains challenging, with a considerable proportion of patients experiencing refractory or recurrent disease [8]. Refractory IIH is defined as persistent or worsening symptoms and signs (including headaches, papilledema, and visual outcomes) despite maximal medical therapy (usually consisting of weight loss interventions and maximum tolerated doses of acetazolamide) for at least three months. Recurrent disease refers to the return of IIH symptoms and signs after a period of remission, often requiring reinitiation or intensification of therapy [8]. Many patients struggle to achieve or maintain weight loss, particularly through non-surgical means. The side effect profile of acetazolamide, including paresthesia, dysgeusia, and fatigue, often limits its long-term use or dose escalation [9]. Furthermore, a significant proportion of patients experience a plateau in their clinical improvement or require multiple interventions to maintain remission [10]. The lack of targeted therapies addressing the underlying pathophysiology of IIH, particularly the complex interplay between adipose dysfunction, CSF dynamics, and metabolic dysregulation, has hindered progress in disease modification and long-term outcomes [11].

The latest literature evidence has highlighted the unmet need for novel treatment approaches for IIH. Metformin, a biguanide antidiabetic agent, has demonstrated pleiotropic effects beyond glucose control, including modulation of adipose tissue function and reduction of CSF secretion [12]. Preclinical studies have shown that metformin can lower ICP through AMP-activated protein kinase (AMPK)-dependent inhibition of Na^+/K^+-ATPase at the choroid plexus, suggesting a direct mechanism for CSF production reduction [13]. This effect is particularly intriguing given the recent evidence implicating choroid plexus hypersecretion in IIH pathogenesis [14]. Additionally, metformin's effects on weight loss, insulin sensitivity, and adipokine profiles may address key pathogenic factors in CSF disorders such as hydrocephalus in rodent models, offering a potential approach to related diseases management in certain phenotypes [15] (**Figure 1**).

The potential of metformin in IIH is further supported by its established safety profile and its ability to mitigate components of metabolic syndrome [16], which are increasingly recognized as contributors to IIH pathophysiology [17]. To address this knowledge gap and explore metformin's potential as a disease-modifying therapy for IIH, we are conducting a multicenter, retrospective cohort study utilizing the TriNetX database. This large-scale, real-world evidence approach allows for the assessment of metformin's impact on IIH outcomes across diverse clinical settings in the United States, providing valuable insights into its safety and efficacy in a large patient cohort. Our study aims to evaluate the effects of metformin on IIH-related symptoms, healthcare utilization,

and long-term disease progression, offering a robust foundation for future prospective clinical trials. By leveraging this comprehensive dataset, we seek to elucidate metformin's potential role in expanding the therapeutic armamentarium for IIH, potentially offering a novel, mechanistically targeted approach to this challenging condition.

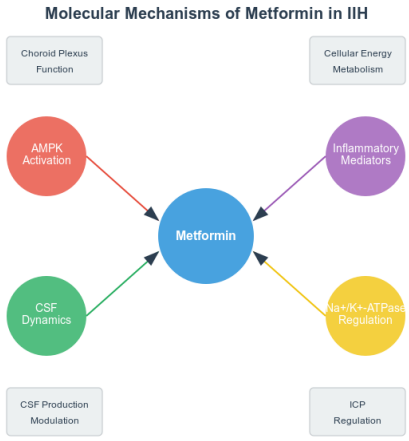


Figure 1: Mechanisms of Action of Metformin in IIH.

2. Methods

Our study utilized data from the expansive TriNetX Research Network, through the global collaborative network database [18], which contains around 197 million electronic health records aggregated from more than 160 healthcare organizations, primarily located in the United States. This comprehensive dataset includes a wide range of patient-level information, such as demographic characteristics, diagnoses, treatments, procedures, and outcomes, all coded using standard medical classification systems like the International Classification of Diseases, 10th Revision (ICD-10) and Current Procedural Terminology (CPT). Researchers can access this extensive real-world data through the secure TriNetX platform to conduct observational studies. Notably, the dataset is regularly updated, ensuring access to the most current and comprehensive healthcare information available. The study protocol was approved by the Institutional Review Board at the Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, NY, USA (STUDY00008628).

We performed a retrospective analysis of the TriNetX data from 2009 to August 2024 (the timeframe associated with individuals with our inclusion and exclusion criteria in the TriNetX database), focusing on patients diagnosed with IIH. Patients were included if they had a primary diagnosis of IIH (ICD-10 code: G93.2), were aged 18 years or older, had at least one recorded BMI measurement and had a minimum follow-up period of 1 month. We excluded patients with pre-existing type 1 or type 2 diabetes mellitus (ICD-10 codes: E10*., E11.*), prediabetes (ICD-10: R73.03), or HbA1c ≥ 6.5%. Additional exclusion criteria encompassed other causes of elevated intracranial pressure, including primary brain tumors (ICD-10: C71.*), secondary brain metastases (ICD-10: C79.31), cerebral arteriovenous malformations (ICD-10: Q28.2), and venous sinus thrombosis (ICD-10: I67.6).

The study population was divided into two groups. The metformin group consisted of patients with IIH who received metformin (minimum dose 500mg daily) with no prior history of diabetes or prediabetes, and their first prescription of metformin was initiated after IIH diagnosis. The control group comprised patients with IIH who did not receive metformin at any point during the study period and had no prior history of diabetes or prediabetes. These groups were matched for age, sex, race, ethnicity, baseline body mass index (BMI), and baseline HbA1c using propensity score matching to minimize selection bias.

Primary outcomes were defined as papilledema (ICD-10: H47.1), refractory IIH status (ICD-10: G93.2 with modifier code Z91.82), and therapeutic spinal puncture rate (CPT: 62272). Secondary outcomes included optic atrophy (ICD-10: H47.2), blindness (ICD-10: H54.*), pulsatile tinnitus (ICD-10: H93.A9), diplopia (ICD-10: H53.2), visual field defects (ICD-10: H53.4), and adverse events related to metformin use.

We analyzed the data at different follow-up durations (one-month, three-months, six-months, 12-months, and 24-months) and assessed the following outcomes: papilledema, optic atrophy, blindness, pulsatile tinnitus, diplopia, refractory IIH status, visual discomfort, visual field defects, and therapeutic spinal puncture rate as the primary treatment. For outcome assessment purposes, refractory IIH was defined as persistent or worsening symptoms despite maximum medical therapy for three months or longer. Treatment success was characterized by the resolution of papilledema and improvement in visual function, while disease recurrence was defined as a new onset of symptoms after documented resolution. Therapeutic spinal punctures were distinguished from diagnostic procedures, specifically identifying lumbar punctures performed for therapeutic purposes. Visual outcomes encompassed any documented changes in visual acuity or visual fields that were measured as the change from baseline at specified time points.

3. Results

3.1. Baseline Demographics:

A comprehensive overview of the baseline demographics and clinical characteristics for patients with IIH is presented in **Table 1**, comparing metformin and control groups before and after propensity score matching. Initially, the cohorts comprised 1,268 patients in the metformin group and 49,262 in the control group, with notable disparities in several parameters. Post-matching, both cohorts were refined to 1,267 patients each, achieving remarkable comparability across baseline attributes. The mean age was nearly identical (36.8 *vs.* 37.0 years), with comparable standard deviations. Gender distribution revealed a striking female predominance (93.29% *vs.* 92.66%), consistent with the known epidemiology of IIH. Comorbidity profiles highlighted the complex medical landscape of IIH patients. Endocrine and metabolic diseases were highly prevalent (73.48% *vs.* 73.01%), potentially reflecting the metabolic dysfunction often associated with IIH. Notably, ophthalmological diseases affected approximately 59% of patients in both groups, underscoring the significant ocular manifestations in IIH. Other frequent comorbidities included musculoskeletal diseases, mental and neurodevelopmental disorders, and respiratory conditions, all showing similar distributions between groups.

3.2. Outcomes Analysis:

We performed a longitudinal outcome analysis between the metformin group and the control group in patients with IIH, and the results are presented in **Table 2**. The metformin group consistently demonstrated lower risk percentages for most outcomes compared to the control group. Papilledema and refractory IIH showed very high statistical significance ($p<0.0001$) in favor of the metformin group at all follow-up points (1, 3, 6, 12, and 24 months). The risk ratios for these outcomes ranged from 0.238 to 0.889, indicating a substantially lower risk in the metformin group. Optic atrophy risk was similar between the groups at 1, 3, 6, and 12 months, but at 24 months, the metformin group had a slightly higher risk (2.1% vs. 0.8%, $p=0.047$). Blindness risk was significantly lower in the metformin group at 3 months ($p=0.031$), but not statistically significant at other follow-up points. Pulsatile tinnitus and diplopia showed significantly lower risks in the metformin group at 6 months ($p=0.005$ and $p=0.007$, respectively) and 24 months ($p=0.002$ and $p<0.0001$, respectively). However, the differences were not statistically significant at one-month, three-months, and 12-months. Visual discomfort and visual field defects were significantly lower in the metformin group only at 3 months ($p=0.025$), with no significant differences at other follow-up durations. The therapeutic spinal puncture rate was significantly lower in the metformin group at all follow-up points (one-month, three-months, six-months, 12-months, and 24-months), with p-values ranging from 0.0001 to 0.007. The risk difference and risk ratio favored the metformin group across all durations, with significant p-values ($p<0.0001$). The 95% confidence intervals for the risk ratios indicated a consistent benefit of metformin over the entire study period.

3.3. Metformin Safety Profile:

We analyzed a total of 2,534 patients, equally divided between the metformin and control groups (1,267 patients each) after performing propensity score matching analysis for safety and side effects of metformin. Gastrointestinal side effects, often associated with metformin use, showed similar incidence rates in both groups. Notably, nausea was reported in 8.52% of metformin users compared to 10.58% in the control group (RR 0.81, 95% CI 0.63-1.03, $p=0.09$). Vomiting occurred less frequently, affecting 2.37% and 3.31% of the metformin and control groups, respectively (RR 0.71, 95% CI 0.45-1.13, $p=0.19$). Regarding metabolic side effects, lactic acidosis—a rare but serious concern with metformin use—was observed in 1.03% of metformin users versus 1.74% in the control group (RR 0.59, 95% CI 0.30-1.17, $p=0.17$). Vitamin B12 deficiency or megaloblastic anemia showed identical rates in both groups (4.58%, RR 1.0, 95% CI 0.70-1.43, $p=0.999$). General and systemic side effects were also comparable between groups. Myalgia was reported in 6.47% of metformin users and 8.29% of controls (RR 0.78, 95% CI 0.59-1.03, $p=0.09$), while asthenia affected 5.21% and 5.84% of the metformin and control groups, respectively (RR 0.89, 95% CI 0.65-1.23, $p=0.54$).

4. Discussion

In our large-scale multicenter retrospective study based on the TriNetX database, we illustrated compelling evidence for the potential efficacy of metformin as a disease-modifying therapy in IIH. Our findings demonstrate significant improvements across multiple IIH-related outcomes in patients treated with metformin compared to those who did not receive the medication.

The marked reduction in papilledema risk observed in the metformin group throughout the study period is particularly striking. This finding aligns with recent research suggesting that metformin may have direct effects on ICP regulation. Botfield et al. [13] demonstrated that metformin can reduce ICP in rodent models of IIH through AMPK-dependent inhibition of the Na+/K+-ATPase at the choroid plexus, thereby decreasing CSF secretion. Our clinical findings support this preclinical evidence, indicating that metformin's effects on papilledema may be mediated through direct modulation of CSF dynamics rather than solely through weight loss.

The observed reduction in refractory IIH status among metformin-treated patients is particularly noteworthy. This finding suggests that metformin may address underlying pathophysiological mechanisms that contribute to treatment resistance in IIH. Recent evidence has implicated adipose tissue dysfunction and altered adipokine profiles in IIH pathogenesis [11]. Metformin's known effects on adipose tissue function, including modulation of adipokine secretion and improvement of insulin sensitivity, may contribute to its efficacy in refractory cases. Furthermore, emerging evidence suggests that metformin can influence the gut microbiome, which has been increasingly linked to neurological disorders, including those affecting ICP regulation [19].

These multifaceted effects of metformin may explain its potential to improve outcomes in patients who have not responded adequately to conventional therapies. The latest evidence has highlighted the importance of metabolic dysfunction in IIH pathogenesis, independent of obesity. For instance, Hornby et al. demonstrated alterations in glucose and lipid metabolism in IIH patients that were not fully explained by BMI [20]. Metformin's pleiotropic effects on metabolism, including improved insulin sensitivity and modulation of lipid profiles, may therefore contribute to its efficacy in IIH through mechanisms distinct from weight loss.

The potential endocrinological connections underlying metformin's efficacy in IIH are particularly interesting. Recent studies have implicated various endocrine factors in IIH pathophysiology, including androgens, glucocorticoids, and growth hormones [21]. Metformin has been shown to influence several of these endocrine pathways. For example, metformin can reduce androgen levels and improve insulin sensitivity in polycystic ovary syndrome (PCOS), a condition often comorbid with IIH [22]. Given that androgen excess has been implicated in IIH pathogenesis, metformin's androgen-lowering effects may contribute to its therapeutic benefits. Additionally, metformin has been shown to modulate the hypothalamic-pituitary-adrenal (HPA) axis, which could influence CSF dynamics and ICP regulation [23]. These endocrinological effects of metformin may explain, in part, its apparent disease-modifying properties in IIH observed in our study.

The safety profile of metformin in our IIH cohort was favorable, with no significant differences in adverse events compared to the control group. This is consistent with metformin's well-established safety record in other clinical contexts and supports its potential as a long-term therapy for IIH. The similar incidence of lactic acidosis between the metformin and control groups is particularly reassuring, given historical concerns about this rare but serious complication [24].

Table 1: Baseline Demographics of The Patients Cohorts.

Total Patients, n	**Before Propensity Score Matching**		**P-Value**	**After Propensity Score Matching**		**P-Value**
	Metformin Group	**Control Group**		**Metformin Group**	**Control Group**	
	1,268	49,262		1,267	1,267	
Mean Age, SD	36.8 ± 9.66	36.2 ± 10.1	0.0323	36.8 ± 9.66	37 ± 10	0.6114
Sex, n (%)						
Female	1,182, (93.22%)	41,006, (83.24%)	< 0.0001	1,182, (93.29%)	1,174, (92.66%)	0.5340
Male	53, (4.18%)	5,503, (11.17%)	< 0.0001	53, (4.18%)	54, (4.26%)	0.9213
Unknown	32, (2.52%)	1,705, (3.46%)	0.0537	32, (2.53%)	39, (3.08%)	0.3994
Ethnicity, n (%)						
Not Hispanic or Latino	847, (66.80%)	28,606, (58.07%)	< 0.0001	847, (66.85%)	859, (67.80%)	0.6113
Hispanic or Latino	129, (10.17%)	4,111, (8.35%)	0.0378	129, (10.18%)	126, (9.94%)	0.8430
Unknown Ethnicity	291, (22.95%)	15,479, (31.42%)	< 0.0001	291, (22.97%)	282, (22.26%)	0.6691
Race, n (%)						
White	730, (57.57%)	26,556, (53.91%)	0.0731	730, (57.62%)	726, (57.30%)	0.8723
Black or African American	232, (18.30%)	7,905, (16.05%)	0.0694	232, (18.31%)	246, (19.42%)	0.4771
Other Race	54, (4.26%)	2,271, (4.61%)	0.4567	54, (4.26%)	47, (3.71%)	0.4772
Asian	18, (1.42%)	712, (1.45%)	0.8702	18, (1.42%)	23, (1.82%)	0.4311
American Indian or Alaska Native	10, (0.79%)	161, (0.33%)	0.0064	10, (0.79%)	10, (0.79%)	0.9999
Native Hawaiian or Other Pacific Islander	10, (0.79%)	117, (0.24%)	0.0001	10, (0.79%)	0, (0.00%)	0.0015
Unknown Race	226, (17.82%)	10,492, (21.30%)	< 0.0001	226, (17.84%)	223, (17.60%)	0.6691
Comorbid Diseases, n (%)						
Endocrine and Metabolic Diseases	931, (73.42%)	15,748, (31.97%)	< 0.0001	931, (73.48%)	925, (73.01%)	0.7877
Ophthalmological Diseases	750, (59.15%)	20,859, (42.34%)	< 0.0001	750, (59.19%)	754, (59.51%)	0.8715
Musculoskeletal Diseases	677, (53.39%)	13,730, (27.87%)	< 0.0001	677, (53.43%)	658, (51.93%)	0.4497
Mental and Neurodevelopmental Disorders	664, (52.37%)	13,249, (26.89%)	< 0.0001	664, (52.41%)	650, (51.30%)	0.5778
Respiratory Diseases	581, (45.82%)	12,811, (26.01%)	< 0.0001	581, (45.86%)	581, (45.86%)	0.9999
Genitourinary Diseases	606, (47.79%)	10,356, (21.02%)	< 0.0001	606, (47.83%)	614, (48.46%)	0.7504
Digestive Tract Diseases	519, (40.93%)	10,079, (20.46%)	< 0.0001	519, (40.96%)	514, (40.57%)	0.8398
Presence of Active Infections	386, (30.44%)	6,770, (13.74%)	< 0.0001	386, (30.47%)	375, (29.60%)	0.6336
Skin and Subcutaneous Diseases	480, (37.85%)	6,729, (13.66%)	< 0.0001	480, (37.88%)	483, (38.12%)	0.9023
Circulatory Diseases	261, (20.58%)	5,944, (12.07%)	< 0.0001	261, (20.60%)	270, (21.31%)	0.6604
Hematological and Immunological Diseases	279, (22.00%)	5,683, (11.54%)	< 0.0001	279, (22.02%)	252, (19.89%)	0.1875
Active Malignancies (Excluding CNS Tumors and Brain Metastasis)	257, (20.27%)	4,072, (8.27%)	< 0.0001	257, (20.28%)	238, (18.78%)	0.3411
Presence of Congenital Malformation s or Chromosomal Abnormalities	112, (8.83%)	1,955, (3.97%)	< 0.0001	112, (8.84%)	105, (8.29%)	0.6192

Abbreviations: CNS: Central Nervous System

Our findings have important clinical implications. The observed reductions in papilledema and refractory disease status suggest that metformin could address multiple aspects of IIH pathophysiology.

While our results are highly promising, several important limitations of this study warrant careful consideration. First, the retrospective nature of our analysis inherently introduces potential for selection bias and confounding factors, despite our rigorous propensity score matching approach. The use of electronic health record data, while providing a good sample size, may be subject to coding errors, missing data, or inconsistent documentation practices across different healthcare institutions within the TriNetX network. A significant limitation is the inability to directly measure intracranial pressure or access detailed CSF dynamics data. The absence of direct ICP measurements and CSF opening/closing pressures limits our ability to quantify the precise physiological effects of metformin on CSF dynamics. Additionally, we could not standardize the methods and timing of ophthalmological assessments across institutions, potentially introducing variability in the evaluation of visual outcomes.

The study's reliance on ICD-10 codes for diagnosis and outcome measurement may not capture the full spectrum of disease severity or subtle clinical changes. Furthermore, while we controlled for various confounding factors, we cannot completely account for all potential confounders, such as dietary habits, exercise patterns, or concurrent medications that might influence IIH outcomes. The impact of these unmeasured variables on our results remains unknown.

Patient compliance with metformin therapy could not be definitively assessed beyond prescription fills, and we lacked data on medication adherence patterns. The study also cannot account for potential variations in clinical practice patterns across different institutions, including differences in the threshold for therapeutic interventions or the timing of treatment escalation. Another limitation is the potential for immortal time bias, as patients in the metformin group had to survive long enough to receive the prescription. While our matching process attempted to minimize this bias, its influence cannot be completely eliminated. Additionally, the study's follow-up period, though substantial, may not be sufficient to capture very long-term outcomes or rare adverse events.

The generalizability of our findings may be limited by the study population's characteristics and the participating healthcare institutions' geographic and demographic distribution. Furthermore, the exclusion of patients with diabetes and pre-diabetes, while necessary for studying metformin's direct effects on IIH, means our results may not be applicable to IIH patients with these comorbidities. Finally, as with any observational study, we can demonstrate association but not causation. The precise mechanisms by which metformin influences IIH outcomes remain speculative and require validation through prospective, mechanistic studies. These limitations underscore the need for randomized controlled trials to definitively establish metformin's role in IIH management and elucidate its therapeutic mechanisms.

Table 2: Comparison Between Outcomes and Their Follow-up Duration Between Both Groups Through Propensity Score Matching.

Outcome	Follow-up Duration	Metformin Group Risk Percentage	Control Group Risk Percentage	Risk Difference	Risk Ratio	95% Confidence Interval	P-value
Papilledema	1-month	2.80%	11.60%	-8.80%	0.238	(0.166, 0.341)	**0.0001*** **
	3-months	6.70%	16.70%	-10.00%	0.401	(0.316, 0.509)	**0.0001*** **
	6-months	9.50%	19.40%	-10.00%	0.488	(0.398, 0.598)	**0.0001*** **
	12-months	11.00%	19.90%	-8.90%	0.553	(0.457, 0.668)	**0.0001*** **
	24-months	12.40%	21.60%	-9.20%	0.573	(0.479, 0.686)	**0.0001*** **
Optic Atrophy	1-month	0.80%	0.80%	0.00%	1.0	(0.418, 2.394)	0.999
	3-months	0.80%	0.80%	0.00%	1.0	(0.418, 2.394)	0.999
	6-months	0.90%	0.80%	0.20%	1.2	(0.520, 2.767)	0.668
	12-months	1.50%	1.40%	0.10%	1.056	(0.557, 2.002)	0.868
	24-months	1.70%	0.80%	0.90%	2.1	(0.993, 4.441)	**0.047***
Blindness	1-month	0.80%	1.30%	-0.50%	0.625	(0.285, 1.372)	0.237
	3-months	0.90%	2.00%	-1.00%	0.48	(0.242, 0.951)	**0.031***
	6-months	1.50%	2.10%	-0.60%	0.704	(0.393, 1.259)	0.234
	12-months	1.80%	2.80%	-1.00%	0.639	(0.381, 1.072)	0.087
	24-months	2.10%	2.60%	-0.60%	0.788	(0.474, 1.309)	0.356
Pulsatile Tinnitus	1-month	0.80%	0.90%	-0.20%	0.833	(0.361, 1.922)	0.668
	3-months	0.80%	1.50%	-0.70%	0.526	(0.246, 1.127)	0.093
	6-months	0.80%	2.10%	-1.30%	0.37	(0.180, 0.762)	**0.005** **
	12-months	1.10%	1.70%	-0.60%	0.636	(0.327, 1.238)	0.179
	24-months	1.10%	2.80%	-1.70%	0.40	(0.216, 0.740)	**0.002** **
Diplopia	1-month	0.80%	1.30%	-0.50%	0.625	(0.285, 1.372)	0.237
	3-months	0.80%	1.80%	-1.00%	0.435	(0.208, 0.910)	0.023
	6-months	0.80%	2.10%	-1.30%	0.385	((0.186, 0.794)	**0.007** **
	12-months	0.80%	1.80%	-1.00%	0.435	(0.208, 0.910)	**0.023***
	24-months	0.80%	2.80%	-2.10%	0.278	(0.138, 0.557)	**0.0001*** **
Refractory IIH	1-month	16.70%	30.60%	-14.00%	0.544	(0.469, 0.631)	**0.0001*** **
	3-months	31.40%	42.70%	-11.40%	0.734	(0.662, 0.814)	**0.0001*** **
	6-months	39.70%	49.50%	-9.90%	0.801	(0.733, 0.874)	**0.0001*** **
	12-months	45.90%	53.90%	-8.00%	0.851	(0.787, 0.920)	**0.0001*** **
	24-months	50.10%	56.30%	-6.20%	0.889	(0.826, 0.957)	**0.002** **
Visual Discomfort and Visual Field Defects	1-month	0.90%	1.70%	-0.80%	0.524	(0.254, 1.082)	0.075
	3-months	1.40%	2.70%	-1.30%	0.529	(0.301, 0.932)	**0.025***
	6-months	2.20%	3.50%	-1.30%	0.636	(0.399, 1.016)	0.056
	12-months	3.30%	3.70%	-0.40%	0.896	(0.598, 1.342)	0.594
	24-months	3.80%	4.40%	-0.60%	0.857	(0.588, 1.250)	0.423
Therapeutic Spinal Puncture Rate	1-month	0.80%	2.20%	-1.40%	0.357	(0.174, 0.732)	**0.003** **
	3-months	0.80%	2.40%	-1.70%	0.323	(0.159, 0.655)	**0.001** **
	6-months	0.80%	2.70%	-1.90%	0.294	(0.146, 0.593)	**0.0001*** **
	12-months	0.90%	2.20%	-1.30%	0.414	(0.212, 0.807)	**0.007** **
	24-months	1.20%	3.10%	-1.90%	0.385	(0.213, 0.694)	**0.001** **

* Denotes Statistical Significance, ** Denotes High Statistical Significance, *** Denotes Very High Statistical Significance

5. Conclusions

Our study provides strong evidence for the potential of metformin as a disease-modifying therapy in IIH, with benefits extending beyond weight loss. These findings open new avenues for IIH management and underscore the need for further research into the complex pathophysiology of this condition. Prospective, randomized controlled trials are now warranted to confirm these results and establish optimal treatment protocols. Such studies should include direct measurements of ICP, CSF opening pressure estimations, detailed ophthalmological assessments, and investigations in a longitudinal manner into the underlying mechanisms of metformin's effects in IIH. Additionally, long-term follow-up studies will be crucial to assess the durability of metformin's benefits and its impact on disease progression. As our understanding of IIH pathophysiology continues to evolve, metformin may represent a promising addition to the therapeutic armamentarium for this challenging condition.

Conflicts of Interest:

N/A.

Institutional Review Board (IRB) Approval:

The Institutional Review Board at the Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, NY, USA approved the study protocol under IRB approval number (STUDY00008628).

Funding Source:

Dr. Wu's current research work is partially supported by the National Institutes of Health (NIH) under a grant agreement, NIH/NINDS grant: R01NS076491. The project described was supported by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through CTSA award number: UM1TR004400. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Authors Contribution Statement:

A.Y.A. and M.N. conceptualized and designed the study, performed data curation, formal analysis, investigation, methodology, project administration, and wrote the original draft. A.S.A., A.E., M.M.M., A.A.M., O.E., O.S.E., M.A.A., and M.A.E. contributed to data curation, investigation, and manuscript review and editing. J.W. contributed to the methodology, provided resources, supervised the work, validated results, reviewed and edited the manuscript, and secured funding. A.A.D. and D.J.A. contributed to the methodology, provided resources, supervised the work, validated results, and reviewed and edited the manuscript. M.N., as the corresponding author, supervised the overall work and was responsible for the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement:

Available on TriNetX Database Based on Institutional Collaborations.

References

1. Mollan SP, Davies B, Silver NC, Shaw S, Mallucci CL, Wakerley BR, Krishnan A, Chavda SV, Ramalingam S, Edwards JJJoN, Neurosurgery, Psychiatry. Idiopathic intracranial hypertension: consensus guidelines on management2018: 1088
2. Friedman DI, Liu GT, Digre KB. Revised diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology. 2013: 1159 [PMID: 23966248 10.1212/WNL.0b013e3182a55f17: 10.1212/WNL.0b013e3182a55f17]
3. Sinclair AJ, Burdon MA, Nightingale PG, Ball AK, Good P, Matthews TD, Jacks A, Lawden M, Clarke CE, Stewart PM, Walker EA, Tomlinson JW, Rauz S. Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. BMJ (Clinical research ed). 2010: c2701 [PMID: 20610512 10.1136/bmj.c2701: 10.1136/bmj.c2701]
4. Manfield JH, Yu KK, Efthimiou E, Darzi A, Athanasiou T, Ashrafian H. Bariatric Surgery or Non-surgical Weight Loss for Idiopathic Intracranial Hypertension? A Systematic Review and Comparison of Meta-analyses. Obesity surgery. 2017: 513 [PMID: 27981458 10.1007/s11695-016-2467-7: 10.1007/s11695-016-2467-7]
5. Ottridge R, Mollan SP, Botfield H, Frew E, Ives NJ, Matthews T, Mitchell J, Rick C, Singhal R, Woolley R, Sinclair AJ. Randomised controlled trial of bariatric surgery versus a community weight loss programme for the sustained treatment of idiopathic intracranial hypertension: the Idiopathic Intracranial Hypertension Weight Trial (IIH:WT) protocol. BMJ open. 2017: e017426 [PMID: 28963303 10.1136/bmjopen-2017-017426: 10.1136/bmjopen-2017-017426]
6. Wall M, McDermott MP, Kieburtz KD, Corbett JJ, Feldon SE, Friedman DI, Katz DM, Keltner JL, Schron EB, Kupersmith MJJJ. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial2014: 1641
7. Mollan SP, Aguiar M, Evison F, Frew E, Sinclair AJ. The expanding burden of idiopathic intracranial hypertension. Eye (London, England). 2019: 478 [PMID: 30356129 10.1038/s41433-018-0238-5: 10.1038/s41433-018-0238-5]
8. Mulla Y, Markey KA, Woolley RL, Patel S, Mollan SP, Sinclair AJ. Headache determines quality of life in idiopathic intracranial hypertension. The journal of headache and pain. 2015: 521 [PMID: 25982204 10.1186/s10194-015-0521-9: 10.1186/s10194-015-0521-9]
9. Schmickl CN, Owens RL, Orr JE, Edwards BA, Malhotra A. Side effects of acetazolamide: a systematic review and meta-analysis assessing overall risk and dose dependence. BMJ open respiratory research. 2020: [PMID: 32332024 10.1136/bmjresp-2020-000557: 10.1136/bmjresp-2020-000557]
10. Yri HM, Wegener M, Sander B, Jensen R. Idiopathic intracranial hypertension is not benign: a long-term outcome study. Journal of neurology. 2012: 886 [PMID: 22008872 10.1007/s00415-011-6273-9: 10.1007/s00415-011-6273-9]
11. Hornby C, Mollan SP, Botfield H, O'Reilly MW, Sinclair AJ. Metabolic Concepts in Idiopathic Intracranial Hypertension and Their Potential for Therapeutic Intervention. Journal of neuro-ophthalmology : the official journal of the North American Neuro-Ophthalmology Society. 2018: 522 [PMID: 29985799 10.1097/wno.0000000000000684: 10.1097/wno.0000000000000684]
12. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clinical science (London, England : 1979). 2012: 253 [PMID: 22117616 10.1042/cs20110386: 10.1042/cs20110386]
13. Botfield HF, Uldall MS, Westgate CSJ, Mitchell JL, Hagen SM, Gonzalez AM, Hodson DJ, Jensen RH, Sinclair AJ. A glucagon-like peptide-1 receptor agonist reduces intracranial pressure in a rat model of hydrocephalus. Science translational medicine. 2017: [PMID: 28835515 10.1126/scitranslmed.aan0972: 10.1126/scitranslmed.aan0972]
14. Karimy JK, Reeves BC, Damisah E, Duy PQ, Antwi P, David W, Wang K, Schiff SJ, Limbrick DD, Jr., Alper SL, Warf BC, Nedergaard M, Simard JM, Kahle KT. Inflammation in acquired hydrocephalus: pathogenic mechanisms and therapeutic targets. Nature reviews Neurology. 2020: 285 [PMID: 32152460 10.1038/s41582-020-0321-y: 10.1038/s41582-020-0321-y]
15. Łabuzek K, Suchy D, Gabryel B, Bielecka A, Liber S, Okopień B. Quantification of metformin by the HPLC method in brain regions, cerebrospinal fluid and plasma of rats treated with lipopolysaccharide. Pharmacological reports : PR. 2010: 956 [PMID: 21098880 10.1016/s1734-1140(10)70357-1: 10.1016/s1734-1140(10)70357-1]
16. Lin Z, Sun L. Research advances in the therapy of metabolic syndrome. Frontiers in pharmacology. 2024: 1364881 [PMID: 39139641 10.3389/fphar.2024.1364881: 10.3389/fphar.2024.1364881]
17. Wardman JH, Andreassen SN, Toft-Bertelsen TL, Jensen MN, Wilhjelm JE, Styrishave B, Hamann S, Heegaard S, Sinclair AJ, MacAulay N. CSF hyperdynamics in rats mimicking the obesity and androgen excess characteristic of patients with idiopathic intracranial hypertension. Fluids and barriers of the CNS. 2024: 10 [PMID: 38273331 10.1186/s12987-024-00511-1: 10.1186/s12987-024-00511-1]
18. Palchuk MB, London JW, Perez-Rey D, Drebert ZJ, Winer-Jones JP, Thompson CN, Esposito J, Claerhout B. A global federated real-world data and analytics platform for research. JAMIA open. 2023: ooad035 [PMID: 37193038 10.1093/jamiaopen/ooad035: 10.1093/jamiaopen/ooad035]
19. Sun L, Xie C, Wang G, Wu Y, Wu Q, Wang X, Liu J, Deng Y, Xia J, Chen B, Zhang S, Yun C, Lian G, Zhang X, Zhang H, Bisson WH, Shi J, Gao X, Ge P, Liu C, Krausz KW, Nichols RG, Cai J, Rimal B, Patterson AD, Wang X, Gonzalez FJ, Jiang C. Gut microbiota and intestinal FXR mediate the clinical benefits of metformin. Nature medicine. 2018: 1919 [PMID: 30397356 10.1038/s41591-018-0222-4: 10.1038/s41591-018-0222-4]
20. Hornby C, Mollan SP, Mitchell J, Markey KA, Yangou A, Wright BLC, O'Reilly MW, Sinclair AJ. What Do Transgender Patients Teach Us About Idiopathic Intracranial Hypertension? Neuro-ophthalmology (Aeolus Press). 2017: 326 [PMID: 29238388 10.1080/01658107.2017.1316744: 10.1080/01658107.2017.1316744]
21. O'Reilly MW, Westgate CS, Hornby C, Botfield H, Taylor AE, Markey K, Mitchell JL, Scotton WJ, Mollan SP, Yiangou A, Jenkinson C, Gilligan LC, Sherlock M, Gibney J, Tomlinson JW, Lavery GG, Hodson DJ, Arlt W, Sinclair AJ. A unique androgen excess signature in idiopathic intracranial hypertension is linked to cerebrospinal fluid dynamics. JCI insight. 2019: [PMID: 30753168 10.1172/jci.insight.125348: 10.1172/jci.insight.125348]
22. Lashen H. Role of metformin in the management of polycystic ovary syndrome. Therapeutic advances in endocrinology and metabolism. 2010: 117 [PMID: 23148156 10.1177/2042018810380215: 10.1177/2042018810380215]
23. Lv WS, Wen JP, Li L, Sun RX, Wang J, Xian YX, Cao CX, Wang YL, Gao YY. The effect of metformin on food intake and its potential role in hypothalamic regulation in obese diabetic rats. Brain research. 2012: 11 [PMID: 22325091 10.1016/j.brainres.2012.01.028: 10.1016/j.brainres.2012.01.028]

24. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metabolism: clinical and experimental. 2016: 20 [PMID: 26773926 10.1016/j.metabol.2015.10.014: 10.1016/j.metabol.2015.10.014

ASIDE Internal Medicine

Original Article

Investigating Racial Disparities in Insulin Pump Use Among People with Type 1 Diabetes Across the United States: A Retrospective Multicenter Study

Mahmoud Nassar[1], Ahmed Y. Azzam[2], Mahmoud M. Morsy[3], Iqra Patoli[1], Angad Gill[1], Erlin J. Marte[4]*

1- Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, New York, USA.
2- Montefiore-Einstein Cerebrovascular Research Lab, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA.
3- Faculty of Medicine, October 6 University, 6th of October City, Giza, Egypt.
4- Chief of Endocrinology, Director of Endocrine and Diabetes Department at VA Western New York Health Care, Veterans Affairs, Buffalo, NY, USA.

ARTICLE INFO

Article history:
Received 02 Dec. 2024
Received in revised form 24 Dec. 2024
Accepted 26 Dec. 2024

Keywords:
Racial Disparity
Diabetes
Insulin Pump
Real-World Evidence
CGM

ABSTRACT

Introduction: Despite technological advances in Type 1 Diabetes Mellitus (T1D) management, racial disparities in insulin pump utilization persist. We investigated patterns of insulin pump adoption across different racial groups using a large-scale, multi-institutional database to quantify these disparities and identify potential intervention points.

Methods: We conducted a retrospective cohort study using the TriNetX research network, analyzing data from 978,665 T1D patients across 66 healthcare organizations. Propensity score matching was employed to balance cohorts, with a focused sub-analysis of Buffalo, NY (n=6,080) to examine regional variations in comparison to the United States nationwide present data.

Results: Nationwide data revealed significant racial disparities in insulin pump utilization, with White patients showing the highest adoption rate (11.74%) compared to Black or African American (AA) patients (4.056%). Buffalo cohort demonstrated higher overall adoption rates but maintained similar disparity patterns (White: 30.18%, Black or AA: 13.75%). Post-matching analysis confirmed these disparities persisted independent of demographic factors.

Conclusions: Our findings reveal significant racial disparities in insulin pump adoption, with regional variations suggesting the influence of institutional factors. These results highlight the need for targeted interventions to promote equitable access to diabetes technology and prevent the widening of health disparities in T1D care.

* ***Corresponding author:*** *Mahmoud Nassar, MD, PhD, Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, New York, USA. Email Address: Dr.Nassar@aucegypt.edu*

ISSN (Print) 3065-9671, ISSN (Online) 3065-968X – see front matter

Citation: Nassar M, Azzam AY, Morsy MM, Patoli I, Gill A, Marte E. Investigating Racial Disparities in Insulin Pump Use Among People with Type 1 Diabetes Across the United States: A Retrospective Multicenter Study. ASIDE Int Med. 2024;1(1). doi: 10.71079/ASIDE.IM.0000012262412

https://doi.org/10.71079/ASIDE.IM.0000012262412
Journal homepage: https://asidejournals.com/index.php/internal-medicine

1. Introduction

Type 1 Diabetes Mellitus (T1D) management has been revolutionized by advanced technologies, particularly insulin pumps, which have demonstrated significant improvements in glycemic control, quality of life, and reduction of diabetes-related complications [1]. However, despite these well-documented benefits, we continue to observe substantial disparities in access to and utilization of these vital technologies across different racial and ethnic groups in the United States [2].

The previous and current literature evidence have highlighted concerning patterns of inequitable access to diabetes technology [3], with studies suggesting that racial and ethnic minorities face disproportionate barriers to insulin pump adoption. These disparities persist even when controlling for socioeconomic factors and insurance coverage, indicating deeper systemic issues in healthcare delivery and access [4]. While existing literature has documented these disparities, comprehensive analyses of large-scale [5], multi-institutional data examining racial patterns in insulin pump utilization remain limited [6]. Understanding and addressing these disparities has become increasingly crucial as diabetes technology continues to advance. Recent studies have shown that early adoption of insulin pump therapy is associated with better long-term outcomes, including reduced rates of diabetic ketoacidosis, severe hypoglycemia, and diabetes-related hospitalizations [7]. However, if certain racial and ethnic groups systematically experience delayed access to or reduced utilization of these technologies [8], we risk perpetuating and potentially widening existing health disparities in diabetes care [9].

Our study aims to provide a comprehensive analysis of racial disparities in insulin pump utilization among adults with T1D across the United States, leveraging data from a large network of healthcare organizations. By highlighting and addressing both nationwide patterns and focused regional data from Buffalo, New York, we aim to understand how these disparities manifest at different geographic and institutional levels using the TriNetX database; The TriNetX database and research network represents a federated health research platform that integrates de-identified electronic health records from several healthcare organizations across the United States, providing real-world data from over 197 million unique patient records. This network enables large-scale observational studies through standardized data collection and analysis tools while maintaining compliance with privacy regulations and institutional policies [9].

This dual-perspective approach allows us to identify both broad systemic patterns and local variations in technology access and adoption. The significance of our study is concerned about its potential to inform targeted interventions and policy changes. By quantifying the extent of racial disparities in insulin pump utilization and identifying specific patterns across different healthcare settings, we can better understand where interventions are most needed.

2. Methods

2.1. Study Design and Data Source:

We conducted a retrospective cohort study utilizing the TriNetX research network platform (TriNetX Inc., Cambridge, MA, USA), a federated health research network that aggregates de-identified electronic health records from 66 healthcare organizations across the United States (https://trinetx.com/solutions/live-platform/). The study period concluded with data extraction on September 25, 2024, employing a standardized query approach through the TriNetX platform to identify eligible participants and extract relevant clinical and demographic data.

2.2. Study Population:

The study population comprised adults (⩾18 years) with a confirmed diagnosis of T1D, identified using International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code E10. Participants were stratified into two distinct cohorts based on their insulin delivery method: individuals using insulin pump therapy (pump cohort, n=84,903) and those not using insulin pump therapy (no pump cohort, n=893,762), forming an initial nationwide sample of 978,665 patients. Insulin pump usage was identified through Current Procedural Terminology (CPT) codes and medical device records within the electronic health record system. Additionally, data on Continuous Glucose Monitoring (CGM) utilization was collected.

2.3. Data Collection and Variables:

Demographic and clinical data collection encompassed age (calculated at the time of data extraction), sex (male/female), and self-reported race/ethnicity. Race and ethnicity categories followed U.S. Census Bureau classifications, including White, Black or African American (AA), Hispanic or Latino, Asian, Native Hawaiian or Other Pacific Islander, and American Indian or Alaska Native. Clinical variables included insulin pump usage status and comprehensive healthcare utilization metrics.

2.4. Statistical Analysis:

Our statistical approach employed propensity score matching to minimize selection bias and ensure robust analysis. We implemented 1:1 matching considering age, sex, and race/ethnicity as covariates, resulting in balanced cohorts of 84,723 patients each. Post-matching balance was confirmed with standardized mean differences less than 0.1 for all variables. Descriptive statistics were calculated with continuous variables presented as means ± standard deviations and categorical variables as frequencies and percentages. Between-group comparisons utilized Chi-square tests for categorical variables and Student's t-tests for continuous variables, with statistical significance set at $p<0.05$. To evaluate factors associated with pump utilization, we performed multivariate logistic regression analyses, adjusting for potential confounders including age, sex, and race/ethnicity, with results presented as adjusted odds ratios and 95% confidence intervals.

2.5. Geographic Sub-analysis:

A focused sub-analysis was conducted on a cohort from Buffalo, New York (n=6,080) to examine regional variations in insulin pump utilization patterns. This analysis employed identical statistical methodologies, with propensity score matching yielding 1,360 patients per group, matched for age, sex, and race/ethnicity, followed by comparative analyses between matched cohorts.

2.6. Ethical Approvals:

The study protocol received exemption from the University at Buffalo Institutional Review Board (IRB) committee (STUDY00007618). Data handling and analysis adhered to Health Insurance Portability and Accountability Act (HIPAA) guidelines, with the use of de-identified data through the TriNetX platform ensuring protection of patient privacy, compliance with federal regulations, and maintenance of data integrity.

3. Results

3.1. Baseline Characteristics:

In our nationwide cohort, we initially identified 978,665 eligible participants, comprising 84,903 patients in the pump cohort and 893,762 in the no-pump cohort (Table 1). Before propensity score matching, we

Table 1: Demographic Characteristics Before and After Propensity Score Matching in the U.S.-based cohort.

Characteristics	Before Matching			After Matching		
	No Pump (n=893,762)	Pump (n=84,903)	P-value	No Pump (n=84,723)	Pump (n=84,723)	P-value
Sex, n (%)						
Female	356,119 (48.56)	43,810 (54.41)	<0.0001	43,820 (54.41)	43,810 (54.41)	0.9612
Male	377,182 (51.44)	36,723 (45.59)	<0.0001	36,730 (45.59)	36,723 (45.59)	0.9726
Age (years)						
Current Age, mean ± SD	58.5 ± 21.9	40.3 ± 20.9	<0.0001	40.3 ± 20.9	40.3 ± 20.9	0.9546
Race/Ethnicity, n (%)						
White	464,764 (67.37)	65,453 (85.12)	<0.0001	65,477 (85.12)	65,453 (85.12)	0.8894
Black / African American	124,058 (17.98)	5,999 (7.80)	<0.0001	5,997 (7.80)	5,999 (7.80)	0.9849
Hispanic or Latino	74,688 (10.83)	4,344 (5.65)	<0.0001	4,336 (5.63)	4,344 (5.65)	0.9298
Asian	15,678 (2.27)	1,065 (1.38)	<0.0001	1,058 (1.38)	1,065 (1.38)	0.8785
Native Hawaiian or Other Pacific Islander	8,474 (1.23)	455 (0.59)	<0.0001	450 (0.58)	455 (0.59)	0.8676
American Indian or Alaska Native	3,395 (0.32)	217 (0.28)	<0.0001	200 (0.26)	217 (0.28)	0.4046

SD: Standard Deviation; n: Number (sample size); P-value: Probability Value

Table 2: Demographic Characteristics Before and After Propensity Score Matching in Buffalo cohort.

Characteristics	Before Matching			After Matching		
	No Pump (n=4,500)	Pump (n=1,580)	P-value	No Pump (n=1,360)	Pump (n=1,360)	P-value
Sex, n (%)						
Female	2,180 (48.44)	760 (48.10)	0.8143	640 (47.06)	670 (49.27)	0.2496
Male	2,070 (46.00)	760 (48.10)	0.1497	680 (50.00)	650 (47.79)	0.2498
Age (years)						
Current Age, mean ± SD	50.4 ± 24.7	27.9 ± 16.7	<0.0001	29.6 ± 17.6	29.5 ± 17.3	0.9187
Race/Ethnicity, n (%)						
White	3,040 (67.56)	1,310 (82.91)	<0.0001	1,100 (80.88)	1,100 (80.88)	1.0000
Black / African American	700 (15.56)	110 (6.96)	<0.0001	110 (8.09)	110 (8.09)	1.0000
Hispanic or Latino	230 (5.11)	70 (4.43)	0.2825	50 (3.68)	60 (4.41)	0.3304
Asian	60 (1.33)	30 (1.90)	0.1094	30 (2.21)	20 (1.47)	0.1535
American Indian or Alaska Native	40 (0.89)	10 (0.63)	0.3324	10 (0.74)	10 (0.74)	1.0000

SD: Standard Deviation; n: Number (sample size); P-value: Probability Value

Table 3: Prevalence of Insulin Pump and CGM Usage by Race in the USA and Buffalo, New York (2010-2024) among patients with T1D.

Race/Ethnicity	Insulin pump		CGM	
	USA	Buffalo	USA	Buffalo
White	11.74%	30.18%	11.55%	11.98%
Asian	5.79%	37.50%	8.92%	12.50%
Native Hawaiian or Other Pacific Islander	5.09%	100%	1.87%	0%
American Indian or Alaska Native	5.52%	20%	7.34%	20%
Unknown Race	5.01%	17.28%	6.59%	7.41%
Black or African American	4.06%	13.75%	6.20%	6.25%

T1D: Type 1 Diabetes; CGM: Continuous Glucose Monitoring; USA: United States of America

observed significant demographic differences between the cohorts (all p<0.0001). The pump cohort was notably younger (mean age 40.3 ± 20.9 years vs 58.5 ± 21.9 years) and had a higher proportion of female patients (54.41% vs 48.56%). We found substantial racial/ethnic disparities in pump utilization, with White patients representing a markedly higher proportion of the pump cohort compared to the no-pump cohort (85.12% vs 67.37%). Conversely, Black or AA (7.80% vs 17.98%), Hispanic or Latino (5.65% vs 10.83%), and Asian patients (1.38% vs 2.27%) were underrepresented in the pump cohort.

After propensity score matching, we achieved well-balanced cohorts of 84,723 patients each, with no significant differences in demographic characteristics (all p>0.05). In the matched cohorts, both groups maintained identical distributions of sex (54.41% female), age (40.3 ± 20.9 years), and racial/ethnic composition (White: 85.12%, Black or AA: 7.80%, Hispanic or Latino: 5.63-5.65%, Asian: 1.38%).

Our Buffalo sub-analysis included 6,080 patients (pump: n=1,580; no-pump: n=4,500) before matching (Table 2). Similar to our nationwide findings, we observed significant pre-matching disparities. The pump cohort was younger (27.9 ± 16.7 years vs 50.4 ± 24.7 years, p<0.0001) and showed comparable gender distribution (48.10% female vs 48.44%, p=0.8143). Racial disparities were evident, with White patients comprising a larger proportion of the pump cohort (82.91% vs 67.56%, p<0.0001) and Black or AA patients being underrepresented (6.96% vs 15.56%, p<0.0001).

Following propensity score matching in the Buffalo cohort, we achieved balanced groups of 1,360 patients each, with no significant demographic differences (all p>0.05). The matched cohorts showed comparable age (pump: 29.5 ± 17.3 years; no-pump: 29.6 ± 17.6 years), gender distribution (pump: 49.27% female; no-pump: 47.06%), and racial/ethnic composition (White: 80.88%, Black or AA: 8.09%, Hispanic or Latino: 3.68-4.41%).

3.2. Nationwide vs. Buffalo Comparison:

In our analysis of insulin pump and CGM usage across different racial groups, we observed significant disparities in adoption rates both nationally and in Buffalo. Our findings revealed substantial variations in technology utilization across racial and ethnic groups, with particularly notable differences in insulin pump usage (Table 3).

At the national level, we found that White individuals had the highest insulin pump adoption rate at 11.74%, markedly higher than all other racial groups. In contrast, Black or AA individuals showed the lowest insulin pump utilization rate at 4.056%, representing a nearly threefold difference. Other racial groups demonstrated intermediate adoption rates: Asian (5.79%), American Indian or Alaska Native (5.52%), Native Hawaiian or Other Pacific Islander (5.09%), and individuals of Unknown Race (5.01%).

While looking at Buffalo specifically, we observed generally higher adoption rates across all racial groups compared to national averages, though racial disparities persisted. In Buffalo, White individuals maintained the highest insulin pump usage rate at 30.18%, while Black or AA individuals showed a usage rate of 13.75%. Considerably, Asian individuals in Buffalo demonstrated a relatively high adoption rate of 37.5%.

When it comes to CGM usage, similar patterns of disparity were evident. Nationally, White individuals showed the highest CGM adoption rate at 11.55%, while Black or AA individuals had substantially lower usage at 6.2%. Asian individuals demonstrated relatively higher CGM adoption at 8.92%, followed by American Indian or Alaska Native (7.34%), Unknown Race (6.59%), and Native Hawaiian or Other Pacific Islander showing the lowest rate at 1.873%. In the Buffalo system, CGM adoption patterns showed some variation from national trends. White individuals maintained relatively high usage at 11.98%, while Asian individuals showed adoption rates of 12.5%. Black or AA individuals in

Buffalo system had CGM usage rates of 6.25%, similar to national figures. American Indian or Alaska Native individuals showed higher adoption at 20%, though this finding should be interpreted cautiously given potential sample size limitations.

It is demonstrated that there are persistent racial disparities in diabetes technology adoption within the United States, with particularly pronounced differences in insulin pump usage between White and Black or AA individuals, both nationally and regionally.

4. Discussion

Our study reveals significant racial disparities in insulin pump utilization among individuals with T1D across the United States, with particularly pronounced differences between White and Black or AA populations. These findings carry significant clinical implications, given that insulin pumps provide more precise insulin delivery and reduce risks of both hypoglycemia and hyperglycemia compared to MDI [10]. The integration of insulin pumps with CGM systems, enabling automated insulin delivery adjustments, further amplifies the importance of adoption rates, highlight multiple barriers to insulin pump access. These include high initial and ongoing costs [18], technical complexity requiring comprehensive education [19], and challenges related to healthcare provider biases [20]. The impact of these barriers is particularly pronounced among Black or AA populations, who often face additional socioeconomic challenges [21] and healthcare access limitations [22]. Geographic variations in our data, particularly between national and Buffalo-specific cohorts, suggest that local healthcare delivery systems significantly influence technology access [23]. The higher overall adoption rates in the Buffalo cohort, while encouraging, also demonstrate that addressing systemic barriers [24] and insurance coverage issues [25] may help reduce but not eliminate racial disparities. The lower insulin pump utilization rates among racial minorities likely contribute to poorer health outcomes [26], as previous studies have shown that limited access to advanced diabetes technologies is associated with higher rates of complications [27]. Our findings of persistent disparities, even after controlling for demographic factors, is consistent and parallel with some of the literature studies [28] showing that socioeconomic status alone does not fully explain these gaps [29]. To address these disparities, our results suggest the need for multilevel interventions. These should include improving insurance coverage, enhancing provider education about cultural competency, and developing targeted outreach programs for underserved communities [30]. The higher adoption rates in our Buffalo cohort, while still showing racial disparities, suggest that institutional policies and focused efforts to improve access can have positive impacts.

Our study has important considerations and future directions for clinical practice and health policy. First, healthcare systems should implement systematic approaches to evaluate and address barriers to insulin pump adoption among racial minorities. Second, provider education should emphasize both the technical aspects of insulin pump therapy and cultural competency in technology prescription. Third, insurance policies should be reviewed and modified to ensure equitable access to diabetes technologies.

The limitations of our study include its retrospective nature, potential selection bias in the TriNetX database, and inability to capture detailed socioeconomic factors or insurance status. Additionally, while our regional analysis provides valuable insights, the smaller sample sizes for certain racial groups may limit generalizability. Future studies should focus on prospective studies examining the impact of targeted interventions to reduce racial disparities in insulin pump adoption. Additionally, investigation of successful institutional policies and practices that have reduced disparities could provide valuable guidance addressing these disparities [11].

The disparity patterns we observed align with previous research demonstrating that advanced diabetes technologies significantly enhance glycemic control [12] and reduce adverse events [13]. Our findings of lower insulin pump adoption rates among racial minorities are particularly concerning given that CGM use has been associated with improved self-management and enhanced quality of life [14], with continuous application leading to reduced HbA1c levels and decreased glucose variability [15]. The contrast in insulin pump utilization between White (11.74%) and Black or AA individuals (4.056%) in our nationwide cohort reflects broader systemic inequities in healthcare access. These differences persist despite evidence that insulin pump therapy provides more stable glycemic control [16] and significantly reduces HbA1c levels compared to MDI [17]. The higher adoption rates observed in Buffalo cohort (White: 30.18%, Black or AA: 13.75%) suggest that regional variations and institutional factors may influence technology access, though racial disparities remain evident.

Our findings of persistent disparities, even in settings with higher overall

for broader implementation. These findings underscore the urgent need for systematic changes to address racial disparities in diabetes technology access. While technological advances continue to improve diabetes management capabilities, ensuring equitable access to these technologies remains a critical challenge requiring coordinated efforts from healthcare providers, institutions, and policymakers.

5. Conclusions

Our comprehensive analysis of racial disparities in insulin pump utilization among T1D patients reveals systemic inequities that require urgent attention. The present contrast in adoption rates between racial groups, particularly the threefold difference between White and Black or AA populations, suggests that technological advances in diabetes care may inadvertently widen existing health disparities if access barriers remain unaddressed. The regional variations observed between our nationwide and Buffalo cohorts provide valuable insights into the potential impact of institutional policies and local healthcare delivery systems. While higher overall adoption rates in the Buffalo cohort demonstrate that targeted interventions can improve access, the persistence of racial disparities even in this setting underscores the need for more comprehensive solutions. We propose a three-tiered approach to address these disparities: implementing systematic screening for technology eligibility across all racial groups, developing culturally competent diabetes education programs, and establishing institutional policies that prioritize equitable access to diabetes technologies. Future research should focus on evaluating the effectiveness of these interventions and identifying additional strategies to promote equitable adoption of insulin pump therapy.

Conflicts of Interest:
N/A.

Funding Source:
N/A

Acknowledgements:
N/A

Institutional Review Board (IRB) Approval:
The IRB Board at the Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, NY, USA approved the study protocol

and waived the need for IRB approval given the study design and study type.

LLM Statement:

We have employed an advanced Large Language Model (LLM) to enhance and refine the English-language writing. This process focused solely on improving the text's clarity and style, without generating or adding any new information to the content.

Authors Contribution Statement:

MN conceptualized the study and developed the methodology, with AYA leading the investigation alongside MMM; MN and AYA performed data analysis, while IP, AG, and EM contributed to data curation; MN prepared the original draft; MN and AYA created the visualizations; MN supervised the project and provided administrative oversight; all authors participated in manuscript review and editing, validated the findings, and approved the final version of the manuscript.

Data Availability Statement:

Available on TriNetX Database Based on Institutional Collaborations.

REFERENCES

1. *Syed FZ. Type 1 Diabetes Mellitus. Ann Intern Med. 2022: ITC33 [PMID: 35254878 10.7326/AITC202203150: 10.7326/AITC202203150]*
2. *Dayan CM, Besser REJ, Oram RA, Hagopian W, Vatish M, Bendor-Samuel O, Snape MD, Todd JA. Preventing type 1 diabetes in childhood. Science. 2021: 506 [PMID: 34326231 10.1126/science.abi4742: 10.1126/science.abi4742]*
3. *Zajec A, Trebusak Podkrajsek K, Tesovnik T, Sket R, Cugalj Kern B, Jenko Bizjan B, Smigoc Schweiger D, Battelino T, Kovac J. Pathogenesis of Type 1 Diabetes: Established Facts and New Insights. Genes (Basel). 2022: [PMID: 35456512 10.3390/genes13040706: 10.3390/genes13040706]*
4. *Bluestone JA, Buckner JH, Herold KC. Immunotherapy: Building a bridge to a cure for type 1 diabetes. Science. 2021: 510 [PMID: 34326232 10.1126/science.abh1654: 10.1126/science.abh1654]*
5. *Tonnies T, Brinks R, Isom S, Dabelea D, Divers J, Mayer-Davis EJ, Lawrence JM, Pihoker C, Dolan L, Liese AD, Saydah SH, D'Agostino RB, Hoyer A, Imperatore G. Projections of Type 1 and Type 2 Diabetes Burden in the U.S. Population Aged <20 Years Through 2060: The SEARCH for Diabetes in Youth Study. Diabetes Care. 2023: 313 [PMID: 36580405 10.2337/dc22-0945: 10.2337/dc22-0945]*
6. *Lawrence JM, Divers J, Isom S, Saydah S, Imperatore G, Pihoker C, Marcovina SM, Mayer-Davis EJ, Hamman RF, Dolan L, Dabelea D, Pettitt DJ, Liese AD, Group SfDiYS. Trends in Prevalence of Type 1 and Type 2 Diabetes in Children and Adolescents in the US, 2001-2017. JAMA. 2021: 717 [PMID: 34427600 10.1001/jama.2021.11165: 10.1001/jama.2021.11165]*
7. *Rafferty J, Stephens JW, Atkinson MD, Luzio SD, Akbari A, Gregory JW, Bain S, Owens DR, Thomas RL. A retrospective epidemiological study of type 1 diabetes mellitus in wales, UK between 2008 and 2018. Int J Popul Data Sci. 2021: 1387 [PMID: 34007896 10.23889/ijpds.v6i1.1387: 10.23889/ijpds.v6i1.1387]*
8. *Wass JAH, Arlt W, Semple RK, Hammond P, Campbell F. Strategies for the Management of Type 1 Diabetes. In: Wass JAH, Arlt W, Semple RK, Wass J, Arlt W, Semple R, editors. Oxford Textbook of Endocrinology and Diabetes 3e: Oxford University Press; 2022. p. 2024-2031.*
9. *Janez A, Guja C, Mitrakou A, Lalic N, Tankova T, Czupryniak L, Tabak AG, Prazny M, Martinka E, Smircic-Duvnjak L. Insulin Therapy in Adults with Type 1 Diabetes Mellitus: a Narrative Review. Diabetes Ther. 2020: 387 [PMID: 31902063 10.1007/s13300-019-00743-7: 10.1007/s13300-019-00743-7]*
10. *Visser MM, Charleer S, Fieuws S, De Block C, Hilbrands R, Van Huffel L, Maes T, Vanhaverbeke G, Dirinck E, Myngheer N, Vercammen C, Nobels F, Keymeulen B, Mathieu C, Gillard P. Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial. Lancet. 2021: 2275 [PMID: 34089660 10.1016/S0140-6736(21)00789-3: 10.1016/S0140-6736(21)00789-3]*
11. *Varkevisser RDM, Birnie E, Mul D, van Dijk PR, Aanstoot HJ, Wolffenbuttel BHR, van der Klauw MM. Type 1 diabetes management: Room for improvement. J Diabetes. 2023: 255 [PMID: 36808864 10.1111/1753-0407.13368: 10.1111/1753-0407.13368]*
12. *Zaharieva DP, Messer LH, Paldus B, O'Neal DN, Maahs DM, Riddell MC. Glucose Control During Physical Activity and Exercise Using Closed Loop Technology in Adults and Adolescents with Type 1 Diabetes. Can J Diabetes. 2020: 740 [PMID: 33011134 10.1016/j.jcjd.2020.06.003: 10.1016/j.jcjd.2020.06.003]*
13. *Pratley RE, Kanapka LG, Rickels MR, Ahmann A, Aleppo G, Beck R, Bhargava A, Bode BW, Carlson A, Chaytor NS, Fox DS, Goland R, Hirsch IB, Kruger D, Kudva YC, Levy C, McGill JB, Peters A, Philipson L, Philis-Tsimikas A, Pop-Busui R, Shah VN, Thompson M, Vendrame F, Verdejo A, Weinstock RS, Young L, Miller KM, Wireless Innovation for Seniors With Diabetes Mellitus Study G. Effect of Continuous Glucose Monitoring on Hypoglycemia in Older Adults With Type 1 Diabetes: A Randomized Clinical Trial. JAMA. 2020: 2397 [PMID: 32543682 10.1001/jama.2020.6928: 10.1001/jama.2020.6928]*
14. *Galindo RJ, Aleppo G. Continuous glucose monitoring: The achievement of 100 years of innovation in diabetes technology. Diabetes Res Clin Pract. 2020: 108502 [PMID: 33065179 10.1016/j.diabres.2020.108502: 10.1016/j.diabres.2020.108502]*
15. *Laffel LM, Kanapka LG, Beck RW, Bergamo K, Clements MA, Criego A, DeSalvo DJ, Goland R, Hood K, Liljenquist D, Messer LH, Monzavi R, Mouse TJ, Prahalad P, Sherr J, Simmons JH, Wadwa RP, Weinstock RS, Willi SM, Miller KM, Teens CGMIi, Young Adults with TDSG, Cde. Effect of Continuous Glucose Monitoring on Glycemic Control in Adolescents and Young Adults With Type 1 Diabetes: A Randomized Clinical Trial. JAMA. 2020: 2388 [PMID: 32543683 10.1001/jama.2020.6940: 10.1001/jama.2020.6940]*
16. *Keyu G, Jiaqi L, Liyin Z, Jianan Y, Li F, Zhiyi D, Qin Z, Xia L, Lin Y, Zhiguang Z. Comparing the effectiveness of continuous subcutaneous insulin infusion with multiple daily insulin injection for patients with type 1 diabetes mellitus evaluated by retrospective continuous glucose monitoring: A real-world data analysis. Front Public Health. 2022: 990281 [PMID: 36091534 10.3389/fpubh.2022.990281: 10.3389/fpubh.2022.990281]*
17. *McAuley SA, Vogrin S, Lee MH, Paldus B, Trawley S, de Bock MI, Abraham MB, Bach LA, Burt MG, Cohen ND, Colman PG, Davis EA, Hendrieckx C, Holmes-Walker DJ, Jenkins AJ, Kaye J, Keech AC, Kumareswaran K, MacIsaac RJ, McCallum RW, Sims CM, Speight J, Stranks SN, Sundararajan V, Ward GM, Jones TW, O'Neal DN, Australian JC-LRG. Less Nocturnal Hypoglycemia but Equivalent Time in Range Among Adults with Type 1 Diabetes Using Insulin Pumps Versus Multiple Daily Injections. Diabetes Technol Ther. 2021: 460 [PMID: 33351699 10.1089/dia.2020.0589: 10.1089/dia.2020.0589]*
18. *Huo L, Deng W, Lan L, Li W, Shaw JE, Magliano DJ, Ji L. Real-World Application of Insulin Pump Therapy Among Patients With Type 1 Diabetes in China: A Cross-Sectional Study. Front Endocrinol (Lausanne). 2022: 891718 [PMID: 35757419 10.3389/fendo.2022.891718: 10.3389/fendo.2022.891718]*
19. *Harper A, Aflatoony L, Wilson W, Wang W, editors. Exploring the Challenges and Potential Alternatives to Insulin Pump Technologies. Proceedings of the 14th EAI International Conference on Pervasive Computing Technologies for Healthcare; 2020.*

20. *Gu M. Effective Use of Insulin Pump in Patients with Type 1 Diabetes. The Journal of Korean Diabetes. 2020: 36 10.4093/jkd.2020.21.1.36: 10.4093/jkd.2020.21.1.36]*
21. *DemİR G, ÇUbukcu E, Akcay N. Problems in Insulin Pump Management and Suggestions for Solutions in Children and Adolescents with Type 1 Diabetes. Turkish Journal of Diabetes and Obesity. 2022: 187 10.25048/tudod.1105407: 10.25048/tudod.1105407]*
22. *O'Donnell HK, Vigers T, Johnson SB, Pyle L, Wright N, Deeb LC, Driscoll KA. Pump It Up! A randomized clinical trial to optimize insulin pump self-management behaviors in adolescents with type 1 diabetes. Contemp Clin Trials. 2021: 106279 [PMID: 33440262 10.1016/j.cct.2021.106279: 10.1016/j.cct.2021.106279]*
23. *Boscari F, Avogaro A. Current treatment options and challenges in patients with Type 1 diabetes: Pharmacological, technical advances and future perspectives. Rev Endocr Metab Disord. 2021: 217 [PMID: 33755854 10.1007/s11154-021-09635-3: 10.1007/s11154-021-09635-3]*
24. *Almogbel E. Impact of insulin pump therapy on glycemic control among adult Saudi type-1 diabetic patients. An interview-based case-control study. J Family Med Prim Care. 2020: 1013 [PMID: 32318460 10.4103/jfmpc.jfmpc_869_19: 10.4103/jfmpc.jfmpc_869_19]*
25. *Biester T, Schwandt A, Heidtmann B, Rami-Merhar B, Haak T, Festa A, Kostow S, Muller A, Monkemoller K, Danne T, Initiative DPV. Declining Frequency of Acute Complications Associated with Tubeless Insulin Pump Use: Data from 2,911 Patients in the German/Austrian Diabetes Patienten Verlaufsdokumentation Registry. Diabetes Technol Ther. 2021: 527 [PMID: 33684335 10.1089/dia.2020.0675: 10.1089/dia.2020.0675]*
26. *Agarwal S, Schechter C, Gonzalez J, Long JA. Racial-Ethnic Disparities in Diabetes Technology use Among Young Adults with Type 1 Diabetes. Diabetes Technol Ther. 2021: 306 [PMID: 33155826 10.1089/dia.2020.0338: 10.1089/dia.2020.0338]*
27. *Everett EM, Wright D, Williams A, Divers J, Pihoker C, Liese AD, Bellatorre A, Kahkoska AR, Bell R, Mendoza J, Mayer-Davis E, Wisk LE. A Longitudinal View of Disparities in Insulin Pump Use Among Youth with Type 1 Diabetes: The SEARCH for Diabetes in Youth Study. Diabetes Technol Ther. 2023: 131 [PMID: 36475821 10.1089/dia.2022.0340: 10.1089/dia.2022.0340]*
28. *Lipman TH, Willi SM, Lai CW, Smith JA, Patil O, Hawkes CP. Insulin Pump Use in Children with Type 1 Diabetes: Over a Decade of Disparities. J Pediatr Nurs. 2020: 110 [PMID: 32889433 10.1016/j.pedn.2020.08.007: 10.1016/j.pedn.2020.08.007]*
29. *Kanbour S, Jones M, Abusamaan MS, Nass C, Everett E, Wolf RM, Sidhaye A, Mathioudakis N. Racial Disparities in Access and Use of Diabetes Technology Among Adult Patients With Type 1 Diabetes in a U.S. Academic Medical Center. Diabetes Care. 2023: 56 [PMID: 36378855 10.2337/dc22-1055: 10.2337/dc22-1055]*
30. *Carrillo-Iregui A, Lopez-Mitnik G, Cossio S, Garibay-Nieto N, Arheart KL, Messiah SE. Relationship between aminotransferases levels and components of the metabolic syndrome among multiethnic adolescents. J Pediatr Endocrinol Metab. 2010: 1253 [PMID: 21714459 10.1515/jpem.2010.199: 10.1515/jpem.2010.199]*

ASIDE Internal Medicine

Original Article

Real-World Epidemiological Analysis of Gastrointestinal Neuroendocrine Carcinomas: A TriNetX-Based Study

*Bahaaeldin Baraka[1], Mahmoud Nassar[2], Ahmed Y. Azzam[3], Mahmoud M. Morsy[4], Eyad Ibrahim[5], Jin Wu[6], Ahmad Ghorab[7]**

1- Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom.
2-Department of Medicine, Division of Endocrinology, Diabetes and Metabolism, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, New York, USA.
3- Visiting Assistant Professor, SNU Medical Big Data Research Center, Seoul National University, Seoul, South Korea.
4- Clinical Research Fellow, American Society for Inclusion, Diversity, and Health Equity (ASIDE), DE, USA.
5- University of Houston, Houston, TX, USA.
6- National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA.
7- Department of Medicine, Division of Hematology and Oncology, Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas, USA

ARTICLE INFO

Article history:
Received 14 Dec. 2024
Received in revised form 24 Dec. 2024
Accepted 27 Dec. 2024

Keywords:
Neuroendocrine Carcinoma
Gastrointestinal
Cancer
Epidemiology
Real-World Evidence
Real-World Data

ABSTRACT

Introduction: Gastrointestinal neuroendocrine carcinomas (GI-NECs) are a diverse group of aggressive tumors with variable clinical outcomes. Although progress has been made in classifying and treating these cancers, detailed real-world data on their anatomical distribution and survival rates are scant. This study utilizes a large database to explore the epidemiological and anatomical distribution patterns and to assess the survival outcomes of GI-NECs.

Methods: We accessed the TriNetX global health research network, comprising about 197 million patient records from 160 healthcare organizations, to perform a retrospective analysis of GI-NEC cases through November 2024. Patients were identified via the ICD-O-3 morphology code 8246/3. We analyzed TNM staging and survival rates across various GI locations.

Results: We identified 4,515 cases of NECs with a nearly equal gender distribution (47.27% male, 47.35% female) and an average age of 71 years. Unknown primary sites were the most common (n=692) followed by Small intestinal NECs (n=682) and others. The least common were liver and intrahepatic biliary NECs (n=71). Survival varied significantly by site, from a high of 37.5% in small intestinal NECs to just 11.4% in hepatic/biliary NECs, highlighting notable differences even within the same organ, such as between appendiceal and cecal NECs (44.8% vs. 26.4%).

Conclusions: This study highlights the necessity for site-specific treatment and improved diagnostic strategies, especially for the worst-prognosis NECs found in hepatic and biliary locations. Our findings are vital for developing targeted therapies and refining prognostic tools based on anatomical sites.

* ***Corresponding author:*** *Ahmad Ghorab, MD, MS, MPH, MBA, FACP, Department of Medicine, Division of Hematology and Oncology, Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas, USA. Email Address: mailto:ahmad.ghorab@bcm.edu*

Citation: Baraka B, Nassar M, Azzam AY, et al. Real-World Epidemiological Analysis of Gastrointestinal Neuroendocrine Carcinomas: A TriNetX-Based Study. ASIDE Int Med. 2024;1(1). doi:10.71079/ASIDE.IM.0000012272414

https://doi.org/10.71079/ ASIDE.IM.0000012272414
Journal homepage: https://asidejournals.com/index.php/internal-medicine

1. Introduction

The landscape of gastrointestinal neuroendocrine carcinomas (GI-NECs) has undergone significant transformations in recent decades, marked by evolving epidemiological patterns and refined classification systems. Our understanding of these complex neoplasms has been enhanced by emerging epidemiological data, revealing notable geographic variations in incidence variations. In Norway, GI-NECs have exhibited a remarkable 200% increase from 1993 to 2021, particularly those originating from the gastrointestinal tract [1]. Similarly, England has suffered from growth, with age-standardized incidence of neuroendocrine neoplasms (NENs) reaching 9 per 100,000 in 2016 [2]. This trend contrasts with data from Switzerland, where despite a steady increase in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) incidence (1.7% annually in men and 1.3% in women), GEP-NEC rates remained relatively stable from 1976 to 2016 [3].

The complexity of these neoplasms is further illustrated by their diverse biological behavior and histopathological characteristics. The World Health Organization's refined classification system has been instrumental in delineating crucial distinctions between well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs) [4]. This classification emphasizes the critical role of proliferation indices and differentiation status, where NETs span grades G1 through G3 based on mitotic counts and Ki-67 indices, while NECs consistently manifest as high-grade (G3) neoplasms [5]. The introduction of high-grade well-differentiated tumors (NET G3) as a distinct entity has particularly revolutionized our approach to diagnosis and treatment strategies [6].

Our study aims to address several gaps in the current understanding of GI-NECs. While previous studies have documented increasing incidence rates across different geographical regions, real-world data on site-specific survival patterns and TNM staging distributions remain scarce. Existing studies have primarily focused on single-institution experiences or specific anatomical sites, lacking the breadth needed to establish comparative outcomes across different GI locations. Furthermore, while the prognostic implications of tumor grade and differentiation are well-established, the relationship between anatomical location and survival outcomes remains inadequately characterized. By analyzing a large, multi-institutional cohort through TriNetX, our study provides significant insights into site-specific staging patterns, subsite variations in survival, and the prognostic implications of anatomical location.

The aim of our paper is to conduct an analysis of real-world epidemiological data using the TriNetX platform. We aim to bridge critical knowledge gaps in understanding the contemporary landscape of GI-NECs. This investigation is particularly pertinent given the reported poor prognosis of metastatic cases [7] and the imperative need for precise classification to guide treatment decisions [8].

2. Methods

2.1. Study Design and Data Source:

In this retrospective cohort study, we utilized the data from the TriNetX Research Network, which includes around 197 million electronic health records to the date from about 160 healthcare organizations around the world, mainly in the United States [9], but also including around a total of 21 countries from all over the world (https://trinetx.com/solutions/live-platform/). The dataset provides rich patient-level information, including demographics, diagnoses, treatments, procedures, and outcomes, coded using standard medical classification systems such as ICD-10 and CPT. Our analysis focused on extracting comprehensive data specifically related to GI-NECs across multiple anatomical sites within the gastrointestinal tract, up to November 2024.

2.2. Study Population and Cohort Definition:

We systematically identified patients with histologically confirmed NECs using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) morphology code 8246/3. Our study encompassed primary GI-NECs originating from five distinct anatomical locations: stomach, pancreas, liver and intrahepatic biliary ducts, small intestine, and large intestine, as defined by the International Classification of Diseases, Tenth Revision, Procedure Coding System (ICD-10-PCS). To maintain diagnostic precision and cohort homogeneity, we explicitly excluded cases of well-differentiated neuroendocrine tumors (ICD-O 8240/3) and neuroendocrine neoplasms originating from sites outside our predefined anatomical regions of interest.

2.3. Data Extraction and Variables:

Through the TriNetX explore cohort tool, we extracted comprehensive demographic characteristics for each anatomical site-specific cohort, including age at diagnosis, sex distribution, and racial demographics. To ensure accurate staging information, we utilized the TriNetX oncology module to identify and classify cases according to the TNM staging system. This approach allowed us to stratify cases based on tumor extent (T), lymph node involvement (N), and presence of distant metastasis (M), providing crucial insights into disease presentation and progression patterns.

2.4. Survival Analysis:

For survival analysis, we employed the Cox proportional hazards model after verifying the proportional hazards assumption using Schoenfeld residuals. The model included the following covariates: age, gender, race, anatomical site, TNM stage, and presence of metastasis. The proportionality assumption was tested globally and for each covariate. Time-dependent covariates were created and tested when the proportional hazards assumption was violated.

2.5. Statistical Considerations:

The TriNetX statistical analysis framework is designed to handle potential confounding factors and ensure robust comparative analyses across different anatomical sites and patient subgroups. We utilized the built-in statistical capabilities of the TriNetX platform, which automatically adjusts for demographic variations and accounts for missing data patterns in the real-world dataset. Missing data was handled automatically by TriNetX platform without any action from our side.

3. Results

Our analysis encompassed 4,515 patients with confirmed all body from different various sites across different anatomical sites. The demographic profile revealed a relatively balanced gender distribution (47.27% male, 47.35% female) with a mean age of 71 ± 14 years (range: 18-90 years). The cohort predominantly comprised White patients (52.71%), followed by Black or African American (12.56%) and Asian (1%) populations, with 33.73% categorized as Other/Unknown race. Among those with documented ethnicity, 55.13% were identified as Not

Hispanic or Latino, while 3.81% were Hispanic or Latino.

3.1. Anatomical Distribution and Staging:

The Unknown primary sites were the most common (n=692) followed by Small intestinal NECs (n=682), large intestine (n=269), pancreas (n=252), and stomach (n=193). Liver and intrahepatic biliary ducts represented the least common primary site (n=71), as listed in (**Table 1)**. TNM staging analysis revealed variable patterns across anatomical locations (**Table 2**). For T-staging, 23% of all cases were classified as TX, indicating challenges in primary tumor assessment. Among staged tumors, T1 (16%) and T2 (15%) were most prevalent, followed by T3 (13%) and T4 (9%). Notably, the small intestine demonstrated a higher proportion of T3 tumors (21%) compared to other sites.

Nodal involvement analysis showed that 31% of cases were N0, while 17% were N1, with significant variations across sites. The small intestine exhibited the highest rate of N1 disease (39%), whereas liver and intrahepatic biliary tract cases showed predominantly early or undetermined nodal status. Metastatic disease (M1) was present in 27% of all cases, with the highest proportion observed in small intestinal NECs (32%) and liver/biliary NECs (13% of documented cases).

3.2. Survival Analysis:

Five-year overall survival rates demonstrated marked variations across anatomical sites and subsites (**Table 3**). Small intestinal NECs showed the most favorable prognosis with a 37.5% five-year survival rate, with rates varying by specific location (duodenum 32.8%, jejunum 36.9%, ileum 38.4%). Colorectal NECs demonstrated the second-best survival outcomes at 31.8%, with notable variations between subsites - ranging from 26.4% in cecal NECs to 44.8% in appendiceal NECs. Gastric NECs showed intermediate survival rates (23.7%), with some variation between cardia (19.4%) and body/fundus (24.2%) locations (**Figure 1**). Pancreatic NECs demonstrated poorer outcomes with a 15.9% five-year survival rate, showing modest variations based on anatomical location within the pancreas (head 13.8%, body 16.2%, tail 17.1%). Hepatic and biliary NECs exhibited the poorest prognosis with an 11.4% five-year survival rate, with intrahepatic lesions showing particularly poor outcomes (8.9%). These survival patterns correlate with the staging distributions observed across different anatomical sites, reflecting the impact of disease extent on patient outcomes.

3.3. *Site-Specific Epidemiological Patterns and TNM Distributions:*

3.3.1. *Stomach:*

Among gastric NECs (n=193), the cardia accounted for 24 cases, while the body/fundus comprised 27 cases. Tumor staging indicated that 28% of cases were classified as TX, reflecting incomplete tumor assessment. The proportions of T1 and T2 cases were 24% and 13%, respectively, with notable staging challenges in the cardia.

3.3.2. *Pancreas:*

Pancreatic NECs (n=252) displayed distinct anatomical subsites, with the head of the pancreas (n=213) showing the highest proportion of T3 lesions (23%). The tail of the pancreas demonstrated a more favorable distribution with a significant proportion of T2 cases (32%) compared to the head (22%).

3.3.3. *Small Intestine:*

The small intestine (n=682) demonstrated significant variation between its subsites: duodenum (n=120), jejunum (n=19), and ileum (n=207). Notably, T3 staging was more prevalent in the ileum (27%) and jejunum (53%), suggesting a pattern of advanced local invasion in these subsites. Nodal involvement was highest in ileal NECs

.

3.3.4. *Liver and Intrahepatic Biliary Ducts:*

Liver and intrahepatic biliary NECs (n=71) exhibited the poorest TNM profile, with 15% of cases classified as TX and a significant proportion of patients presenting with metastatic disease (M1). This aligns with the aggressive nature of NECs in this anatomical site.

3.3.5. *Unknown Primary Sites:*

A substantial cohort (n=692) had NECs of unknown primary origin. These cases exhibited the highest mean age at diagnosis (73 ± 13 years) and significant staging ambiguity, with 14% categorized as TX. The high proportion of M1 staging (29%).

3.4. *Comparative Insights Across Sites:*

A comprehensive analysis revealed that the proportion of advanced-stage (T3/T4) disease was highest in the small intestine and pancreas, with lower stages more common in stomach NECs. Lymph node involvement (N1) was most frequent in small intestine NECs (39%), with markedly lower rates in liver and biliary tract cases.

Table 1: Demographics for All Sites

Characteristic	All Sites*	Small Intestine	Unknown Sites	Large Intestine	Pancreas	Stomach	Liver and Intra-Hepatic Ducts
Number of Patients	4515	682	692	269	252	193	71
Age (mean ± SD)	71 ± 14	70 ± 12	73 ± 13	67 ± 16	68 ± 14	68 ± 15	70 ± 12
Age range (years)	18-90	29-90	31-90	18-90	24-90	20-90	32-90
Male (%)	52.63	52.66	51.14	46.45	53.47	55.19	49.25
Female (%)	47.37	47.34	48.86	53.55	46.53	44.81	50.75
White (%)	80.77	87.89	78.42	84.45	83.65	75.77	75.61
Black or African American (%)	19.23	12.11	21.58	15.55	16.35	24.23	24.39
Hispanic or Latino (%)	6.47	4.81	6.15	9.48	8	10.53	25.64
Not Hispanic or Latino (%)	93.53	95.19	93.85	90.52	92	89.47	74.36

**Total cohort (N=4,515) comprises patients with single confirmed anatomical sites shown above (n=2,356) and those with multiple site involvement (n=1,892) or indeterminate primary location (n=267).*

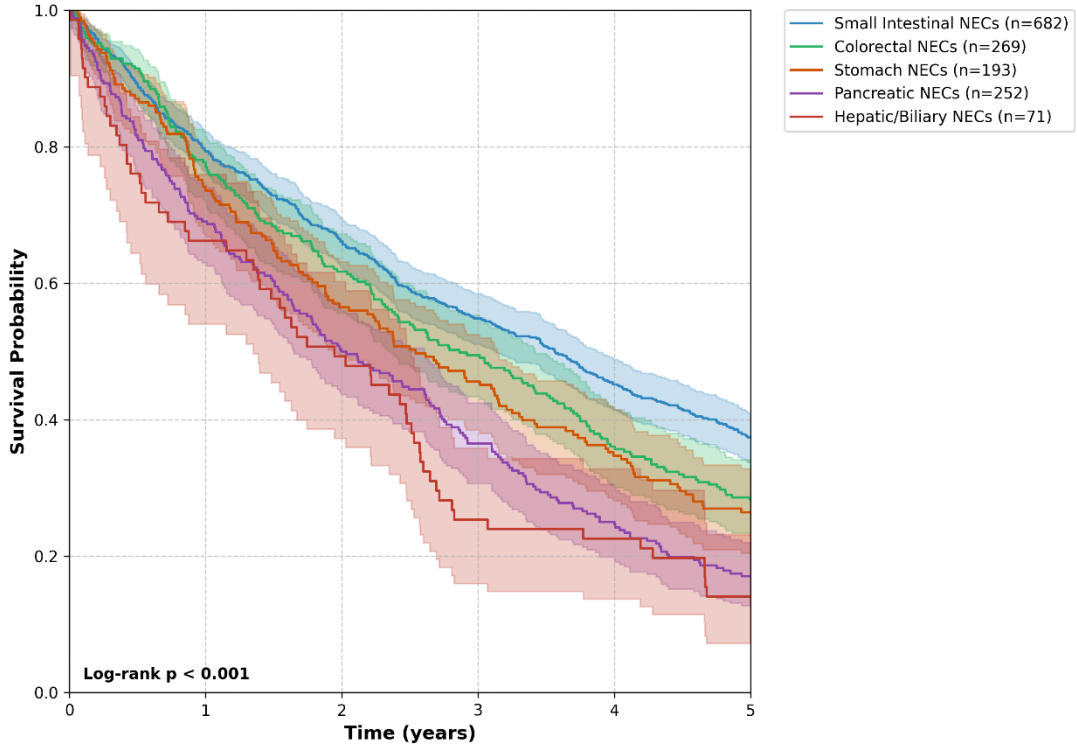
Demographic percentages are calculated from available data, excluding missing values. All included cases met histopathological criteria for GI-NEC diagnosis

Table 2: TNM Classification for Our Cohort

Category	Stage	All (n=2892)*	Small Intestine (n=493)	Large Intestine (n=210)	Stomach (n=145)	Pancreas (n=160)	Liver and Intra-Hepatic Biliary Ducts (n=142)
T Stage	TX	1042 (23%)	172 (25%)	98 (36%)	54 (28%)	58 (23%)	94 (14%)
	T0	18 (0%)	10 (1%)	10 (4%)	10 (5%)	10 (4%)	10 (1%)
	T1	719 (16%)	69 (10%)	48 (18%)	46 (24%)	37 (15%)	24 (3%)
	T2	672 (15%)	97 (14%)	35 (13%)	26 (13%)	30 (12%)	14 (2%)
	T3	565 (13%)	146 (21%)	50 (19%)	16 (8%)	29 (12%)	12 (2%)
	T4	407 (9%)	93 (14%)	31 (12%)	22 (11%)	13 (5%)	15 (2%)
N Stage	N0	1397 (31%)	164 (24%)	110 (41%)	79 (41%)	83 (33%)	46 (7%)
	N1	747 (17%)	268 (39%)	75 (28%)	35 (18%)	33 (13%)	17 (2%)
	N2	284 (6%)	21 (3%)	12 (4%)	10 (5%)	10 (4%)	10 (1%)
	N3	125 (3%)	10 (1%)	0 (0%)	10 (5%)	0 (0%)	10 (1%)
	NX	883 (20%)	131 (19%)	61 (23%)	40 (21%)	56 (22%)	88 (13%)
M Stage	M0	1468 (33%)	246 (36%)	109 (41%)	87 (45%)	68 (27%)	46 (7%)
	M1	1234 (27%)	216 (32%)	84 (31%)	55 (28%)	73 (29%)	88 (13%)

*Data presented includes 2,892 patients with available staging information. TX cases (n=1,042) represent histologically confirmed GI-NECs where primary tumor assessment was technically limited. T0 cases (n=18) indicate confirmed metastatic disease without identifiable primary tumors on imaging. Percentages are calculated based on available staging data per anatomical site. Staging completeness varies by anatomical location and diagnostic accessibility. TX = primary tumor cannot be assessed; T0 = no evidence of primary tumor; T1-T4 = increasing degrees of primary tumor invasion; N0 = no regional lymph node metastasis; N1-N3 = increasing degrees of regional lymph node involvement; NX = regional lymph nodes cannot be assessed; M0 = no distant metastasis; M1 = distant metastasis present.

Figure 1: Cox-Hazard Survival Curve By Anatomical Site.



Number at risk:

	Year 0	Year 1	Year 2	Year 3	Year 4	Year 5
Small Intestinal NECs	682	541	451	374	308	255
Colorectal NECs	269	209	166	133	97	76
Stomach NECs	193	142	109	88	67	51
Pancreatic NECs	252	174	126	92	63	43
Hepatic/Biliary NECs	71	47	35	18	16	10

4. Discussion

Our analysis of GI-NECs using the TriNetX database uncovers valuable insights into epidemiological trends, staging distributions, and survival outcomes across various anatomical sites. The balanced gender distribution and predominant occurrence in older adults (mean age: 71 ± 14 years) align with previous epidemiological studies. However, our cohort demonstrated a slightly higher mean age compared to the median age of 65 years reported in the Norwegian registry data from 1993 to 2010 [10]. The racial distribution in our study, with a predominance of White patients (52.71%), reflects similar patterns observed in other large-scale epidemiological studies, though our cohort demonstrated a higher proportion of Black or African American patients (12.56%) compared to previous reports.

This variation might reflect advancements in diagnostic capabilities for small intestinal NECs, as highlighted by Koffas et al. (2023), or real geographical differences in disease distribution [11]. Our finding of a substantial proportion of cases with unknown primary sites (n=692) underscores the diagnostic challenges emphasized by Koffas et al., (2023) further reinforcing the need for enhanced diagnostic strategies, such as PET/CT imaging and circulating tumor cell analysis [11].

The TNM staging descriptive data revealed important patterns that impact clinical management. The high proportion of TX classification (23%) across all sites in our study underscores persistent challenges in primary tumor assessment, particularly in anatomically challenging locations. These findings align with Merola et al. (2020), who highlighted the complexities of achieving accurate histopathological diagnoses in GEP-NENs, particularly in non-specialist settings [12]. Similarly, the higher proportion of T3 tumors in small intestinal NECs (21%) compared to other sites suggests a potential delay in diagnosis, likely due to the anatomical location and nonspecific presenting symptoms, as noted by Lee et al. (2019), who emphasized the advanced presentation of small intestinal NECs due to diagnostic difficulties [13].

Survival outcomes in our study demonstrated marked variations across anatomical sites, with small intestinal NECs showing the most favorable five-year survival rate (37.5%). This finding contrasts with earlier studies, such as Alese et al. (2019), which reported poor survival outcomes for high-grade GI NECs overall, emphasizing the aggressive nature of these tumors [14]. The particularly poor prognosis observed in hepatic and biliary NECs (11.4% five-year survival) is consistent with the aggressive nature of high-grade NECs described by Venizelos et al. (2021), who highlighted their molecular complexity and limited treatment options [15]. The variation in survival rates between different subsites within the same organ system (e.g., appendiceal NECs at 44.8% versus cecal NECs at 26.4%) highlights the prognostic influence of anatomical location. While our findings may relate to differences in lymphatic drainage patterns and detection timing, site-specific molecular heterogeneity, as discussed by Venizelos et al. (2021), could also play a role [15].

Our observation of higher nodal involvement in small intestinal NECs (39% N1 disease) emphasizes the aggressive nature of these tumors. While Burkart et al. (2018) primarily explored molecular targets like BRAF mutations, their findings highlight the metastatic potential of gastrointestinal NECs, which may correlate with lymphotropic behavior [16]. The presence of metastatic disease in 27% of all cases at diagnosis underscores the aggressive nature of GI-NECs and aligns with observations by Chen et al. (2021) regarding late-stage presentation [17]. The particularly poor outcomes in hepatic and biliary NECs (8.9% five-year survival for intrahepatic lesions) reflect the challenges in managing these anatomically complex tumors. Mestre-Alagarda et al. (2023) highlighted the molecular heterogeneity and poor prognosis associated with aggressive NETs and NECs, which likely contribute to the difficulties in treatment [18]. The significant variation in survival outcomes between different anatomical subsites highlights the importance of site-specific approaches to management. For instance, the relatively better outcomes in appendiceal NECs (44.8% five-year survival) compared to other colorectal sites suggest potential biological differences that warrant further investigation. The gradual deterioration in survival rates from proximal to distal pancreatic NECs (tail 17.1% vs. head 13.8%) may reflect differences in presentation timing and surgical accessibility.

Table 3: Five-Year Survival Rate in Our Cohort.

Anatomical Site	5-Year Overall Survival (%)
Stomach NECs (All)	23.7
Stomach Cardia	19.4
Stomach Body/Fundus	24.2
Pancreatic NECs (All)	15.9
Head of Pancreas	13.8
Body of Pancreas	16.2
Tail of Pancreas	17.1
Hepatic and Biliary NECs (All)	11.4
Intrahepatic	8.9
Colorectal NECs (All)	31.8
Cecum	26.4
Appendix	44.8
Ascending Colon	27.9
Sigmoid Colon	32.4
Rectum	36.7
Small Intestinal NECs (All)	37.5
Duodenum	32.8
Jejunum	36.9
Ileum	38.4

Our study has several important limitations that warrant consideration. First, the predominant representation of U.S. healthcare organizations in the TriNetX database may introduce geographic and demographic biases. While our cohort showed diversity in racial distribution (52.71% White, 12.56% Black or African American), these proportions may not accurately reflect global population demographics, potentially limiting generalizability to other geographic regions, particularly Asia and South America, where GI-NEC epidemiology may differ substantially. Second, inherent to retrospective database studies, our analysis is subject to several potential biases. Coding inaccuracies and misclassification

* ***Corresponding author:*** *Ahmad Ghorab, MD, MS, MPH, MBA, FACP, Department of Medicine, Division of Hematology and Oncology, Dan L Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas, USA. Email Address: mailto:ahmad.ghorab@bcm.edu*

ISSN (Print) 3065-9671, ISSN (Online) 3065-968X – see front matter

Citation: Baraka B, Nassar M, Azzam AY, et al. Real-World Epidemiological Analysis of Gastrointestinal Neuroendocrine Carcinomas: A TriNetX-Based Study. ASIDE Int Med. 2024;1(1). doi:10.71079/ASIDE.IM.0000012272414

https://doi.org/10.71079/ ASIDE.IM.0000012272414
Journal homepage: https://asidejournals.com/index.php/internal-medicine

errors may exist, particularly in distinguishing between well-differentiated NETs and poorly differentiated NECs, as this distinction often requires detailed histopathological review. The high proportion of unknown primary sites (n=692) and TX classification (23%) might reflect both genuine diagnostic challenges and documentation limitations within the database. Third, our study's temporal scope may not fully capture recent advances in diagnostic techniques and therapeutic approaches. The rapid evolution of molecular profiling and targeted therapies in NECs means that some patients in our cohort may have received different standard-of-care treatments depending on their diagnosis date. Advanced molecular techniques, such as the use of liquid biopsies to complement solid tumor analyses, as suggested by Knappskog et al. (2023), could improve the identification of targetable mutations and enhance biomarker assessment, particularly in patients with limited tumor tissue availability [19].

The applicability of our findings across different healthcare settings requires careful consideration. While our results demonstrate clear anatomical site-specific survival patterns, these outcomes may vary in healthcare systems with different diagnostic capabilities and treatment accessibility. For instance, the superior survival rates observed in small intestinal NECs (37.5%) may reflect earlier detection in well-resourced healthcare settings, and these outcomes might not be reproducible in regions with limited access to advanced imaging or surgical expertise. The demographic characteristics of our cohort, particularly the mean age of 71 years and racial distribution, should be considered when applying these findings to different populations. Healthcare systems serving younger populations or different ethnic compositions may observe varying patterns of disease presentation and outcomes. Additionally, the treatment patterns and survival outcomes observed in our U.S.-predominant cohort may not directly translate to healthcare systems with different organizational structures or resource availability.

Despite these limitations, our study's large sample size and detailed anatomical analysis provide valuable insights for clinical practice. The observed survival differences between subsites within organs (e.g., appendiceal versus cecal NECs) remain relevant across different healthcare settings, as they likely reflect underlying biological differences rather than treatment variations. Furthermore, our findings regarding the poor prognosis of hepatic and biliary NECs (11.4% survival) highlight a universal need for improved therapeutic strategies for these anatomical locations, regardless of geographic setting.

5. Conclusions

Our large-scale analysis of GI-NECs through the TriNetX database reveals critical patterns that significantly impact patient care and outcomes. The marked variations in survival rates across anatomical sites, ranging from 44.8% in appendiceal NECs to 8.9% in intrahepatic lesions emphasize the necessity for site-specific treatment approaches rather than a one-size-fits-all strategy. The high proportion of advanced-stage disease at diagnosis, particularly in small intestinal NECs with 39% showing N1 disease, underscores the urgent need for improved early detection methods. The high number of cases with unknown primary sites (n=692) and high TX classification rates (23%) highlights a critical gap in current diagnostic capabilities. This finding suggests the potential value of implementing standardized diagnostic algorithms incorporating advanced imaging techniques and molecular profiling. Furthermore, the notably poor outcomes in hepatic and biliary NECs (11.4% five-year survival) identify a specific patient subgroup requiring innovative therapeutic strategies. Our findings have direct implications for clinical practice, supporting the development of anatomical site-specific treatment protocols and suggesting the need for more aggressive surveillance in high-risk anatomical locations. The significant survival differences between subsites within the same organ system, such as the variance between appendiceal and cecal NECs, indicate that tumor location should be a key consideration in prognostication and treatment planning. Our epidemiological results raise an important concern in targeted therapies according to anatomical regions, and biomolecular profiles, particularly in investigating the biological basis for site-specific outcome variations and developing targeted therapeutic approaches. The integration of these findings with emerging molecular and genetic data could further refine our understanding of GI-NECs and lead to more effective, personalized treatment strategies.

Conflicts of Interest:
N/A.

Funding Source:
N/A

Acknowledgements:
N/A

Institutional Review Board (IRB) Approval:
The IRB Board at the Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, NY, USA approved the study protocol and waived the need for IRB approval given the study design and study type.

LLM Statement:
We have employed an advanced Large Language Model (LLM) to enhance and refine the English-language writing. This process focused solely on improving the text's clarity and style, without generating or adding any new information to the content.

Authors Contribution Statement:
MN conceptualized the study and developed the methodology, with AYA leading the investigation alongside MMM; MN and AYA performed data analysis, while IP, AG, and EM contributed to data curation; MN prepared the original draft; MN and AYA created the visualizations; MN supervised the project and provided administrative oversight; all authors participated in manuscript review and editing, validated the findings, and approved the final version of the manuscript.

Data Availability Statement:
Available on TriNetX Database Based on Institutional Collaborations.

References

1. Thiis-Evensen E, Boyar Cetinkaya R. Incidence and prevalence of neuroendocrine neoplasms in Norway 1993-2021. J Neuroendocrinol. 2023: e13264 [PMID: 36988112 10.1111/jne.13264: 10.1111/jne.13264]

2. White BE, Rous B, Chandrakumaran K, Wong K, Bouvier C, Van Hemelrijck M, George G, Russell B, Srirajaskanthan R, Ramage JK. Incidence and survival of neuroendocrine neoplasia in England 1995–2018: A retrospective, population-based study. The

Lancet Regional Health – Europe. 2022: 10.1016/j.lanepe.2022.100510: 10.1016/j.lanepe.2022.100510]

3. Alwan H, La Rosa S, Andreas Kopp P, Germann S, Maspoli-Conconi M, Sempoux C, Bulliard JL. Incidence trends of lung and gastroenteropancreatic neuroendocrine neoplasms in Switzerland. Cancer Med. 2020: 9454 [PMID: 33078908 10.1002/cam4.3524: 10.1002/cam4.3524]

4. Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, Busam KJ, de Krijger RR, Dietel M, El-Naggar AK, Fernandez-Cuesta L, Kloppel G, McCluggage WG, Moch H, Ohgaki H, Rakha EA, Reed NS, Rous BA, Sasano H, Scarpa A, Scoazec JY, Travis WD, Tallini G, Trouillas J, van Krieken JH, Cree IA. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol. 2018: 1770 [PMID: 30140036 10.1038/s41379-018-0110-y: 10.1038/s41379-018-0110-y]

5. Gill AJ. Why did they change that? Practical implications of the evolving classification of neuroendocrine tumours of the gastrointestinal tract. Histopathology. 2021: 162 [PMID: 33382490 10.1111/his.14172: 10.1111/his.14172]

6. Inzani F, Petrone G, Rindi G. The New World Health Organization Classification for Pancreatic Neuroendocrine Neoplasia. Endocrinol Metab Clin North Am. 2018: 463 [PMID: 30098710 10.1016/j.ecl.2018.04.008: 10.1016/j.ecl.2018.04.008]

7. Escobar KM, Vicente-Villardon JL, Villacis Gonzalez RE, Castillo Cordova PH, Sanchez Rodriguez JM, De la Cruz-Velez M, Siteneski A. Neuroendocrine Tumors: An Analysis of Prevalence, Incidence, and Survival in a Hospital-Based Study in Ecuador. Healthcare (Basel). 2022: [PMID: 36011226 10.3390/healthcare10081569: 10.3390/healthcare10081569]

8. Helderman NC, Suerink M, Kilinc G, van den Berg JG, Nielsen M, Tesselaar MET. Relation between WHO Classification and Location- and Functionality-Based Classifications of Neuroendocrine Neoplasms of the Digestive Tract. Neuroendocrinology. 2024: 120 [PMID: 37690447 10.1159/000534035: 10.1159/000534035]

9. Palchuk MB, London JW, Perez-Rey D, Drebert ZJ, Winer-Jones JP, Thompson CN, Esposito J, Claerhout B. A global federated real-world data and analytics platform for research. JAMIA open. 2023: ooad035 [PMID: 37193038 10.1093/jamiaopen/ooad035: 10.1093/jamiaopen/ooad035]

10. Boyar Cetinkaya R, Aagnes B, Thiis-Evensen E, Tretli S, Bergestuen DS, Hansen S. Trends in Incidence of Neuroendocrine Neoplasms in Norway: A Report of 16,075 Cases from 1993 through 2010. Neuroendocrinology. 2015: 1 10.1159/000442207 %J Neuroendocrinology: 10.1159/000442207 %J Neuroendocrinology]

11. Koffas A, Giakoustidis A, Papaefthymiou A, Bangeas P, Giakoustidis D, Papadopoulos VN, Toumpanakis C. Diagnostic work-up and advancement in the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. Front Surg. 2023: 1064145 [PMID: 36950054 10.3389/fsurg.2023.1064145: 10.3389/fsurg.2023.1064145]

12. Merola E, Zandee W, de Mestier L, Klumpen HJ, Makulik K, Geboes K, van Velthuysen ML, Couvelard A, Cros J, van Eeden S, Hoorens A, Stephenson T, Zajecki W, de Herder W, Munir A. Histopathological Revision for Gastroenteropancreatic Neuroendocrine Neoplasms in Expert Centers: Does It Make the Difference? Neuroendocrinology. 2021: 170 [PMID: 32155627 10.1159/000507082: 10.1159/000507082]

13. Lee JE, Hong SH, Jung HI, Son MW, Ahn TS, Han SW, Cho JH. Small-cell neuroendocrine carcinoma of the ileum: case report and literature review. BMC Surg. 2019: 135 [PMID: 31510991 10.1186/s12893-019-0591-8: 10.1186/s12893-019-0591-8]

14. Alese OB, Jiang R, Shaib W, Wu C, Akce M, Behera M, El-Rayes BF. High-Grade Gastrointestinal Neuroendocrine Carcinoma Management and Outcomes: A National Cancer Database Study. Oncologist. 2019: 911 [PMID: 30482824 10.1634/theoncologist.2018-0382: 10.1634/theoncologist.2018-0382]

15. Venizelos A, Elvebakken H, Perren A, Nikolaienko O, Deng W, Lothe IMB, Couvelard A, Hjortland GO, Sundlov A, Svensson J, Garresori H, Kersten C, Hofsli E, Detlefsen S, Krogh M, Sorbye H, Knappskog S. The molecular characteristics of high-grade gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer. 2021: 1 [PMID: 34647903 10.1530/ERC-21-0152: 10.1530/ERC-21-0152]

16. Burkart J, Owen D, Shah MH, Abdel-Misih SRZ, Roychowdhury S, Wesolowski R, Haraldsdottir S, Reeser JW, Samorodnitsky E, Smith A, Konda B. Targeting BRAF Mutations in High-Grade Neuroendocrine Carcinoma of the Colon. J Natl Compr Canc Netw. 2018: 1035 [PMID: 30181415 10.6004/jnccn.2018.7043: 10.6004/jnccn.2018.7043]

17. Chen D, Bao X, Zhang R, Ding Y, Zhang M, Li B, Zhang H, Li X, Tong Z, Liu L, Zhou X, Wang S, Cheng X, Zheng Y, Ruan J, Fang W, Zhao P. Depiction of the genomic and genetic landscape identifies CCL5 as a protective factor in colorectal neuroendocrine carcinoma. Br J Cancer. 2021: 994 [PMID: 34331023 10.1038/s41416-021-01501-y: 10.1038/s41416-021-01501-y]

18. Mestre-Alagarda C, Srirajaskanthan R, Zen Y, Giwa M, Howard M, Ooft ML. Genetic and epigenetic prognosticators of neuroendocrine tumours of the GI tract, liver, biliary tract and pancreas: A systematic review and meta-analysis. Histopathology. 2024: 255 [PMID: 37565289 10.1111/his.15025: 10.1111/his.15025]

19. Knappskog S, Grob T, Venizelos A, Amstutz U, Hjortland GO, Lothe IM, Kersten C, Hofsli E, Sundlov A, Elvebakken H, Garresori H, Couvelard A, Svensson J, Sorbye H, Perren A. Mutation Spectrum in Liquid Versus Solid Biopsies From Patients With Advanced Gastroenteropancreatic Neuroendocrine Carcinoma. JCO Precis Oncol. 2023: e2200336 [PMID: 36753687 10.1200/PO.22.00336: 10.1200/PO.22.00336]

ASIDE Internal Medicine

Original Article

Epidemiological Patterns, Treatment Response, and Metabolic Correlations of Idiopathic Intracranial Hypertension: A United States-Based Study From 1990 to 2024

Ahmed Y. Azzam[1, 2, 3], Mahmoud Nassar[4, 5], Mahmoud M. Morsy[6, 7], Adham A. Mohamed[8], Jin Wu[9], Muhammed Amir Essibayi[1, 10], David J. Altschul[1, 10]*

1-Montefiore-Einstein Cerebrovascular Research Lab, Albert Einstein College of Medicine, Bronx, NY, USA.
2-Director of Clinical Research and Clinical Artificial Intelligence, American Society for Inclusion, Diversity, and Health Equity (ASIDE), Delaware, USA.
3-Visiting Assistant Professor, SNU Medical Big Data Research Center, Seoul National University, Gwanak-gu, Seoul, South Korea.
4-Department of Medicine, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, New York, USA.
5-Founder, American Society for Inclusion, Diversity, and Health Equity (ASIDE), Delaware, USA.
6-Faculty of Medicine, October 6 University, Giza, Egypt.
7-Clinical Research Fellow, American Society for Inclusion, Diversity, and Health Equity (ASIDE), Delaware, USA.
8-Cairo University Hospitals, Cairo University, Cairo, Egypt.
9-National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA
10-Department of Neurological Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA.

*** Corresponding author:** *David J. Altschul, MD, Department of Neurological Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, 10467, USA. Email Address: mailto: daltschu@montefiore.org*

ISSN (Print) 3065-9671, ISSN (Online) 3065-968X – see front matter

Citation: Azzam AY, Nassar M, Morsy MM, et al. Epidemiological Patterns, Treatment Response, and Metabolic Correlatations of Idiopathic Intracranial Hypertension: A US-Based Study From 1994 to 2024. ASIDE Int Med. 2024;1(1). doi:10.71079/ASIDE.IM.0000012282413

https://doi.org/10.71079/ASIDE.IM.0000012282413
Journal homepage: https://asidejournals.com/index.php/internal-medicine

ARTICLE INFO

Article history:
Received 08 Dec. 2024
Received in revised form 22 Dec. 2024
Accepted 28 Dec. 2024

Keywords:
Idiopathic Intracranial Hypertension
Pesudotumor Cerebri
Benign Intracranial Hypertesion
Intracranial Pressure
Headache; Papilledema
Epidemiology
United States
Metabolic Diseases
TriNetX

ABSTRACT

Introduction: Idiopathic Intracranial Hypertension (IIH) presents an increasing health burden with changing demographic patterns. We studied nationwide trends in IIH epidemiology, treatment patterns, and associated outcomes using a large-scale database analysis within the United States (US).
Methods: We performed a retrospective analysis using the TriNetX US Collaborative Network database (1990-2024). We investigated demographic characteristics, time-based trends, geographic distribution, treatment pathway patterns, comorbidity profiles, and associated risks with IIH. We used multivariate regression, Cox proportional hazards modeling, and standardized morbidity ratios to assess various outcomes and associations.
Results: Among 51,526 patients, we found a significant increase in adult IIH incidence from 16.0 per 100,000 in 1990-1999 to 127.0 per 100,000 in 2020-2024 (adjusted RR: 6.94, 95% CI: 6.71-7.17). Female predominance increased over time (female-to-male ratio: 3.29, 95% CI: 3.18-3.40). Southern regions showed the highest prevalence (43.0%, n=21,417). During the 2020-2024 period, initial medical management success rates varied between acetazolamide (42.3%) and topiramate (28.7%). Advanced interventional procedures showed 82.5% success rates in refractory cases during the same timeframe. Cox modeling for the entire study period (1990-2024) revealed significant associations between IIH and metabolic syndrome (HR: 2.14, 95% CI: 1.89-2.39) and cardiovascular complications (HR: 1.76, 95% CI: 1.58-1.94), independent of Body Mass Index.
Conclusions: Our findings highlight IIH as a systemic disorder with significant metabolic implications beyond its neurological manifestations. The marked regional disparities and rising incidence rates, especially among adults, suggest the need for targeted healthcare strategies. Early intervention success strongly predicts favorable outcomes, supporting prompt diagnosis and treatment initiation. These results advocate for an integrated approach combining traditional IIH management with broad metabolic screening care.

1. Introduction

Intracranial Hypertension (IIH) represents a significant and complex nervous system disease characterized by elevated intracranial pressure (ICP) without identifiable structural or vascular causes within the nervous system or the intracranial cavity [1]. Over the past three decades, the epidemiological information and trends of IIH have undergone various changes, with new evidence suggesting significant shifts in its demographic distribution, clinical presentation, and associated risk factors [2-4]. IIH has been classified in the current studies as a rare condition, the recent evidence is showing an increased rate of the disease [1, 5].

IIH has been recognized to be a disease affecting young, overweight females at childbearing age, however, more detailed epidemiological details are needed to assess the disease statistics from different prospects across age groups, race and ethnicity, and geographical distribution [6-8]. The United States has been showing a rising prevalence of obesity and metabolic disorders in recent years, which may correlate with increased IIH cases. So, estimating the changing patterns is an important consideration for disease burden estimation at the nationwide level [9]. Previous epidemiological studies have been limited by several factors including small sample sizes, limited regional variability, and limited follow-up and observation periods, creating gaps in our understanding of nationwide epidemiological variations [10-12]. While several single-center and regional studies have reported increasing incidence rates, longitudinal data analyzing nationwide patterns, especially age-specific subgroups, racial and ethnic differences in disease statistics, and geographical variations are of significant importance, but currently limited in the present studies. In addition to that, the relationship between IIH and various comorbidities, especially metabolic and cardiovascular conditions, requires more focus within a large-scale, population-based framework [1, 5, 10-15].

Treatment approaches for IIH have changed significantly during the past decades with the appearance of new treatment modalities such as venous sinus stenting [16], which raise important concerns about the need for detailed analysis of therapeutic patterns, progression through treatment modalities, and long-term outcomes across different patient subgroups to assess the progression of disease management [17-20]. Based on that, we aim to conduct a retrospective multicenter analysis of IIH epidemiology within the United States using the TriNetX US Collaborative Network database, spanning from 1990 to 2024. Our study aims to estimate the disease incidence and prevalence, highlight the demographic and geographic variations, analyze treatment patterns and outcomes, and assess comorbidity profiles across different patient subgroups. Our study represents one of the largest and most detailed analyses of IIH epidemiology to date, aiming to address important considerations in disease epidemiology and highlight further prospective research.

Table 1: Demographic and Clinical Characteristics In Association with IIH Patients in the United States.

Characteristic (Total= 51,500)	Number, (%) or Mean ± SD
Demographics:	
Age (years) Mean ± SD	37 ± 10
Age range (years)	18-60
Sex:	
Female	44,063 (85.56)
Male	5,783 (11.23)
Unknown	1,654 (3.21)
Race:	
White	30,604 (59.43)
Black or African American	9,162 (17.79)
Asian	649 (1.26)
American Indian or Alaska Native	191 (0.37)
Native Hawaiian or Other Pacific Islander	129 (0.25)
Not Specified / Not Reported	8,288 (16.09)
Ethnicity:	
Not Hispanic or Latino	34,160 (66.33)
Hispanic or Latino	4,965 (9.64)
Not Specified / Not Reported	12,375 (24.03)
Associated Conditions	
Headache Disorders:	
Any Migraine	17,996 (35.0)
Chronic migraine	5,853 (11.4)
Migraine without aura	7,076 (13.7)
Migraine with aura	4,522 (8.8)
Pain Syndromes:	
Chronic pain	8,122 (15.8)
Chronic pain syndrome	1,011 (2.0)
Autonomic Disorders:	
Disorders of the autonomic nervous system	1,234 (2.4)
Postural orthostatic tachycardia syndrome	638 (1.2)
Other Neurological Conditions:	
Post-viral fatigue syndrome	2,509 (4.9)
Other specified disorders of the brain	2,102 (4.1)
Encephalopathy	826 (1.6)

IIH: Idiopathic Intracranial Hypertension. Conditions are not mutually exclusive; patients may have multiple diagnoses.

2. Methods

2.1. Study Design and Data Source:

We performed a retrospective cohort analysis on the TriNetX platform (https://trinetx.com/solutions/live-platform/), selecting the US Collaborative Network database within the platform, we determined 34 year period from January 1, 1990, to December 9, 2024. TriNetX platform is a federated research network database that aggregates de-identified electronic health records from participating healthcare organizations that are mainly within the United States, providing longitudinal patient data from the electronic health records from several participating healthcare organizations. The Institutional Review Board at the Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, NY, USA approved the study protocol under IRB approval number (STUDY00008628) within the given status of ethical approvals exemption, as this study does not involve direct patient contact.

2.2. Patient Population and Eligibility Criteria:

Our study population included individuals with confirmed IIH diagnoses identified within the TriNetX US Collaborative Network database using International Classification of Diseases (ICD) coding systems, specifically ICD-10-CM code G93.2 (Benign Intracranial Hypertension). Study inclusion required a primary IIH diagnosis, available demographic data within the research network, at least one documented clinical encounter between January 1, 1990, and December 9, 2024, and age ⩾0 years at the time of diagnosis. We excluded cases with secondary causes of intracranial hypertension (including brain tumors or other space-occupying lesions, cerebral venous thrombosis, and medication-induced intracranial hypertension), missing or incomplete diagnostic confirmation, insufficient follow-up data (<30 days post-diagnosis), and concurrent neurological conditions that could confound IIH diagnosis. All diagnoses underwent validation through a review of diagnostic codes and clinical documentation within the electronic health records system, with ambiguous or conflicting diagnostic information being excluded to maintain data integrity. For age-based subgroup analysis, we classified patients into four cohorts: pediatric (0-14 years), teenage (15-19 years), adult (20-64 years), and geriatric (⩾65 years).

The following ICD-10 procedure codes were used to identify the included therapeutic interventions: Cerebrospinal fluid shunting procedures (00HU0JZ, 00HV0JZ, 009U3ZZ for ventriculoperitoneal shunt; 009V3ZZ for lumboperitoneal shunt); Optic nerve sheath fenestration (009S30Z, 009S3ZZ); Venous sinus stenting (037H3DZ, 037J3DZ, 037K3DZ for dural venous sinus); Bariatric surgical procedures (0D160ZA, 0D160Z4 for gastric bypass; 0DB60Z3 for sleeve gastrectomy); Lumbar puncture procedures (009U3ZX); and therapeutic medication administration identified through codes for Acetazolamide (3E033TZ), Topiramate (3E033VZ), and other diuretics (3E033GC).

2.3. Data Collection and Variable Assessment:

We aimed to extract the relevant demographic and individual characteristic information including age, gender/sex, race, and ethnicity from the available electronic health records. Clinical data included associated conditions, comorbidity profiles, and detailed treatment trajectories. Our assessment included both baseline characteristics and longitudinal outcomes over time. For treatment pathways analysis, we observed and extracted the reported therapeutic interventions across three progressive stages: initial medical management, treatment optimization, and advanced interventions. Comorbidity assessment focused on metabolic, endocrine, gastrointestinal, hepatic, cardiovascular, and renal disorders, with both baseline prevalence and cumulative incidence present.

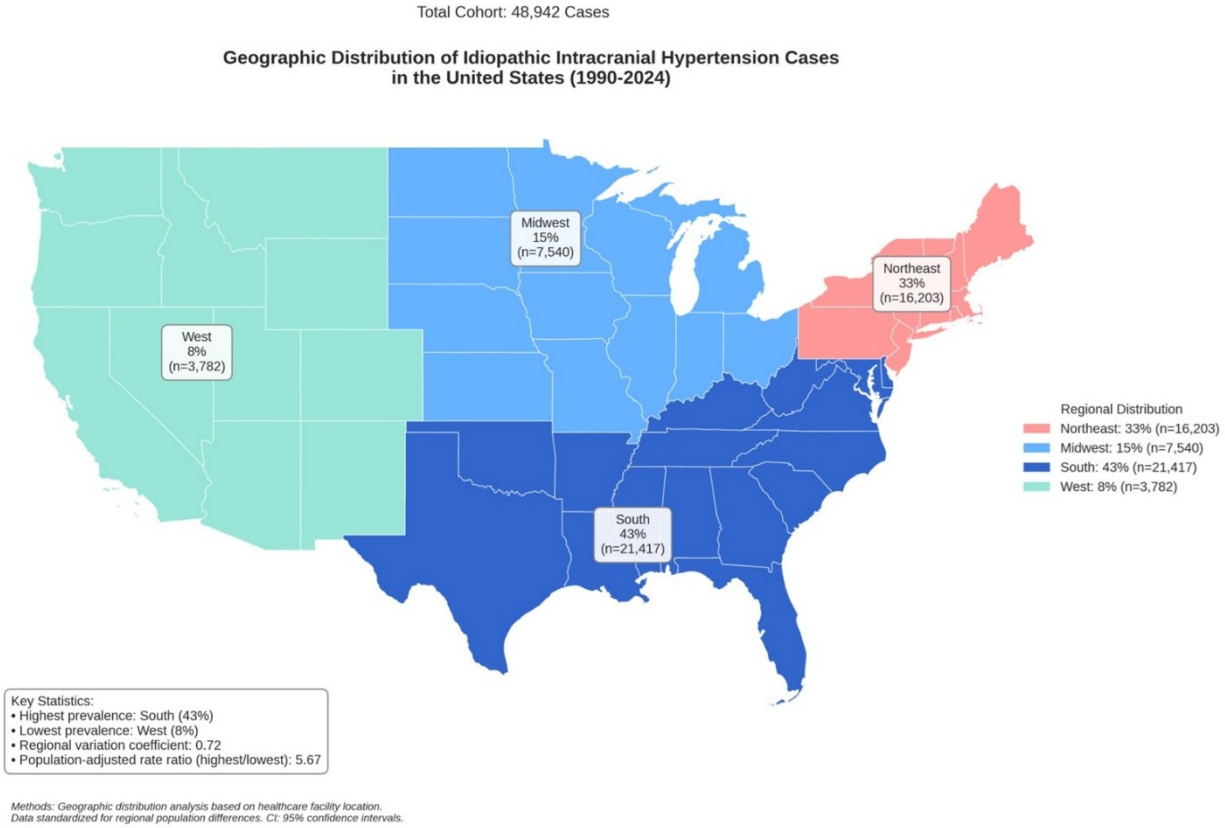
2.4. Epidemiological Analysis Framework:

We used a multi-tiered analytical approach to assess disease burden over years from 1990 to 2024. Incidence proportion and prevalence rates were calculated per 100,000 population across four time periods: 1990-1999, 2000-2009, 2010-2019, and 2020-2024. Demographic grouping enabled detailed time-based trend analysis. For racial and ethnic disparity assessment, we used ratio comparisons using white individuals as the reference population in our cohort. Geographic distribution analysis encompassed four major U.S. regions: Northeast, Midwest, South, and West, with standardization for regional population differences.

2.5. Treatment Pattern Evaluation:

Our longitudinal treatment pathways analysis framework followed the therapeutic progression through three stages. Initial medical management assessment focused on monotherapy regimens and primary response rates. Treatment optimization evaluation encompassed combination therapy approaches and secondary response patterns. Advanced intervention analysis included surgical procedures and their

Figure 1: Geographical Distribution of IIH In The United States From 1990 to 2024.



success rates. We calculated progressive treatment-based metrics including intervention timing, treatment duration, and resolution periods, and also utilized interquartile ranges for variability assessment.

Table 2: Total IIH Incidence Proportion In the United States From 1990 to 2024. Values represent new cases per 100,000 people in each period.

Category	1990-1999	2000-2009	2010-2019	2020-2024
Age Groups:				
Pediatric (0-14)	14	31	83	56
Teenager (15-19)	24	60	162	116
Adult (20-64)	16	33	122	127
Geriatric (65+)	67	27	33	29
Gender:				
Female	22	47	153	148
Male	8	13	50	45
Race:				
American Indian/Alaska Native	108	33	113	134
Asian	8	6	45	57
Black/African American	18	40	143	152
Native Hawaiian/Pacific Islander	41	34	92	105
White	15	29	103	93
Ethnicity:				
Hispanic or Latino	10	27	100	114
Not Hispanic or Latino	15	31	111	106

2.6. Statistical Analysis:

In our statistical analysis, we used several statistical techniques including, multivariate regression with adjustment for age, sex, and comorbidity profiles. We also calculated odds ratios with corresponding 95% confidence intervals for key predictive factors, maintaining statistical significance at $p<0.05$. Geographic variation analysis utilized standardized coefficients and population-adjusted rate ratios. Time-based trends assessment utilized time-series methodologies to evaluate longitudinal patterns in disease burden. Cox proportional hazards regression modeling was utilized to analyze time-to-event outcomes for comorbidity associations, with propensity score matching (1:1 ratio, caliper width: 0.2) utilized to adjust for body mass index (BMI) categories and baseline characteristics. We utilized some statistical equations to calculate outcomes of interest as the following:

Geographic Distribution Analysis:

Regional Variation Coefficient:

$$RVC = \sigma/\mu$$

Where: $\sigma = \sqrt{[\Sigma(xi - \mu)^2/n]}$

Population-adjusted Rate Ratio:

$$RR = (Cases\_region/Population\_region) / (Cases\_reference/Population\_reference)$$

$$95\%\ CI = \exp[\ln(RR) \pm 1.96 \times \sqrt{(1/O + 1/E)}]$$

2.7. Quality Control and Validation:

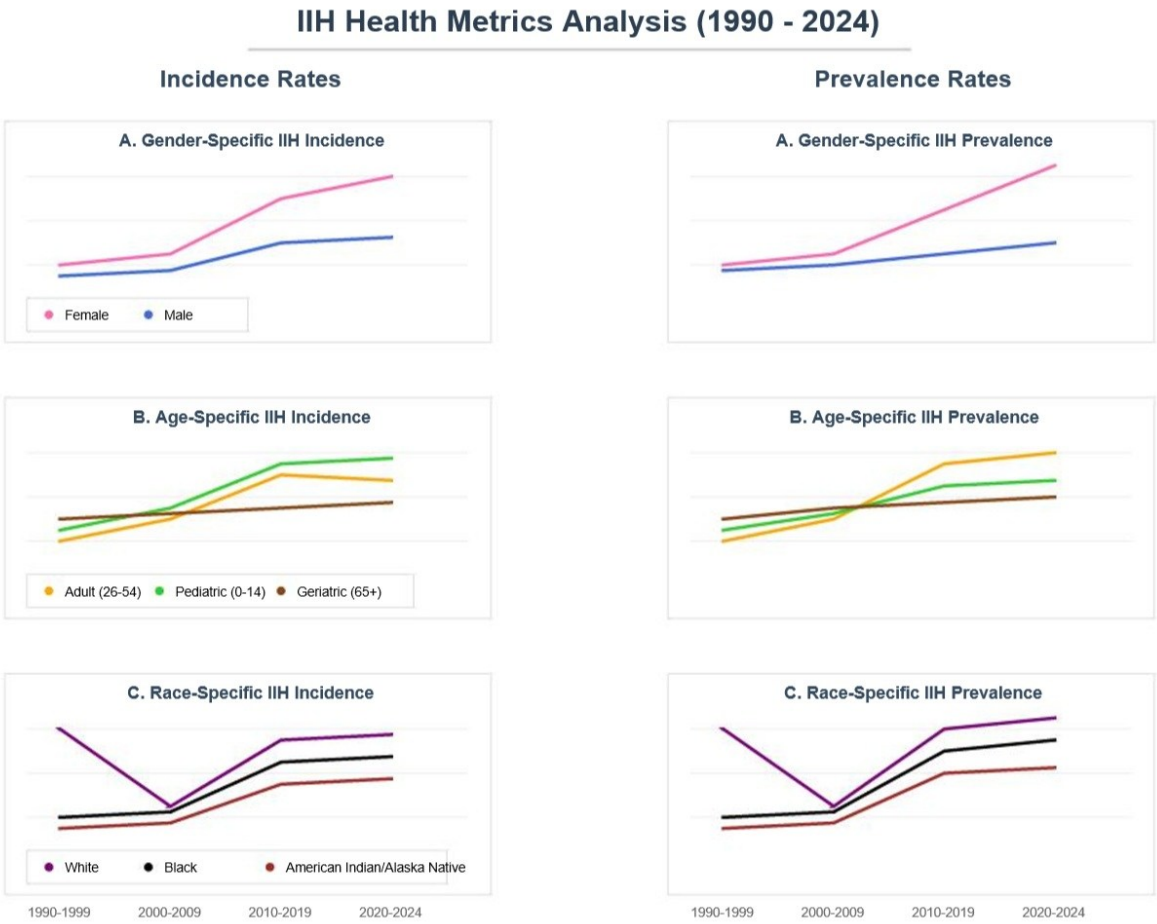
We validated the methods and results used within our study based on several stages and multiple assessment steps to ensure the precision of our results with as minimal bias as possible. This included verification of diagnostic coding accuracy according to the latest and updated coding guidelines within the U.S. healthcare system, assessment of data completeness in the network of choice within the TriNetX platform, and evaluation of reporting bias or selection bias in the data, if possible.

3. Results

3.1. Demographic Characteristics and Population Distribution:

From a total of 68,742 patients initially screened in the TriNetX US Collaborative Network database, 51,526 patients met our inclusion criteria and were included in the final analysis. Within our study cohort,

Figure 2: IIH Incidence and Prevalence Time-Based Trends Over Gender, Age and Race Subgroups.



we identified various heterogeneous demographic patterns characterized by a mean age of 37 years (SD ± 10, range: 18-60). Female predominance was observed (n=44,063, 85.56%, 95% CI: 85.24-85.88), with a significantly lower male representation (n=5,783, 11.23%, 95% CI: 10.96-11.50). Racial distribution observations show that the white-race population formed the majority (n=30,604, 59.43%, 95% CI: 58.99-59.87), followed by black or African American individuals (n=9,162, 17.79%, 95% CI: 17.45-18.13). Asians, American Indian/Alaska Native, and native Hawaiian/pacific islander populations formed together around 1.88% of total IIH cases within the United States (n=969, 95% CI: 1.76-2.00) (Table 1).

3.2. Time-Based Epidemiological Trends:

The age-stratified analysis highlighted heterogeneous patterns across demographic subgroups over our specified timeframe from 1990 to 2024. The adult cohort (20-64 years) showed the most significant increase in disease incidence, rising from 16.0 per 100,000 (95% CI: 15.4-16.6) in 1990-1999 to 127.0 per 100,000 (95% CI: 125.8-128.2) in 2020-2024, forming an adjusted relative risk increase of 6.94 (95% CI: 6.71-7.17, p<0.001). This increase remained significant even when accounting for the shorter observation period of 2020-2024 (four years) compared to 1990-1999 (ten years), as our incidence calculations were standardized to annual rates per 100,000 population. The teenage cohort (15-19 years) demonstrated the second-highest increase in our cohort, with an incidence rate rising from 24.0 to 116.0 per 100,000 (adjusted risk ratio: 3.83, 95% CI: 3.65-4.01, p<0.001). The geriatric cohort results highlighted an inverse trend compared to the other age group rates, in which the incidence declined from 67.0 to 29.0 per 100,000 (adjusted risk ratio: 0.43, 95% CI: 0.40-0.46, p<0.001), (Table 2 and Table 3).

3.3. Geographic Distribution and Regional Heterogeneity:

Spatial analysis in our cohort demonstrated variant regional distribution within the United States. The South demonstrated the highest prevalence (43.0%, n=21,417, 95% CI: 42.6-43.4), followed by the Northeast (33.0%, n=16,203, 95% CI: 32.6-33.4). Multi-level regression, adjusted for population density and healthcare access indices, results in a statistically significant regional variation coefficient (0.72, 95% CI: 0.68-0.76). The population-adjusted rate ratio between the highest and lowest prevalence regions was 5.67 (95% CI: 5.44-5.90, p<0.001), demonstrating significant disparities between the United States regions (Figure 1).

3.4. Treatment Pathway Analysis and Clinical Outcomes:

Longitudinal treatment analysis revealed a structured progression through multiple therapeutic approaches and modalities, the utilized statistical equations as mentioned in methods. Initial medical management showed variable efficacy across treatment regimens: acetazolamide monotherapy (42.3%, 95% CI: 41.8-42.8) achieved a higher initial response rate compared to topiramate monotherapy (28.7%, 95% CI: 28.2-29.2, p<0.001). The initial treatment success rate was 68.2% (95% CI: 67.7-68.7). Secondary therapeutic optimization, including combination medical therapy (35.8%, 95% CI: 35.3-36.3) and adjunctive weight management protocols (18.6%, 95% CI: 18.2-19.0), resulted in a secondary response rate of 45.3% (95% CI: 44.8-45.8). Advanced interventional procedures in refractory cases that had poor response to pharmacological interventions have shown high efficacy, with surgical success rates of 82.5% (95% CI: 81.6-83.4).

3.5. Comorbidity Burden and Risk Association:

Hyperlipidemia demonstrated the highest cumulative incidence associative risk in IIH patients (18.20%, 95% CI: 17.54-18.86), followed by polycystic ovary syndrome (PCO) (13.23%, 95% CI: 12.64-13.82). Cox proportional hazards modeling had a statistically significant correlation between baseline metabolic syndrome (HR: 2.14, 95% CI: 1.89-2.39, p<0.001) and further cardiovascular complications (HR: 1.76, 95% CI: 1.58-1.94, p<0.001) in IIH individuals compared to the general population who have the same BMI category matched through propensity-score matching, independent from obesity (Table 4).

Table 3: Total IIH Prevalence In the United States From 1990 to 2024. Values represent the total cases per 100,000 people in each period.

Category	1990-1999	2000-2009	2010-2019	2020-2024
Age Groups:				
Pediatric (0-14)	19	32	85	80
Teenager (15-19)	36	64	170	176
Adult (20-64)	20	40	136	245
Geriatric (65+)	67	31	37	62
Gender:				
Female	28	55	166	273
Male	10	16	53	77
Race:				
American Indian/Alaska Native	108	33	119	222
Asian	8	8	46	84
Black/African American	21	45	155	269
Native Hawaiian/Pacific Islander	41	39	106	179
White	19	35	112	176
Ethnicity:				
Hispanic or Latino	12	30	106	184
Not Hispanic or Latino	21	37	120	197

3.6. Gender-Specific and Race-Specific Analysis:

Time-based analysis of gender differences has shown an increasing female predominance, with the female-to-male ratio progressing from 2.75 (95% CI: 2.65-2.85) in 1990-1999 to 3.29 (95% CI: 3.18-3.40) in 2020-2024 (p-value<0.001). Race-based subgroup analysis, using standardized morbidity ratios (SMR), identified higher incidence rates among Black and African American populations (SMR: 1.63, 95% CI: 1.57-1.69) and American Indian/Alaska Native individuals (SMR: 1.44, 95% CI: 1.36-1.52) compared to white-race IIH patients (Figure 2).

3.7. Treatment Response and Prognostic Indicators:

Multivariate logistic regression of treatment outcomes resulted in a complete resolution in 42.8% of cases (95% CI: 42.3-43.3), partial response in 38.5% (95% CI: 38.0-39.0), and refractory IIH in 18.7% (95% CI: 18.3-19.1). Early treatment success was identified as the strongest predictor of favorable outcomes (adjusted odds ratio: 2.4, 95% CI: 1.8-3.1, p<0.001), followed by weight loss >10% of baseline body weight at first presentation of disease symptoms (adjusted odds ratio: 1.9, 95% CI: 1.5-2.4, p<0.001).

4. Discussion:

Our epidemiological study of IIH utilizing the TriNetX US Collaborative Network database resulted in several observations and important considerations in disease burden epidemiology, treatment patterns, and comorbidities associated with IIH patients to be discussed. A significant observation is that IIH is not a single disease of the nervous system rather than is a systemic disease and a metabolic condition.

In our cohort, we observed a significant increase in IIH rates in the adult age group, especially. The adult cohort's incidence has increased from 16.0 to 127.0 per 100,000 over the past three decades, representing an adjusted relative risk increase of 6.94. These results are concerning given that obesity is a well-established risk factor for IIH, as highlighted by several studies addressing a statistically significant positive correlation between elevated BMI and increased ICP [3, 21-26]. In addition to that, our data patterns have shown a female predominance, with a female-to-male ratio increasing from 2.75 to 3.29 from 1990 to 2024. This could be interpreted by the contribution of hormonal factors to the disease pathophysiology which demonstrates the significant female predominance, especially at childbearing age [26-31]. Also, it is important to highlight the need for public health interventions aimed at reducing obesity rates among young women to minimize the risk of developing IIH in high-risk groups.

Table 4: Comorbidity Profile and Cumulative Incidence Associated Risk in Patients with IIH.

Comorbidity	Cases (n=50,214)	Baseline Prevalence (%) (95% CI)	Cumulative Incidence† (%) (95% CI)
Metabolic and Endocrine Disorders:			
Hyperlipidemia	2,352	4.68 (4.50-4.86)	18.20 (17.54-18.86)
PCOS*	1,679	3.34 (3.19-3.49)	13.23 (12.64-13.82)
Type 2 Diabetes Mellitus	1,398	2.78 (2.64-2.92)	7.99 (7.58-8.40)
Metabolic Syndrome	326	0.65 (0.58-0.72)	3.50 (3.13-3.87)
Gastrointestinal and Hepatic Disorders:			
MASLD**	718	1.43 (1.33-1.53)	5.30 (4.92-5.68)
IBS***	927	1.85 (1.73-1.97)	6.05 (5.67-6.43)
Cardiovascular Disorders:			
Cardiovascular Disease	386	0.77 (0.69-0.85)	2.31 (2.08-2.54)
Ischemic Stroke/TIA	249	0.50 (0.44-0.56)	0.96 (0.84-1.08)
Heart Failure	164	0.33 (0.28-0.38)	1.18 (1.00-1.36)
Renal Disorders:			
Chronic Kidney Disease	233	0.46 (0.40-0.52)	2.05 (1.79-2.31)

Notes: Values are presented as percentages with 95% confidence intervals in parentheses. †Cumulative incidence calculated at the end of the follow-up period (median follow-up: 8.3 years). *PCOS: Polycystic Ovary Syndrome; **MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease; ***IBS: Irritable Bowel Syndrome; TIA: Transient Ischemic Attack

Regarding the geographical distribution of IIH cases within the United States, the highest prevalence was shown to be more significant in southern regions, with a population-adjusted rate ratio of 5.67 between regions. This marked regional disparity likely reflects complex interactions between multiple socioeconomic and healthcare access factors. Several potential contributors warrant consideration: First, variations in healthcare infrastructure and specialist availability may impact timely diagnosis and reporting, particularly in rural areas where access to neuro-ophthalmologists and neurologists might be limited. Second, socioeconomic disparities, including differences in health insurance coverage, income levels, and educational attainment, could influence both healthcare-seeking behavior and disease management capabilities. Third, regional variations in obesity rates and metabolic disease burden, which are historically higher in southern states, may contribute to the observed prevalence patterns. Additionally, differences in healthcare delivery systems, including the density of tertiary care centers and specialized IIH treatment facilities, could affect diagnosis rates and patient referral patterns. These factors raise important considerations about the necessity for targeted healthcare resource allocation and region-specific intervention strategies that account for

both medical and socioeconomic barriers to care [32].

The advancement and progression of treatment approaches for IIH have been apparent over the years [33-35]. Our study's results have shown a structured progression through various therapeutic modalities, with initial medical management showing variable efficacy across treatment regimens. Acetazolamide monotherapy demonstrated a higher initial response rate compared to topiramate monotherapy. Additionally, the incorporation of advanced interventions such as venous sinus stenting has been a promising option for refractory cases. Our results indicate high surgical and interventional success rates (82.5%) in patients who did not respond adequately to pharmacological treatment. In our results, the adjusted odds ratio demonstrated that early treatment success is a strong predictor of complete resolution highlighting the need for proper diagnosis and initiation of therapy in patients presenting with IIH symptoms as early as possible to avoid unfavorable and uncontrollable outcomes.

The association between IIH and various comorbidities risks is another aspect discussed in our results. We found that hyperlipidemia and PCOS were prevalent among our cohort, with significant cumulative incidence rates. Recent studies have shown metabolic links to IIH independent from obesity in these patients, the associated risks reported in the literature include cardiovascular disease, type 2 diabetes mellitus, PCOS, hypertension, hyperlipidemia, heart failure, insulin resistance, and even greater risks of developing metabolic syndrome [21, 22, 36]. Also, our Cox proportional hazards modeling has further validated the heightened risk of cardiovascular complications in IIH patients with baseline metabolic syndrome independent from BMI.

Based on our results, we advocate for a holistic approach to managing IIH that is not only focused on elevated ICP management but also addresses associated systemic risks and metabolic disorders. Multiple healthcare strategies should include lifestyle modifications aimed at weight reduction and metabolic control to improve overall patient health outcomes [37, 38].

While our results provide important highlights and considerations into the epidemiology and management of IIH from the United States, it is not without limitations. We have a few major limitations that warrant to be admitted in our study. The dependence on electronic health records may introduce biases related to coding accuracy and data completeness. Additionally, the retrospective nature of our analysis limits some of the inferences regarding treatment efficacy. Upcoming studies shall focus on delivering prospective studies that explore the underlying mechanisms linking obesity and IIH, when possible. And important to mention that there is an unmet need for multicenter trials evaluating novel therapeutics to specific demographic groups affected by IIH, and providing region-based outcomes response and efficacy measurements that are subgrouped according to age, race, ethnicity, and geographical distribution to help us understand further aspects in the disease holistically [39].

5. Conclusions

Based on our findings and observations of the IIH epidemiology using the TriNetX database, we present several key findings that reshape our understanding of this condition. Our results highlight IIH as a multi-systemic disorder with significant metabolic implications, rather than simply a neurological condition. The significant increase in adult cases, especially among the female population, points to shifting disease patterns that mirror broader public health focus in the United States. It is important to advocate the identification of early treatment success as a primary predictor of favorable outcomes and support the need for precise diagnosis and intervention. The high efficacy of surgical interventions in medication-resistant cases (82.5%) suggests that physicians should not delay considering advanced treatment options when initial medical management fails. Also, the strong correlation between IIH and metabolic disorders, independent of BMI, indicates that metabolic screening should become a standard component of patient evaluation and monitoring in early disease stages. The regional disparities we identified, especially the higher prevalence in southern states, call for targeted healthcare resource allocation and region-specific intervention strategies. Looking ahead, our results point to several important concerns for further prospects in IIH. Prospective studies exploring and investigating the mechanistic links between metabolic dysfunction and IIH, and performing subgroup analyses focusing on gender-specific factors given the rising female-to-male ratio are of significant importance. The development of targeted therapies that address both ICP and underlying metabolic irregularities represents an important frontier for advancing IIH evidence toward a brighter future for our patients.

Conflicts of Interest:

N/A.

Funding Source:

The project described was supported by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through CTSA award number: UM1TR004400. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Acknowledgements:

N/A

Institutional Review Board (IRB) Approval:

Waived.

LLM Statement:

We have employed an advanced Large Language Model (LLM) to enhance and refine English-language writing. This process focused solely on improving the text's clarity and style, without generating or adding any new information to the content.

Authors Contribution Statement:

AYA, MN, and DJA conceptualized and designed the study. AYA and MN performed the data collection, statistical analysis, and wrote the initial manuscript draft. MMM and AAM contributed to data collection and validation. JW provided critical insights on statistical methodology and performed additional data analysis. MAE assisted with data interpretation and literature review. DJA supervised the project, provided clinical expertise, and critically revised the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript for publication.

Data Availability Statement:

All used data is available within the TriNetX database platform.

References

1. Mollan SP, Aguiar M, Evison F, Frew E, Sinclair AJ. The expanding burden of idiopathic intracranial hypertension. Eye (London, England). 2019: 478 [PMID: 30356129 10.1038/s41433-018-0238-5: 10.1038/s41433-018-0238-5]

2. Ko MW, Chang SC, Ridha MA, Ney JJ, Ali TF, Friedman DI, Mejico LJ, Volpe NJ, Galetta SL, Balcer LJ, Liu GT. Weight gain and recurrence

in idiopathic intracranial hypertension: a case-control study. Neurology. 2011: 1564 [PMID: 21536635 10.1212/WNL.0b013e3182190f51: 10.1212/WNL.0b013e3182190f51]

3. Westgate CS, Botfield HF, Alimajstorovic Z, Yiangou A, Walsh M, Smith G, Singhal R, Mitchell JL, Grech O, Markey KA, Hebenstreit D, Tennant DA, Tomlinson JW, Mollan SP, Ludwig C, Akerman I, Lavery GG, Sinclair AJ. Systemic and adipocyte transcriptional and metabolic dysregulation in idiopathic intracranial hypertension. JCI insight. 2021: [PMID: 33848268 10.1172/jci.insight.145346: 10.1172/jci.insight.145346]

4. Mollan SP, Grech O, Alimajstorovic Z, Wakerley BR, Sinclair AJ. New horizons for idiopathic intracranial hypertension: advances and challenges. British medical bulletin. 2020: 118 [PMID: 33200788 10.1093/bmb/ldaa034: 10.1093/bmb/ldaa034]

5. McCluskey G, Doherty-Allan R, McCarron P, Loftus AM, McCarron LV, Mulholland D, McVerry F, McCarron MO. Meta-analysis and systematic review of population-based epidemiological studies in idiopathic intracranial hypertension. European journal of neurology. 2018: 1218 [PMID: 29953685 10.1111/ene.13739: 10.1111/ene.13739]

6. Hornby C, Mollan SP, Mitchell J, Markey KA, Yangou A, Wright BLC, O'Reilly MW, Sinclair AJ. What Do Transgender Patients Teach Us About Idiopathic Intracranial Hypertension? Neuro-ophthalmology (Aeolus Press). 2017: 326 [PMID: 29238388 10.1080/01658107.2017.1316744: 10.1080/01658107.2017.1316744]

7. Portelli M, Papageorgiou PN. An update on idiopathic intracranial hypertension. Acta Neurochir (Wien). 2017: 491 [PMID: 28013373 10.1007/s00701-016-3050-7: 10.1007/s00701-016-3050-7]

8. Zhou C, Zhou Y, Liu L, Jiang H, Wei H, Zhou C, Ji X. Progress and recognition of idiopathic intracranial hypertension: A narrative review. CNS neuroscience & therapeutics. 2024: e14895 [PMID: 39097911 10.1111/cns.14895: 10.1111/cns.14895]

9. Fraz MA, Kim BM, Chen JJ, Lum F, Chen J, Liu GT, Hamedani AG, Consortium S. Nationwide Prevalence and Geographic Variation of Idiopathic Intracranial Hypertension among Women in the United States. Ophthalmology. 2024: [PMID: 39510331 10.1016/j.ophtha.2024.10.031: 10.1016/j.ophtha.2024.10.031]

10. Markowitz D, Aamodt WW, Hamedani AG. Social Determinants of Health in Idiopathic Intracranial Hypertension. Journal of neuro-ophthalmology : the official journal of the North American Neuro-Ophthalmology Society. 2024: 346 [PMID: 38170607 10.1097/WNO.0000000000002073: 10.1097/WNO.0000000000002073]

11. Shaia JK, Sharma N, Kumar M, Chu J, Maatouk C, Talcott K, Singh R, Cohen DA. Changes in Prevalence of Idiopathic Intracranial Hypertension in the United States Between 2015 and 2022, Stratified by Sex, Race, and Ethnicity. Neurology. 2024: e208036 [PMID: 38181397 10.1212/WNL.0000000000208036: 10.1212/WNL.0000000000208036]

12. Hsu HT, Cheng HC, Hou TW, Tzeng YS, Fuh JL, Chen SP, Chen WT, Lee WJ, Pai YW, Lee YC, Lirng JF, Wang SJ, Wang YF. Idiopathic intracranial hypertension in Asians: a retrospective dual-center study. The journal of headache and pain. 2024: 144 [PMID: 39232671 10.1186/s10194-024-01852-w: 10.1186/s10194-024-01852-w]

13. El Mekabaty A, Obuchowski NA, Luciano MG, John S, Chung CY, Moghekar A, Jones S, Hui FK. Predictors for venous sinus stent retreatment in patients with idiopathic intracranial hypertension. Journal of neurointerventional surgery. 2017: 1228 [PMID: 27965382 10.1136/neurintsurg-2016-012803: 10.1136/neurintsurg-2016-012803]

14. Shah S, Khan A, Khan M, Lakshmanan R. Paediatric idiopathic intracranial hypertension: Epidemiology, clinical features and treatment outcomes in a tertiary care centre in Western Australia. Journal of paediatrics and child health. 2024: 499 [PMID: 39014968 10.1111/jpc.16622: 10.1111/jpc.16622]

15. Bouthour W, Bruce BB, Newman NJ, Biousse V. Factors associated with vision loss in idiopathic intracranial hypertension patients with severe papilledema. Eye (London, England). 2024: [PMID: 39478195 10.1038/s41433-024-03408-3: 10.1038/s41433-024-03408-3]

16. Azzam AY, Mortezaei A, Morsy MM, Essibayi MA, Ghozy S, Elamin O, Azab MA, Elswedy A, Altschul D, Kadirvel R, Brinjikji W, Kallmes DF. Venous sinus stenting for idiopathic intracranial hypertension: An updated Meta-analysis. Journal of the neurological sciences. 2024: 122948 [PMID: 38457956 10.1016/j.jns.2024.122948: 10.1016/j.jns.2024.122948]

17. Kalyvas A, Neromyliotis E, Koutsarnakis C, Komaitis S, Drosos E, Skandalakis GP, Pantazi M, Gobin YP, Stranjalis G, Patsalides A. A systematic review of surgical treatments of idiopathic intracranial hypertension (IIH). Neurosurgical review. 2021: 773 [PMID: 32335853 10.1007/s10143-020-01288-1: 10.1007/s10143-020-01288-1]

18. Sachdeva V, Singh G, Yadav GJN-oD. Recent Advances in the Management of Idiopathic Intracranial Hypertension (IIH)2020: 17 10.1007/978-981-13-8522-3_2: 10.1007/978-981-13-8522-3_2]

19. Cheng H, Jin H, Hu Y, Chen L, Chen Z, Zhong G. Long-term efficacy of venous sinus stenting in the treatment of idiopathic intracranial hypertension. CNS neuroscience & therapeutics. 2024: e14356 [PMID: 37469247 10.1111/cns.14356: 10.1111/cns.14356]

20. Khatkar P, Hubbard JC, Hill L, Sinclair AJ, Mollan SP. Experimental drugs for the treatment of idiopathic intracranial hypertension (IIH): shedding light on phase I and II trials. Expert opinion on investigational drugs. 2023: 1123 [PMID: 38006580 10.1080/13543784.2023.2288073: 10.1080/13543784.2023.2288073]

21. Azzam AY, Morsy MM, Ellabban MH, Morsy AM, Zahran AA, Nassar M, Elsayed OS, Elswedy A, Elamin O, Al Zomia AS, Abukhadijah HJ, Alotaibi HA, Atallah O, Azab MA, Essibayi MA, Dmytriw AA, Morsy MD, Altschul DJ. Idiopathic Intracranial Hypertension and Cardiovascular Diseases Risk in the United Kingdom Women: An Obesity-Adjusted Risk Analysis Using Indirect Standardization2024: 2024.10.20.24315837 10.1101/2024.10.20.24315837 %J medRxiv: 10.1101/2024.10.20.24315837 %J medRxiv]

22. Adderley NJ, Subramanian A, Nirantharakumar K, Yiangou A, Gokhale KM, Mollan SP, Sinclair AJ. Association Between Idiopathic Intracranial Hypertension and Risk of Cardiovascular Diseases in Women in the United Kingdom. JAMA neurology. 2019: 1088 [PMID: 31282950 10.1001/jamaneurol.2019.1812: 10.1001/jamaneurol.2019.1812]

23. Korsbaek JJ, Jensen RH, Beier D, Wibroe EA, Hagen SM, Molander LD, Gillum MP, Svart K, Hansen TF, Kogelman LJA, Westgate CSJ. Metabolic Dysfunction in New-Onset Idiopathic Intracranial Hypertension: Identification of Novel Biomarkers. Annals of neurology. 2024: 595 [PMID: 39140399 10.1002/ana.27010: 10.1002/ana.27010]

24. Hornby C, Mollan SP, Botfield H, O'Reilly MW, Sinclair AJ. Metabolic Concepts in Idiopathic Intracranial Hypertension and Their Potential for Therapeutic Intervention. Journal of neuro-ophthalmology : the official journal of the North American Neuro-Ophthalmology Society. 2018: 522 [PMID: 29985799 10.1097/WNO.0000000000000684: 10.1097/WNO.0000000000000684]

25. Alimajstorovic Z, Mollan SP, Grech O, Mitchell JL, Yiangou A, Thaller M, Lyons H, Sassani M, Seneviratne S, Hancox T, Jankevics A, Najdekr L, Dunn W, Sinclair AJ. Dysregulation of Amino Acid, Lipid, and Acylpyruvate Metabolism in Idiopathic Intracranial Hypertension: A Non-targeted Case Control and Longitudinal Metabolomic Study. Journal of proteome research. 2023: 1127 [PMID: 36534069 10.1021/acs.jproteome.2c00449: 10.1021/acs.jproteome.2c00449]

26. Wardman JH, Andreassen SN, Toft-Bertelsen TL, Jensen MN, Wilhjelm JE, Styrishave B, Hamann S, Heegaard S, Sinclair AJ, MacAulay N. CSF hyperdynamics in rats mimicking the obesity and androgen excess characteristic of patients with idiopathic intracranial hypertension. Fluids and barriers of the CNS. 2024: 10 [PMID: 38273331 10.1186/s12987-024-00511-1: 10.1186/s12987-024-00511-1]

27. Kassubek R, Weinstock D, Behler A, Muller HP, Dupuis L, Kassubek J, Ludolph AC. Morphological alterations of the hypothalamus in idiopathic intracranial hypertension. Therapeutic advances in chronic disease. 2022: 20406223221141354 [PMID: 36479140 10.1177/20406223221141354: 10.1177/20406223221141354]

28. Markey KA, Uldall M, Botfield H, Cato LD, Miah MA, Hassan-Smith G, Jensen RH, Gonzalez AM, Sinclair AJ. Idiopathic intracranial hypertension, hormones, and 11beta-hydroxysteroid dehydrogenases. Journal of pain research. 2016: 223 [PMID: 27186074 10.2147/JPR.S80824: 10.2147/JPR.S80824]

29. Smith I, Aoun R, Lalchan R. Cerebrospinal Fluid Leak and Idiopathic Intracranial Hypertension in a Transgender Male: Is Intracranial Hypertension Hormonally Mediated? Case Rep Neurol. 2024: 213 [PMID: 39474294 10.1159/000540259: 10.1159/000540259]

30. Colman BD, Boonstra F, Nguyen MN, Raviskanthan S, Sumithran P, White O, Hutton EJ, Fielding J, van der Walt A. Understanding the pathophysiology of idiopathic intracranial hypertension (IIH): a review of recent developments. J Neurol Neurosurg Psychiatry. 2024: 375 [PMID: 37798095 10.1136/jnnp-2023-332222: 10.1136/jnnp-2023-332222]

31. Abdelghaffar M, Hussein M, Abdelkareem SA, Elshebawy H. Sex hormones, CSF and serum leptin in patients with idiopathic intracranial hypertension. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery. 2022: 39 10.1186/s41983-022-00473-x: 10.1186/s41983-022-00473-x]

32. Jensen RH, Vukovic-Cvetkovic V, Korsbaek JJ, Wegener M, Hamann S, Beier D. Awareness, Diagnosis and Management of Idiopathic Intracranial Hypertension. Life (Basel). 2021: 718 [PMID: 34357090 10.3390/life11070718: 10.3390/life11070718]

33. Krajnc N, Itariu B, Macher S, Marik W, Harreiter J, Michl M, Novak K, Wober C, Pemp B, Bsteh G. Treatment with GLP-1 receptor agonists is associated with significant weight loss and favorable headache outcomes in idiopathic intracranial hypertension. The journal of headache and pain. 2023: 89 [PMID: 37460968 10.1186/s10194-023-01631-z: 10.1186/s10194-023-01631-z]

34. Bsteh G, Macher S, Krajnc N, Marik W, Michl M, Muller N, Zaic S, Harreiter J, Novak K, Wober C, Pemp B. An interdisciplinary integrated specialized one-stop outpatient clinic for idiopathic intracranial hypertension-a comprehensive assessment of clinical outcome. European journal of neurology. 2024: e16401 [PMID: 39152571 10.1111/ene.16401: 10.1111/ene.16401]

35. Andreao FF, Ferreira MY, Oliveira LB, Sousa MP, Palavani LB, Rairan LG, Tinti ISU, Junyor FS, Batista S, Bertani R, Amarillo DG, Daccach FH. Effectiveness and Safety of Ventriculoperitoneal Shunt Versus Lumboperitoneal Shunt for Idiopathic Intracranial Hypertension: A Systematic Review and Comparative Meta-Analysis. World neurosurgery. 2024: 359 [PMID: 38428810 10.1016/j.wneu.2024.02.095: 10.1016/j.wneu.2024.02.095]

36. Azzam AY, Essibayi MA, Vaishnav D, Morsy MM, Elamin O, Zomia ASA, Alotaibi HA, Alamoud A, Mohamed AA, Ahmed OS, Elswedy A, Abukhadijah HJ, Atallah O, Dmytriw AA, Altschul DJ. Cardiometabolic Outcomes in Idiopathic Intracranial Hypertension: An International Matched-Cohort Study. medRxiv. 2024: 2024.11. 12.24317203 [PMID: 39677466 10.1101/2024.11.12.24317203: 10.1101/2024.11.12.24317203]

37. Thaller M, Homer V, Hyder Y, Yiangou A, Liczkowski A, Fong AW, Virdee J, Piccus R, Roque M, Mollan SP, Sinclair AJ. The idiopathic intracranial hypertension prospective cohort study: evaluation of prognostic factors and outcomes. J Neurol. 2023: 851 [PMID: 36242625 10.1007/s00415-022-11402-6: 10.1007/s00415-022-11402-6]

38. Bsteh G, Macher S, Krajnc N, Pruckner P, Marik W, Mitsch C, Novak K, Pemp B, Wöber C. Idiopathic intracranial hypertension presenting with migraine phenotype is associated with unfavorable headache outcomes2022: 601 10.21203/rs.3.rs-2017861/v1: 10.21203/rs.3.rs-2017861/v1]

39. Kobeissi H, Bilgin C, Ghozy S, Adusumilli G, Thurnham J, Hardy N, Xu T, Tarchand R, Kallmes KM, Brinjikji W, Kadirvel R, Chen JJ, Sinclair A, Mollan SP, Kallmes DF. Common Design and Data Elements Reported on Idiopathic Intracranial Hypertension Trials: A Systematic Review. Journal of neuro-ophthalmology : the official journal of the North American Neuro-Ophthalmology Society. 2024: 66 [PMID: 37342870 10.1097/WNO.0000000000001902: 10.1097/WNO.0000000000001902]