

Title: Cardiometabolic Outcomes in Idiopathic Intracranial Hypertension: An International Matched-Cohort Study

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Abstract:

Introduction: Idiopathic intracranial hypertension (IIH) has been traditionally viewed as a neuro-ophthalmic disorder, yet emerging evidence suggests broader systemic implications. Our study investigates the cardiometabolic outcomes associated with IIH through a comprehensive matched-cohort analysis.

Methods: We conducted a retrospective analysis of electronic health records from 2009 to 2024. We compared IIH patients with matched controls using propensity score matching based on age, sex, race, ethnicity, and baseline BMI. Cardiovascular and metabolic outcomes were assessed over a ten-year follow-up period, with additional stratified analyses comparing obese and non-obese subgroups.

Results: IIH patients demonstrated significantly increased risks of ischemic stroke/TIA (RR 2.515, 95% CI 2.250-2.812) and non-traumatic hemorrhagic stroke (RR 7.744, 95% CI 6.118-9.801). Notable metabolic findings included elevated risks of insulin resistance (RR 1.470, 95% CI 1.258-1.717) and type 2 diabetes mellitus (RR 1.210, 95% CI 1.171-1.250). These associations persisted in non-obese IIH patients, suggesting pathogenic mechanisms independent of adiposity. Additionally, IIH patients showed increased prevalence of polycystic ovarian syndrome (RR 1.470, 95% CI 1.258-1.717) and metabolic syndrome (RR 1.125, 95% CI 1.045-1.205).

Conclusions: Our findings highlight IIH as a complex multisystem disorder with significant cardiometabolic implications beyond its traditional neuro-ophthalmic presentation. The findings suggest the need for comprehensive cardiovascular and metabolic screening in IIH patients, regardless of BMI status, and indicate potential novel therapeutic targets for investigation.

Keywords: Idiopathic Intracranial Hypertension; Pseudotumor Cerebri; Cardiovascular; Cardiometabolic; Obesity

1. Introduction:

Idiopathic intracranial hypertension (IIH) is a neurological disorder characterized by elevated intracranial pressure without an identifiable cause. While traditionally associated with obesity and female sex, recent evidence suggests that IIH has broader systemic implications beyond its well-known neuro-ophthalmic manifestations [1]. The condition has been linked to various metabolic and cardiovascular comorbidities, indicating a complex interplay between intracranial pressure regulation and systemic physiology [2-4]. Despite significant advances in our understanding of IIH, substantial knowledge gaps persist regarding its pathophysiology and systemic associations. Current evidence is limited by the heterogeneity of study populations, inconsistent diagnostic criteria, and a lack of long-term inclusive data [5].

These limitations underscore the need for a more comprehensive approach to elucidate the underlying mechanisms and potential therapeutic targets in IIH. Exploring the systemic correlations between IIH and other disorders is crucial for developing a more nuanced understanding of the disease. By examining these relationships, we may uncover shared pathophysiological pathways, identify novel risk factors, and potentially reveal new avenues for treatment. For instance, recent research has highlighted connections between IIH and endocrine disorders, suggesting a possible role for hormonal dysregulation in its pathogenesis [6].

A landmark study by Adderley et al. provided compelling evidence for the association between IIH and cardiovascular disease (CVD) in women [7]. Their large-scale cohort study, involving 2,760 women with IIH and 27,125 matched controls, demonstrated a twofold increased risk of CVD in IIH patients, including heart failure, ischemic heart disease, and stroke. Notably, this association persisted after adjusting for traditional risk factors, suggesting that IIH may be an independent risk factor for CVD. The study also revealed a higher incidence of type 2 diabetes and hypertension in the IIH group, further emphasizing the systemic nature of the disorder.

Building upon these findings, our study aims to further explore the cardiometabolic associations of IIH. By examining a comprehensive range of metabolic and cardiovascular parameters in a well-characterized cohort of IIH patients, we seek to extend the work of Adderley et al. [7] and provide additional evidence for the systemic implications of IIH. Our research focuses on elucidating potential mechanisms linking IIH to cardiometabolic dysfunction, with the ultimate goal of identifying novel therapeutic targets and improving patient outcomes. Through this investigation, we hope to contribute to a more holistic understanding of IIH as a multisystem disorder rather than a purely neuro-ophthalmic condition.

2. Methods:

We leveraged data from the comprehensive TriNetX Research Network, encompassing around 197 million electronic health records to the date from about 160 healthcare organizations around the world, predominantly in the United States [8], but also including Australia, Belgium, Brazil, Bulgaria, Estonia, France, Georgia, Germany, Ghana, Israel, Italy, Japan, Lithuania, Malaysia, Poland, Singapore, Spain, Taiwan, United Arab Emirates, and the United Kingdom (<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. The TriNetX platform offers researchers secure access to this vast repository of real-world data for observational studies, with regular updates ensuring the most current and comprehensive healthcare information.

We conducted a retrospective analysis of TriNetX data from 2009 to October 2024 (the available data timeframe on the dataset), focusing on patients diagnosed with IIH. Exclusion criteria encompassed individuals with other known causes of elevated intracranial pressure, including primary brain tumors, secondary brain metastases, cerebral arteriovenous malformations, malignant hypertension (primary and secondary), meningitis, traumatic elevated intracranial pressure, and venous sinus thrombosis, the diagnosis codes and definitions are listed in the **Supplementary File**.

To ensure well-balanced study groups, we employed propensity score matching based on age, sex, race, ethnicity, and baseline body mass index (BMI) in six different cohorts including all IIH individuals, all non-IIH individuals, obese IIH individuals (obesity defined as BMI equal or more than 30), non-IIH obese individuals, IIH non-obese individuals (defined as BMI less than 30), and no-IIH non-obese individuals. Our analysis examined outcomes at a follow-up duration of ten years since the first documented diagnosis of IIH, assessing different outcome including ischemic stroke / transient ischemic attacks (TIA), heart failure, coronary artery disease, atherosclerosis, peripheral arterial disease, essential hypertension, aortic aneurysm and dissection, non-traumatic hemorrhagic stroke, dyslipidemia, gestational diabetes, insulin resistance, metabolic syndrome, type 2 diabetes mellitus, non-alcoholic fatty liver disease, chronic kidney disease, polycystic ovarian syndrome, and systemic autoimmune connective tissue disorders. The outcomes codes and definitions are listed in the **Supplementary File**.

2.1. Statistical Analysis:

The TriNetX platform is equipped with a suite of powerful analytical tools, leveraging programming languages such as Java, R, and Python, which enabled the researchers to efficiently query and analyze the comprehensive dataset to extract meaningful insights [8]. All statistical analyses for the present study were conducted within the TriNetX environment using the "Compare Outcomes" feature. To account for the potential influence of confounding factors, the researchers thoughtfully employed propensity score matching prior to the analyses. This involved a 1:1 matching approach, utilizing the nearest neighbor matching without replacement and a caliper set at 0.1 times the standard deviation. TriNetX's proprietary algorithms derive

propensity scores through logistic regression, drawing upon matrices of covariates with randomized row order to enhance the robustness of the matching process. The criterion for statistical significance was set at a p-value less than 0.05.

3. Results:

3.1. Baseline Characteristics:

Baseline demographics of both the IIH cohort and the non-IIH cohort are demonstrated in **Table 1**. After propensity score matching, we achieved a balanced sample of 1,778 individuals in each cohort to avoid statistical analysis bias as much as possible.

The mean age was 35.7 years (SD 12.6) in the IIH cohort and 35.8 years (SD 12.7) in the non-IIH cohort. Female individuals were forming the majority, accounting for 87.5% of each group, which aligns with the known gender predisposition in IIH. Our results of racial distribution revealed consistency across cohorts. White-race individuals predominated (78.2% IIH, 77.8% non-IIH), followed by black-race individuals (16.4% IIH, 16.6% non-IIH), and other races (5.4% IIH, 5.6% non-IIH). Body Mass Index (BMI) was elevated in both groups, with mean values of 37.6 kg/m² (SD 8.5) and 37.3 kg/m² (SD 8.4) for IIH and non-IIH cohorts.

We observed well-matched comorbidity profiles between the cohorts. Hypertension was the most prevalent comorbidity (31.7% IIH, 31.6% non-IIH), followed by depression (24.5% IIH, 24.4% non-IIH), and diabetes (15.5% in both cohorts). In addition to that, several other relevant comorbidities were found in both cohorts, including obstructive sleep apnea (14.2% IIH, 14.1% non-IIH), polycystic ovary syndrome (8.4% IIH, 8.3% non-IIH), and hypothyroidism (12.3% in both cohorts).

3.2. Cardiovascular Outcomes:

In our study, we conducted a retrospective analysis of cardiovascular outcomes in patients with IIH compared to various control groups, we listed the outcomes comparison in **Table 2**.

Our results revealed significant disparities in cardiovascular outcomes between IIH patients and the general population. We observed that IIH patients, regardless of obesity status, exhibited a markedly higher risk of ischemic stroke or transient ischemic attack (TIA) compared to the non-IIH general population (Risk Ratio [RR] 2.515, 95% Confidence Interval [CI] 2.250-2.812, $p < 0.0001$). This elevated risk persisted when comparing non-obese IIH patients to their non-obese, non-IIH counterparts (RR 2.657, CI 2.180-3.238, $p < 0.0001$).

Heart failure incidence was also significantly higher in the IIH cohort compared to the general population (RR 1.489, CI 1.385-1.601, $p < 0.0001$). This trend was consistent across both obese and non-obese subgroups, with non-obese IIH patients showing a particularly elevated risk compared to non-obese controls (RR 1.579, CI 1.384-1.800, $p < 0.0001$).

Coronary artery disease (CAD) demonstrated a similar pattern, with IHH patients experiencing a higher incidence compared to the general population (RR 1.321, CI 1.240-1.408, $p < 0.0001$). The risk was most pronounced in the non-obese IHH subgroup when compared to non-obese controls (RR 1.442, CI 1.289-1.614, $p < 0.0001$).

Interestingly, our analysis revealed a significant disparity in non-traumatic hemorrhagic stroke risk. IHH patients exhibited a substantially higher risk compared to the general population (RR 7.744, CI 6.118-9.801, $p < 0.0001$). This risk remained markedly elevated even when stratified by obesity status, with non-obese IHH patients showing a particularly high risk compared to non-obese controls (RR 7.769, CI 5.167-11.683, $p < 0.0001$).

Essential/primary hypertension was more prevalent in the IHH cohort compared to the general population (RR 1.202, CI 1.179-1.225, $p < 0.0001$). Although, obese IHH patients had a lower risk of hypertension compared to non-obese IHH patients (RR 0.945, CI 0.924-0.967, $p < 0.0001$), suggesting a complex interplay between IHH, obesity, and hypertension.

Peripheral artery disease (PAD) and aortic aneurysm/dissection showed less consistent patterns across comparisons. While PAD risk was lower in non-obese IHH patients compared to obese IHH patients (RR 0.768, CI 0.669-0.882, $p < 0.0001$), the overall risk in IHH patients was not significantly different from the general population (RR 1.005, CI 0.927-1.090, $p = 0.899$).

Dyslipidemia in IHH revealed several significant associations. The overall IHH cohort demonstrated a higher prevalence of dyslipidemia compared to the general non-IHH population (RR 1.125, 95% CI: 1.045-1.205, $p = 0.023$). Notably, obesity emerged as a crucial factor, with obese IHH patients showing significantly higher dyslipidemia rates compared to both non-obese IHH patients (RR 1.189, 95% CI: 1.095-1.293, $p = 0.005$) and the overall IHH cohort (RR 1.103, 95% CI: 1.012-1.203, $p = 0.043$). Interestingly, obese IHH patients also exhibited a trend towards higher dyslipidemia prevalence compared to obese non-IHH individuals, although this did not reach conventional statistical significance (RR 1.089, 95% CI: 0.994-1.195, $p = 0.030$). In contrast, non-obese IHH patients showed no significant difference in dyslipidemia prevalence compared to non-obese controls (RR 0.943, 95% CI: 0.803-1.083, $p = 0.275$) or the overall IHH cohort (RR 0.987, 95% CI: 0.876-1.112, $p = 0.102$).

3.3. Systemic and Endocrinal Outcomes:

In addition to the cardiovascular outcomes, we performed outcomes analysis according to the systemic and endocrinal outcomes associated with IHH individuals, the results of the comparisons are listed in **Table 3**.

We found that gestational diabetes mellitus (GDM) was significantly more prevalent in the IHH all cohort compared to non-IHH general controls (RR 1.147, 95% CI 1.113-1.182, $p < 0.0001$). Interestingly, when stratified by obesity status, we observed that non-obese IHH patients had a higher risk of GDM compared to non-obese controls (RR 1.141, 95% CI 1.072-1.214, $p < 0.0001$), while obese IHH patients showed a slightly lower risk compared to obese controls

(RR 1.063, 95% CI 1.023-1.104, $p=0.002$). This suggests that the association between IIH and GDM may be partially mediated by factors beyond obesity alone.

Our analysis of insulin resistance revealed interesting findings; IIH patients had a 47% higher risk compared to the general population (RR 1.470, 95% CI 1.258-1.717, $p<0.0001$). This association was particularly pronounced in non-obese IIH patients compared to non-obese IIH controls (RR 1.641, 95% CI 1.239-2.173, $p<0.0001$). These results underscore the potential role of insulin resistance in the pathophysiology of IIH, independent of obesity.

Regarding metabolic syndrome, our study demonstrated a modest but significant increase in risk for IIH patients compared to the general population (RR 1.125, 95% CI 1.045-1.205, $p=0.023$). The association was more pronounced when comparing obese IIH patients to non-obese IIH patients (RR 1.189, 95% CI 1.095-1.293, $p=0.005$), highlighting the compounding effect of obesity on metabolic risk in IIH.

Type 2 diabetes mellitus (T2DM) emerged as a significant comorbidity in our IIH cohort. We observed a 21% increased risk of T2DM in IIH patients compared to the general population (RR 1.210, 95% CI 1.171-1.250, $p<0.0001$). Notably, this association persisted even when comparing non-obese IIH patients to non-obese controls (RR 1.224, 95% CI 1.143-1.310, $p<0.0001$), suggesting that IIH may confer an independent risk for T2DM beyond that attributable to obesity.

Our investigation into non-alcoholic fatty liver disease (NAFLD) revealed a complex relationship with IIH. While IIH patients overall showed an increased risk compared to the general population (RR 1.147, 95% CI 1.113-1.182, $p<0.0001$), the association varied when stratified by obesity status. Non-obese IIH patients had a higher risk compared to non-obese controls (RR 1.141, 95% CI 1.072-1.214, $p<0.0001$), whereas obese IIH patients showed a slightly lower risk compared to obese controls (RR 1.063, 95% CI 1.023-1.104, $p=0.002$). These findings suggest a nuanced interplay between IIH, obesity, and NAFLD risk.

Chronic kidney disease (CKD) presented an intriguing pattern in our analysis. While the overall IIH cohort showed a slightly lower risk compared to the general population (RR 0.970, 95% CI 0.927-1.090, $p=0.049$), non-obese IIH patients exhibited a marginally increased risk compared to non-obese controls (RR 1.030, 95% CI 1.048-1.372, $p=0.004$). This discrepancy warrants further investigation into the potential renal implications of IIH, particularly in non-obese individuals.

Our demonstrated results for polycystic ovarian syndrome (PCOS) in IIH patients yielded compelling results. We observed a significantly higher risk of PCOS in the IIH cohort compared to the general population (RR 1.470, 95% CI 1.258-1.717, $p<0.0001$). This association was particularly pronounced when comparing obese IIH patients to non-obese IIH patients (RR 1.667, 95% CI 1.260-2.205, $p<0.0001$), suggesting a potential synergistic effect between IIH, obesity, and PCOS risk. Also, our analysis of systemic autoimmune connective tissue disorders revealed a modest but significant increase in risk for IIH patients compared to the general population (RR 1.099, 95% CI 1.008-1.200, $p=0.055$). This association was more pronounced

when comparing obese IIH patients to non-obese IIH patients (RR 1.431, 95% CI 1.286-1.593, $p < 0.0001$).

4. Discussion:

IIH has traditionally been viewed primarily through a neuro-ophthalmic lens. However, our study results reveal a complex systemic disorder with significant cardiometabolic implications. These findings build upon emerging evidence suggesting that IIH represents more than just elevated intracranial pressure, but rather a multisystem condition with broad metabolic and cardiovascular manifestations.

Our results demonstrate substantially elevated cardiovascular risks in IIH patients, with particularly striking findings regarding cerebrovascular outcomes. The observed 2.5-fold increased risk of ischemic stroke/TIA and nearly 8-fold higher risk of non-traumatic hemorrhagic stroke highlight the profound vascular implications of IIH. These findings align with previous evidence from Adderley et al, who first identified increased cardiovascular risks in IIH patients [7]. Notably, our study reveals that these elevated risks persist even in non-obese IIH patients, suggesting pathogenic mechanisms independent of obesity. The metabolic dysregulation we observed in IIH patients provides crucial insights into potential underlying mechanisms.

Our finding of a 47% increased risk of insulin resistance in IIH patients compared to controls aligns with the metabolomic studies by Alimajstorovic et al, who identified significant perturbations in multiple metabolic pathways in IIH patients [9]. The persistence of this association in non-obese IIH patients (RR 1.641) particularly supports Hornby et al's proposition that IIH represents a distinct metabolic phenotype beyond simple obesity [6]. Our observation of increased rates of PCOS in IIH patients (RR 1.470) corresponds with emerging evidence of hormonal dysregulation in IIH pathogenesis. This finding supports O'Reilly et al's identification of a unique androgen excess signature in IIH [4], suggesting potential shared pathophysiological mechanisms between IIH and PCOS. The significantly higher risk in obese IIH patients (RR 1.667 compared to non-obese IIH) indicates a possible synergistic effect between metabolic dysfunction and hormonal dysregulation.

The complex relationship we observed between IIH and non-alcoholic fatty liver disease with differential risks in obese versus non-obese patients adds to our understanding of the metabolic implications of IIH. These findings align with recent metabolomic studies showing altered lipid metabolism in IIH patients, particularly in pathways involving acyl carnitines and glycerophospholipids [9, 10].

Our study offers several significant strengths that advance the current understanding of IIH beyond the previous evidence. First, our large-scale analysis and diverse matched pairs represents one of the most comprehensive assessments of IIH's systemic implications to date, substantially extending the scope of previous studies such as Adderley et al's study [7]. Second, our propensity score matching methodology, accounting for crucial variables including age, sex,

race, ethnicity, and baseline BMI, provides more robust control for confounding factors than prior studies. Third, our stratified analysis of obese versus non-obese IIH patients offers novel insights into the obesity-independent effects of IIH, addressing a critical gap in the existing literature highlighted by Markey et al. [11]. Fourth, our examination of a broad spectrum of cardiometabolic outcomes provides a more comprehensive picture of IIH's systemic implications than previous focused studies. Finally, our use of the extensive TriNetX Research Network, including various datapoints included from different electronic health records across multiple countries, offers unprecedented geographical and demographic diversity in IIH research [8].

However, our study has several limitations that warrant consideration. The retrospective nature of our analysis, while allowing for a large sample size, may introduce selection bias and cannot establish causality. Additionally, the use of electronic health records may result in incomplete capture of all relevant comorbidities and outcomes. The relatively short follow-up period of ten years may underestimate the long-term cardiovascular and metabolic implications of IIH. Future research should focus on several key areas. Prospective studies with longer follow-up periods are needed to better characterize the temporal relationship between IIH and its cardiometabolic complications. Investigation of potential shared pathophysiological mechanisms, particularly regarding the role of androgen excess and insulin resistance, could reveal new therapeutic targets. The differential risks we observed between obese and non-obese IIH patients suggest the need for targeted studies of these distinct populations. Additionally, evidence into the potential role of novel biomarkers, such as those identified in recent metabolomic studies [6, 10, 12, 13], could improve risk stratification and guide personalized therapeutic approaches. The significant cardiovascular risks we identified also suggest the need for trials of preventive strategies in IIH patients, particularly regarding cerebrovascular complications.

5. Conclusions:

Our large-scale analysis provides interesting evidence that IIH manifests as a complex multisystem disorder with profound cardiometabolic implications. The results of our study have demonstrated several critical findings. First, IIH patients exhibit markedly elevated cardiovascular and cerebrovascular risks, with a 2.5-fold increased risk of ischemic stroke/TIA and a striking 7.7-fold higher risk of non-traumatic hemorrhagic stroke. Notably, these risks persist in non-obese IIH patients, suggesting underlying pathogenic mechanisms independent of adiposity. Our stratified analyses revealed compelling metabolic associations, particularly a 47% increased risk of insulin resistance in IIH patients compared to matched controls, with an even more pronounced risk (RR 1.641) in non-obese IIH patients. This finding, coupled with our observation of increased rates of polycystic ovarian syndrome (RR 1.470) and type 2 diabetes mellitus (RR 1.210), suggests a distinct metabolic phenotype associated with IIH. The differential risks we observed between obese and non-obese IIH patients across various outcomes, including non-alcoholic fatty liver disease and gestational diabetes, further emphasize

the complex interplay between IIH and metabolic dysfunction. Our findings have significant implications for clinical practice, suggesting the need for comprehensive cardiovascular and metabolic screening in IIH patients, regardless of their BMI status. The substantial risks we identified warrant consideration of targeted preventive strategies. Furthermore, the complex metabolic associations we uncovered suggest potential novel therapeutic targets. Future prospective studies should focus on elucidating the temporal relationship between IIH and its cardiometabolic complications, with particular attention to the role of insulin resistance and hormonal dysregulation in disease pathogenesis.

References:

1. Mollan, S.P., et al., *Evolving evidence in adult idiopathic intracranial hypertension: pathophysiology and management*. J Neurol Neurosurg Psychiatry, 2016. **87**(9): p. 982-92.
2. Zarei, S., et al., *Idiopathic intracranial hypertension associated with polycystic ovarian syndrome, sensorineural hearing loss, and elevated inflammatory markers that lead to bilateral blindness: A case report with literature review*. Surg Neurol Int, 2023. **14**: p. 399.
3. Thaller, M., et al., *Co-morbid Polycystic Ovarian Syndrome with Idiopathic Intracranial Hypertension*. Neuroophthalmology, 2023. **47**(1): p. 49-52.
4. O'Reilly, M.W., et al., *A unique androgen excess signature in idiopathic intracranial hypertension is linked to cerebrospinal fluid dynamics*. JCI Insight, 2019. **4**(6).
5. Markey, K.A., et al., *Understanding idiopathic intracranial hypertension: mechanisms, management, and future directions*. Lancet Neurol, 2016. **15**(1): p. 78-91.
6. Hornby, C., et al., *Metabolic Concepts in Idiopathic Intracranial Hypertension and Their Potential for Therapeutic Intervention*. J Neuroophthalmol, 2018. **38**(4): p. 522-530.
7. Adderley, N.J., et al., *Association Between Idiopathic Intracranial Hypertension and Risk of Cardiovascular Diseases in Women in the United Kingdom*. JAMA Neurol, 2019. **76**(9): p. 1088-1098.
8. Palchuk, M.B., et al., *A global federated real-world data and analytics platform for research*. JAMIA Open, 2023. **6**(2): p. ooad035.
9. Alimajstorovic, Z., et al., *Dysregulation of Amino Acid, Lipid, and Acylpyruvate Metabolism in Idiopathic Intracranial Hypertension: A Non-targeted Case Control and Longitudinal Metabolomic Study*. J Proteome Res, 2023. **22**(4): p. 1127-1137.
10. Korsbæk, J.J., et al., *Metabolic Dysfunction in New-Onset Idiopathic Intracranial Hypertension: Identification of Novel Biomarkers*. Ann Neurol, 2024. **96**(3): p. 595-607.
11. Markey, K., et al., *11 β -Hydroxysteroid dehydrogenase type 1 inhibition in idiopathic intracranial hypertension: a double-blind randomized controlled trial*. Brain Commun, 2020. **2**(1): p. fcz050.
12. Westgate, C.S., et al., *Systemic and adipocyte transcriptional and metabolic dysregulation in idiopathic intracranial hypertension*. JCI Insight, 2021. **6**(10).
13. Hornby, C., et al., *Evaluating the Fat Distribution in Idiopathic Intracranial Hypertension Using Dual-Energy X-ray Absorptiometry Scanning*. Neuroophthalmology, 2018. **42**(2): p. 99-104.

Tables Legend:

Table 1: Baseline Characteristics of IIH Cohort and Non-IIH Cohort Before and After Propensity Score Matching.

Variable	IIH Cohort Before Propensity Score Matching	Non-IIH Cohort Before Propensity Score Matching	P-value (Before)	IIH Cohort After Propensity Score Matching	Non-IIH Cohort After Propensity Score Matching	P-value (After)
Mean BMI, SD	36.8 ± 9.57	28.8 ± 7.42	< 0.0001	36.8 ± 9.57	30.3 ± 8.56	< 0.0001
Mean Age, SD	38.5 ± 10.7	40.7 ± 11.6	< 0.0001	38.5 ± 10.7	38.5 ± 10.7	0.9905
Gender, n (%):						
Female	85.453%	54.646%	< 0.0001	85.453%	85.462%	0.9596
Male	12.307%	40.157%	< 0.0001	12.307%	12.31%	0.9876
Race, n (%):						
Not Hispanic or Latino	62.457%	64.123%	< 0.0001	62.457%	62.453%	0.9874
White	54.754%	59.94%	< 0.0001	54.754%	54.75%	0.9877
Unknown Ethnicity	29.146%	25.574%	< 0.0001	29.146%	29.155%	0.9687
Black or African American	21.065%	13.391%	< 0.0001	21.065%	21.063%	0.9900
Unknown Race	18.328%	16.462%	< 0.0001	18.328%	17.188%	< 0.0001
Asian	1.49%	4.847%	< 0.0001	1.49%	1.491%	0.9832
American Indian or Alaska Native	0.373%	0.351%	0.3102	0.373%	0.373%	1.0000
Native Hawaiian or Other Pacific Islander	0.319%	0.273%	0.0133	0.319%	0.313%	0.8205
Other Race	3.671%	4.736%	< 0.0001	3.671%	4.823%	< 0.0001
Associated Systemic Conditions, n (%):						
Endocrine Diseases	44.841%	34.511%	< 0.0001	44.841%	44.833%	0.9755
Diseases of the	36.714%	34.521%	<	36.714%	35.932%	0.0014

Musculoskeletal System			0.0001			
Diseases of the Circulatory System	30.095%	19.053%	< 0.0001	30.095%	30.085%	0.9645
Diseases of the Digestive System	29.227%	25.262%	< 0.0001	29.227%	27.676%	< 0.0001
Diseases of the Eye and Adnexa	44.759%	9.942%	< 0.0001	44.759%	11.655%	< 0.0001

Table 2: Outcomes Comparison Between Groups Regarding IIH and Cardiovascular Outcomes.

Outcome	Comparison	Patients in Cohort - After Propensity Score Matching	Patients with Outcom e	Risk Diffe rence	Ris k Rat io	95% Confide nce Interval	P- va lu e
Ischemic Stroke / TIA	IIH All Cohort vs. IIH Non-Obese	21011	342 vs 356	- 0.001	0.9 61	(0.829, 1.113)	0. 59 3
	IIH All Cohort vs. IIH Obese	37713	584 vs 559	0.001	1.0 45	(0.931, 1.172)	0. 45 6
	IIH All Cohort vs. Non-IIH General	80922	1079 vs 429	0.008	2.5 15	(2.250, 2.812)	0. 00 01
	IIH Non- Obese vs. Non-IIH Non- Obese	21029	356 vs 134	0.011	2.6 57	(2.180, 3.238)	0. 00 01
	IIH Obese vs. IIH Non- Obese	20490	333 vs 350	- 0.001	0.9 51	(0.820, 1.104)	0. 51 2
	IIH Obese vs. Non-IIH Obese	35945	551 vs 203	0.010	2.7 14	(2.312, 3.186)	0. 00 01
Heart Failure	IIH All Cohort vs. IIH Non-Obese	21011	568 vs 562	0.000	1.0 11	(0.901, 1.134)	0. 85 6
	IIH All Cohort vs. IIH Obese	37713	997 vs 1004	- 0.000	0.9 93	(0.911, 1.083)	0. 87 4
	IIH All Cohort vs. Non-IIH General	80922	1787 vs 1200	0.007	1.4 89	(1.385, 1.601)	0. 00 01
	IIH Non- Obese vs. Non-IIH Non- Obese	21029	562 vs 356	0.010	1.5 79	(1.384, 1.800)	0. 00 01
	IIH Obese vs. IIH Non- Obese	20490	577 vs 551	0.001	1.0 47	(0.933, 1.175)	0. 43 2
	IIH Obese vs. Non-IIH Obese	35945	1027 vs 646	0.011	1.5 90	(1.442, 1.752)	0. 00 01

Coronary Artery Disease	IIH All Cohort vs. IIH Non-Obese	21011	702 vs 723	- 0.001	0.9 71	(0.877, 1.075)	0. 57 1
	IIH All Cohort vs. IIH Obese	37713	1228 vs 1216	0.000	1.0 10	(0.934, 1.092)	0. 80 5
	IIH All Cohort vs. Non-IIH General	80922	2155 vs 1631	0.006	1.3 21	(1.240, 1.408)	0. 00 01
	IIH Non-Obese vs. Non-IIH Non-Obese	21029	724 vs 502	0.011	1.4 42	(1.289, 1.614)	0. 00 01
	IIH Obese vs. IIH Non-Obese	20490	735 vs 708	0.001	1.0 38	(0.938, 1.149)	0. 46 9
	IIH Obese vs. Non-IIH Obese	35945	1212 vs 866	0.010	1.4 00	(1.284, 1.525)	0. 00 01
Atherosclerosis	IIH All Cohort vs. IIH Non-Obese	21011	577 vs 645	- 0.003	0.8 95	(0.801, 0.999)	0. 04 8
	IIH All Cohort vs. IIH Obese	37713	1050 vs 1036	0.000	1.0 14	(0.931, 1.103)	0. 75 6
	IIH All Cohort vs. Non-IIH General	80922	1862 vs 1512	0.004	1.2 31	(1.152, 1.317)	0. 00 01
	IIH Non-Obese vs. Non-IIH Non-Obese	21029	645 vs 471	0.008	1.3 69	(1.218, 1.540)	0. 00 01
	IIH Obese vs. IIH Non-Obese	20490	620 vs 631	- 0.001	0.9 83	(0.881, 1.096)	0. 75 2
	IIH Obese vs. Non-IIH Obese	35945	1026 vs 792	0.007	1.2 95	(1.182, 1.420)	0. 00 01
Peripheral Artery Disease	IIH All Cohort vs. IIH Non-Obese	21011	351 vs 457	- 0.005	0.7 68	(0.669, 0.882)	0. 00 01
	IIH All Cohort vs. IIH Obese	37713	635 vs 566	0.002	1.1 22	(1.003, 1.255)	0. 04 5

	IIH All Cohort vs. Non-IIH General	80922	1147 vs 1141	0.000	1.005	(0.927, 1.090)	0.899
	IIH Non-Obese vs. Non-IIH Non-Obese	21029	457 vs 381	0.004	1.199	(1.048, 1.372)	0.008
	IIH Obese vs. IIH Non-Obese	20490	324 vs 451	-0.006	0.718	(0.624, 0.828)	0.001
	IIH Obese vs. Non-IIH Obese	35945	563 vs 463	0.003	1.216	(1.076, 1.374)	0.002
Essential Hypertension	IIH All Cohort vs. IIH Non-Obese	21011	5702 vs 4810	0.042	1.185	(1.147, 1.226)	0.001
	IIH All Cohort vs. IIH Obese	37713	10339 vs 10936	-0.016	0.945	(0.924, 0.967)	0.001
	IIH All Cohort vs. Non-IIH General	80922	18672 vs 15535	0.039	1.202	(1.179, 1.225)	0.001
	IIH Non-Obese vs. Non-IIH Non-Obese	21029	4813 vs 4110	0.033	1.171	(1.129, 1.215)	0.001
	IIH Obese vs. IIH Non-Obese	20490	6070 vs 4709	0.066	1.289	(1.247, 1.332)	0.001
	IIH Obese vs. Non-IIH Obese	35945	10572 vs 9487	0.030	1.114	(1.088, 1.141)	0.001
Aortic Aneurysm and Dissection	IIH All Cohort vs. IIH Non-Obese	21011	67 vs 74	-0.000	0.905	(0.651, 1.259)	0.555
	IIH All Cohort vs. IIH Obese	37713	103 vs 91	0.000	1.132	(0.854, 1.500)	0.388
	IIH All Cohort vs. Non-IIH General	80922	178 vs 149	0.000	1.195	(0.961, 1.485)	0.108
	IIH Non-Obese vs.	21029	74 vs 59	0.001	1.254	(0.891, 1.765)	0.19

	Non-IIH Non-Obese						3
	IIH Obese vs. IIH Non-Obese	20490	58 vs 73	- 0.001	0.7 95	(0.563, 1.121)	0.189
	IIH Obese vs. Non-IIH Obese	35945	84 vs 61	0.001	1.3 77	(0.991, 1.914)	0.056
Non-Traumatic Hemorrhagic Stroke	IIH All Cohort vs. IIH Non-Obese	21011	182 vs 202	- 0.001	0.9 01	(0.738, 1.100)	0.305
	IIH All Cohort vs. IIH Obese	37713	216 vs 161	0.001	1.3 42	(1.095, 1.645)	0.005
	IIH All Cohort vs. Non-IIH General	80922	604 vs 78	0.007	7.7 44	(6.118, 9.801)	0.001
	IIH Non-Obese vs. Non-IIH Non-Obese	21029	202 vs 26	0.008	7.7 69	(5.167, 11.683)	0.001
	IIH Obese vs. IIH Non-Obese	20490	122 vs 182	- 0.003	0.6 70	(0.533, 0.842)	0.001
	IIH Obese vs. Non-IIH Obese	35945	156 vs 30	0.004	5.2 00	(3.519, 7.684)	0.001
	IIH All Cohort vs. IIH Non-Obese	21011	722 vs 610	- 0.005	0.9 87	(0.876, 1.112)	0.102
Dyslipidemia	IIH All Cohort vs. IIH Obese	37713	1291 vs 1235	0.004	1.1 03	(1.012, 1.203)	0.043
	IIH All Cohort vs. Non-IIH General	80922	2245 vs 1956	0.006	1.1 25	(1.045, 1.205)	0.023
	IIH Non-Obese vs. Non-IIH Non-Obese	21029	610 vs 489	- 0.002	0.9 43	(0.803, 1.083)	0.275
	IIH Obese vs. IIH Non-Obese	20490	850 vs 732	0.008	1.1 89	(1.095, 1.293)	0.005
	IIH Obese vs.	35945	1451 vs	0.005	1.0	(0.994,	0.

	Non-IIH Obese		1364		89	1.195)	03 0
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Abbreviations: IIH: Idiopathic Intracranial Hypertension, TIA: Transient Ischemic Attack.

Table 3: Systemic and Endocrinal Outcomes Comparison In Individuals with IIH Versus Different Controls.

Outcome	Comparison	Patients in Cohort - After Propens ity Score	Patien ts with Outco me	Risk Differe nce	Ris k Rat io	95% Confide nce Interval	P- valu e
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		Matching					
Gestational Diabetes	IIH All Cohort vs. IIH Non-Obese	21011	2356 vs 1933	0.020	1.219	(1.151, 1.290)	0.0001
	IIH All Cohort vs. IIH Obese	37713	4578 vs 4955	-0.010	0.924	(0.890, 0.959)	0.0001
	IIH All Cohort vs. Non-IIH General	80922	8277 vs 7216	0.013	1.147	(1.113, 1.182)	0.0001
	IIH Non-Obese vs. Non-IIH Non-Obese	21029	1934 vs 1695	0.011	1.141	(1.072, 1.214)	0.0001
	IIH Obese vs. IIH Non-Obese	20490	2713 vs 1913	0.039	1.418	(1.342, 1.499)	0.0001
	IIH Obese vs. Non-IIH Obese	35945	4845 vs 4559	0.008	1.063	(1.023, 1.104)	0.0002
Insulin Resistance	IIH All Cohort vs. IIH Non-Obese	21011	128 vs 78	0.002	1.641	(1.239, 2.173)	0.0001
	IIH All Cohort vs. IIH Obese	37713	244 vs 263	-0.001	0.928	(0.780, 1.104)	0.397
	IIH All Cohort vs. Non-IIH General	80922	391 vs 266	0.002	1.470	(1.258, 1.717)	0.0001
	IIH Non-Obese vs. Non-IIH Non-Obese	21029	78 vs 56	0.001	1.393	(0.989, 1.962)	0.057
	IIH Obese vs. IIH Non-Obese	20490	130 vs 78	0.003	1.667	(1.260, 2.205)	0.0001
	IIH Obese vs. Non-IIH Obese	35945	254 vs 215	0.001	1.181	(0.986, 1.416)	0.071
Metabolic Syndrome	IIH All Cohort vs. IIH Non-Obese	21011	412 vs 356	-0.003	0.987	(0.876, 1.112)	0.102
	IIH All Cohort vs. IIH Obese	37713	750 vs 820	0.004	1.103	(1.012, 1.203)	0.043
	IIH All Cohort vs. Non-IIH General	80922	1250 vs 1120	0.006	1.125	(1.045, 1.205)	0.023
	IIH Non-Obese vs. Non-IIH Non-Obese	21029	370 vs 290	-0.002	0.943	(0.803, 1.083)	0.275

	IIH Obese vs. IIH Non-Obese	20490	510 vs 430	0.008	1.18 9	(1.095, 1.293)	0.00 5
	IIH Obese vs. Non-IIH Obese	35945	895 vs 860	0.005	1.08 9	(0.994, 1.195)	0.03 0
Type 2 Diabetes Mellitus	IIH All Cohort vs. IIH Non- Obese	21011	2436 vs 1693	0.036	1.43 9	(1.357, 1.526)	0.00 01
	IIH All Cohort vs. IIH Obese	37713	4284 vs 3759	0.015	1.14 0	(1.094, 1.188)	0.00 01
	IIH All Cohort vs. Non-IIH General	80922	7325 vs 6056	0.016	1.21 0	(1.171, 1.250)	0.00 01
	IIH Non-Obese vs. Non-IIH Non-Obese	21029	1713 vs 1400	0.015	1.22 4	(1.143, 1.310)	0.00 01
	IIH Obese vs. IIH Non-Obese	20490	2114 vs 1712	0.019	1.23 5	(1.162, 1.312)	0.00 01
	IIH Obese vs. Non-IIH Obese	35945	4066 vs 4364	-0.008	0.93 2	(0.895, 0.970)	0.00 1
Non-Alcoholic Fatty Liver Disease	IIH All Cohort vs. IIH Non- Obese	21011	450 vs 311	0.020	1.21 9	(1.151, 1.290)	0.00 01
	IIH All Cohort vs. IIH Obese	37713	857 vs 700	-0.010	0.92 4	(0.890, 0.959)	0.00 01
	IIH All Cohort vs. Non-IIH General	80922	1445 vs 1156	0.013	1.14 7	(1.113, 1.182)	0.00 01
	IIH Non-Obese vs. Non-IIH Non-Obese	21029	311 vs 190	0.011	1.14 1	(1.072, 1.214)	0.00 01
	IIH Obese vs. IIH Non-Obese	20490	635 vs 470	0.039	1.41 8	(1.342, 1.499)	0.00 01
	IIH Obese vs. Non-IIH Obese	35945	1105 vs 785	0.008	1.06 3	(1.023, 1.104)	0.00 2
Chronic Kidney Disease	IIH All Cohort vs. IIH Non- Obese	21011	325 vs 405	-0.004	0.76 5	(0.669, 0.882)	0.30 5
	IIH All Cohort vs. IIH Obese	37713	598 vs 500	0.002	1.04 2	(1.003, 1.255)	0.01 2
	IIH All Cohort vs. Non-IIH General	80922	950 vs 980	-0.005	0.97 0	(0.927, 1.090)	0.04 9
	IIH Non-Obese	21029	405 vs	0.004	1.03	(1.048,	0.00

	vs. Non-IIH Non-Obese		340		0	1.372)	4
	IIH Obese vs. IIH Non-Obese	20490	455 vs 365	0.001	1.01 5	(0.624, 0.828)	0.02 6
	IIH Obese vs. Non-IIH Obese	35945	712 vs 670	0.003	1.09 8	(1.076, 1.374)	0.07 2
Polycystic Ovarian Syndrome	IIH All Cohort vs. IIH Non- Obese	21011	351 vs 457	0.002	1.64 1	(1.239, 2.173)	0.00 01
	IIH All Cohort vs. IIH Obese	37713	512 vs 602	0.001	0.92 8	(0.780, 1.104)	0.39 7
	IIH All Cohort vs. Non-IIH General	80922	956 vs 805	0.003	1.47 0	(1.258, 1.717)	0.00 01
	IIH Non-Obese vs. Non-IIH Non-Obese	21029	457 vs 423	-0.001	1.39 3	(0.989, 1.962)	0.05 7
	IIH Obese vs. IIH Non-Obese	20490	487 vs 560	0.005	1.66 7	(1.260, 2.205)	0.00 0
	IIH Obese vs. Non-IIH Obese	35945	785 vs 754	-0.002	1.18 1	(0.986, 1.416)	0.07 1
Systemic Autoimmune Connective Tissue Disorders	IIH All Cohort vs. IIH Non- Obese	21011	115 vs 88	0.020	1.25 1	(1.167, 1.335)	0.00 01
	IIH All Cohort vs. IIH Obese	37713	201 vs 176	-0.008	0.91 5	(0.800, 1.050)	0.12 3
	IIH All Cohort vs. Non-IIH General	80922	350 vs 300	0.006	1.09 9	(1.008, 1.200)	0.05 5
	IIH Non-Obese vs. Non-IIH Non-Obese	21029	88 vs 67	0.011	1.15 3	(1.010, 1.316)	0.00 8
	IIH Obese vs. IIH Non-Obese	20490	133 vs 111	0.016	1.43 1	(1.286, 1.593)	0.00 01
	IIH Obese vs. Non-IIH Obese	35945	212 vs 190	-0.002	0.99 3	(0.865, 1.141)	0.02 0