



# THE RESEARCH CONTINUES: CYTOKINE PROFILES IN THE CENTRAL DISORDERS OF HYPERSOMNOLENCE

CAROLINE MANESS, MD

CHIEF RESIDENT, PGY4

DEPARTMENT OF NEUROLOGY, EMORY UNIVERSITY SCHOOL OF MEDICINE

# DISCLOSURES

- Hypersomnia Foundation Research Award
- No other financial disclosures

# OVERVIEW

- Introduction
- Cytokine Study Description and Results
- Study Implications
- What's Next?

# JARGON AND ABBREVIATIONS

- Statistical significance – Helps us quantify whether the result we are seeing occurred by chance or represents a real phenomenon
- IH – Idiopathic hypersomnia
- NT2 - Narcolepsy type 2
- EDS – Group of patients that report significant, debilitating sleepiness, but when studied in the sleep lab, they do not fall into the category of a type of narcolepsy or idiopathic hypersomnia

# WHAT ARE CYTOKINES ANYWAY?

- Cytokines are a group of proteins (not "antibodies" though) that carry signals throughout the body to regulate both localized and full-body immune responses.
- Cytokines disturbances are known to underlie rheumatologic diseases like rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.
- In 1998 the FDA approved the first cytokine "regulator" – this was etanercept (brand name Enbrel) – a TNF alpha inhibitor to be used for severe rheumatoid arthritis
- Since then cytokine inhibitors have also been approved for the cytokines IL-1 (anakinra) and IL-6 (tocilizumab), among others.

[Clin Rheumatol](#). 2020 May 30 : 1–10.

doi: [10.1007/s10067-020-05190-5](https://doi.org/10.1007/s10067-020-05190-5) [Epub ahead of print]

PMCID: PMC7260446

PMID: [32474885](https://pubmed.ncbi.nlm.nih.gov/32474885/)

Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment

[Mehmet Soy](#),<sup>✉1</sup> [Gökhan Keser](#),<sup>2</sup> [Pamir Atagündüz](#),<sup>3</sup> [Fehmi Tabak](#),<sup>4</sup> [Işık Atagündüz](#),<sup>5</sup> and [Servet Kayhan](#)<sup>6</sup>

► [Author information](#) ► [Article notes](#) ► [Copyright and License information](#) [Disclaimer](#)

# CYTOKINES AND SLEEP

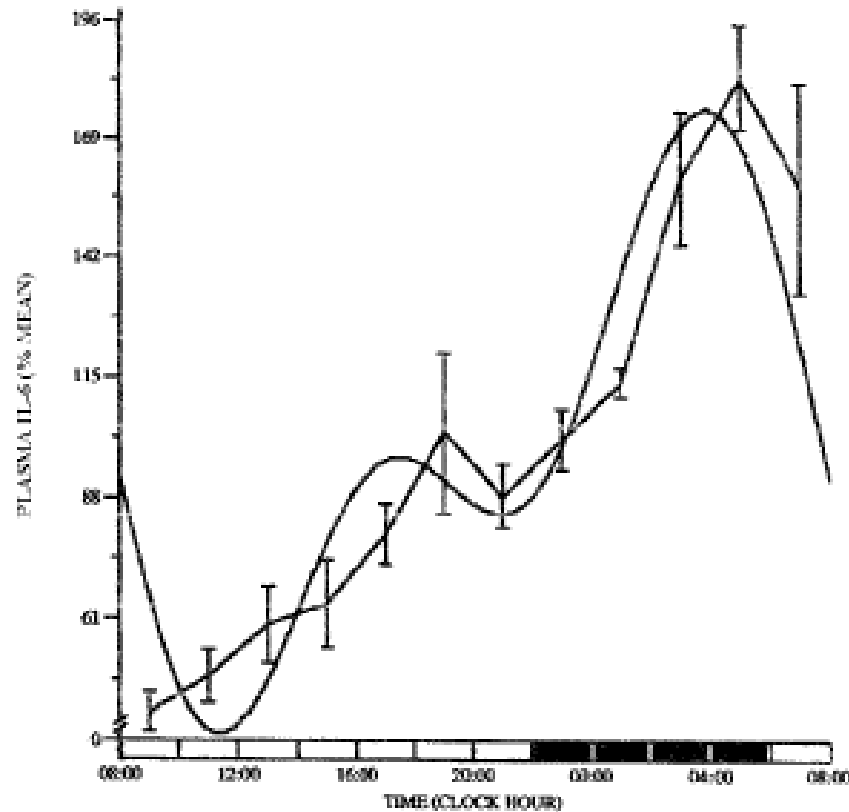
- Cytokines are the link that ties together communication from our immune system and central nervous system to influence the sleep-wake cycle.

Table 1

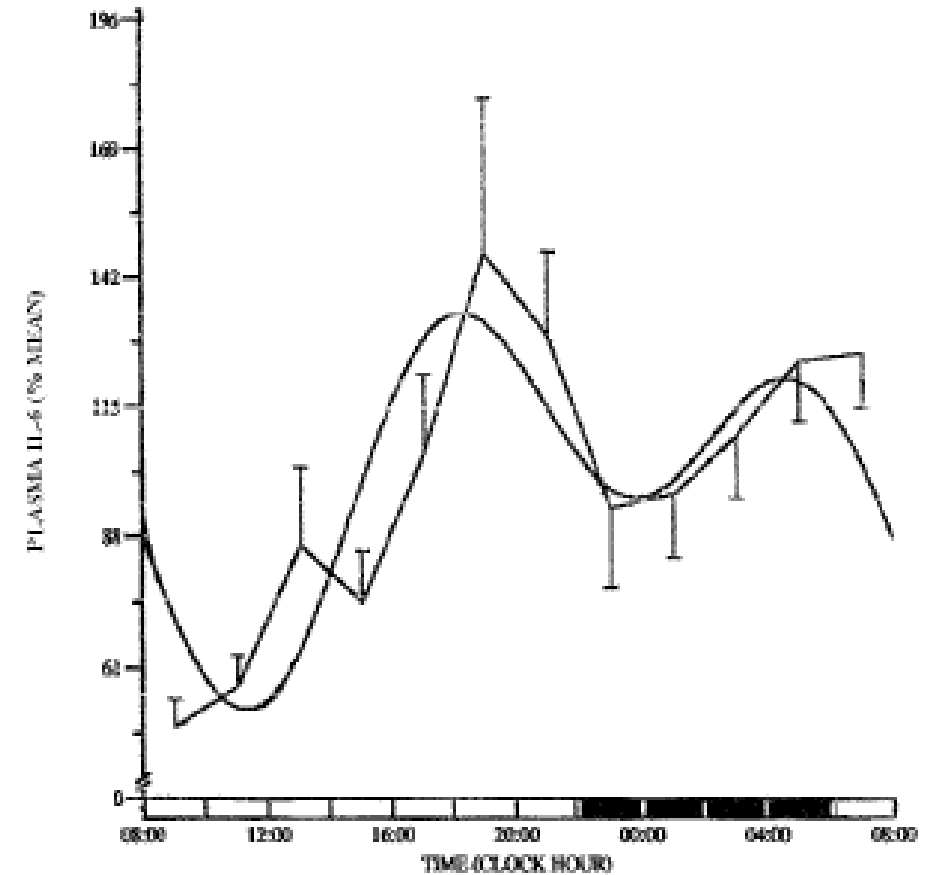
Cytokines involved in abnormal sleep situations

Situation	Cytokines
Sleepiness of acute infections	IL-1 $\beta$ , TNF- $\alpha$ [12,36,37,39]
Sleepiness of chronic illness	TNF- $\alpha$ [43–46]
Sleep deprivation	IL-1 $\beta$ , TNF- $\alpha$ , IL-6, leptin, ghrelin [32–35,51–54]
Obstructive sleep apnea	TNF- $\alpha$ , IL-6 [7,59–61]
Chronic insomnia	TNF- $\alpha$ , IL-6 [93]
Aging-related sleep problems	IL-6 [116]
Alcohol-related sleep disturbance	TNF- $\alpha$ , IL-6 [119]
Depression-related sickness	IL-1, IL-2, IL-6 TNF- $\alpha$ [120,121]
Narcolepsy	TNF- $\alpha$ , IL-6 [122–124]

# CYTOKINES AND SLEEP IN HEALTHY INDIVIDUALS



**Baseline**



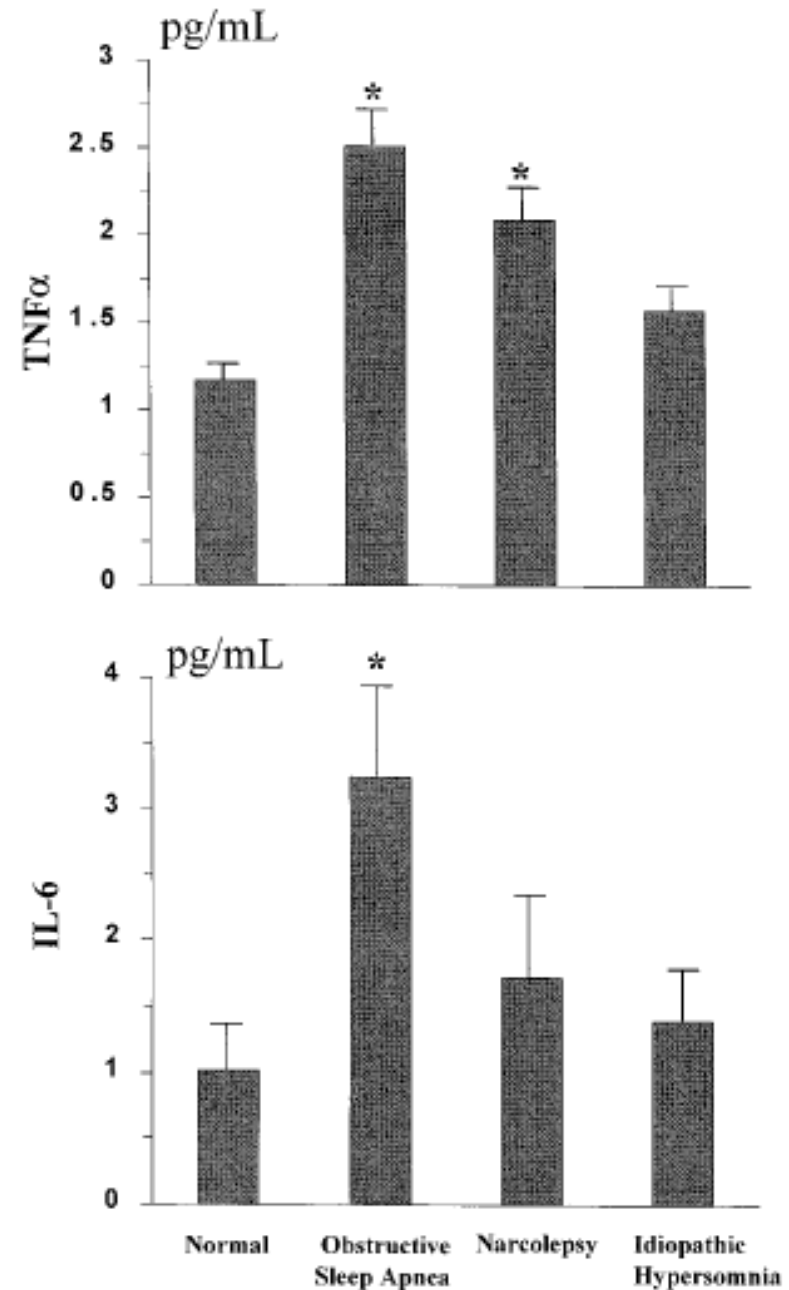
**After Sleep Deprivation**



# CYTOKINES IN PATIENTS WITH SLEEPINESS DISORDERS

Vgontzas, A. N., Papanicolaou, D. A., Bixler, E. O., Kales, A., Tyson, K., & Chrousos, G. P. (1997). Elevation of Plasma Cytokines in Disorders of Excessive Daytime Sleepiness: Role of Sleep Disturbance and Obesity. *The Journal of Clinical Endocrinology & Metabolism*, 82(5), 1313–1316.

<https://doi.org/10.1210/jcem.82.5.3950>



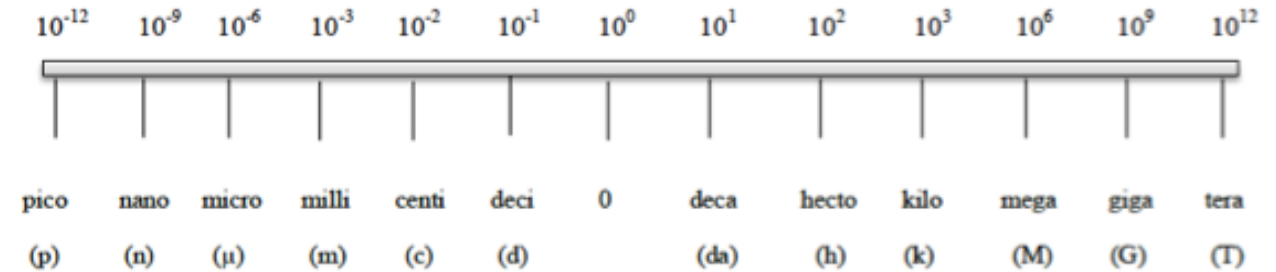


# STUDY DESIGN

- Patients:
  - Convenience sample of 153 patients evaluated at Emory Sleep Center in Atlanta, GA
- Diagnoses
  - Obstructive Sleep Apnea
  - Insufficient Sleep Syndrome
  - Narcolepsy Type 1
  - Narcolepsy Type 2
  - Idiopathic Hypersomnia
  - EDS
  - Controls

# STUDY DESIGN

- Sleep lab examination
  - Overnight polysomnography
  - Daytime multiple sleep latency test
- Survey Data
  - Sleepiness, fatigue, depression, early bird/night owl, sleep inertia (how hard it is to "wake up" when you wake up)
- Cytokine levels (10 different cytokines in total)
  - Measured from blood samples that had been collected in clinic and stored frozen since collection
  - Reported levels of cytokines will be picograms (pg) per milliliter of blood samples



# RESULTS

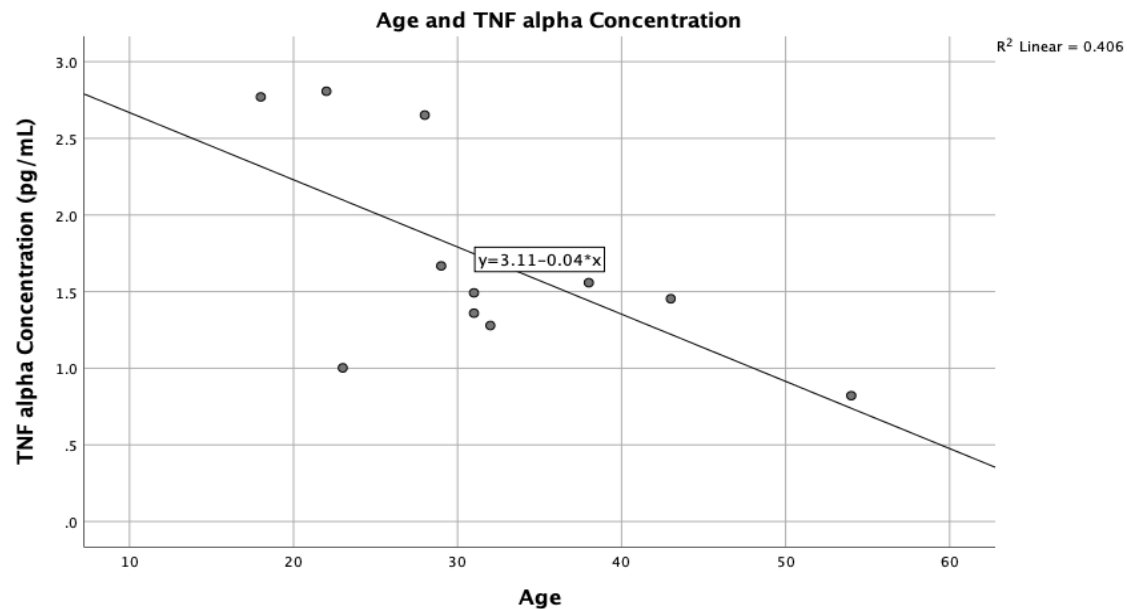
- Total of 111 patients (for brevity, will only discuss groups below)
  - Control: 22
  - IH: 51
  - EDS: 26
  - NT2: 12
- Average age: 33.8 years
- Average BMI: 23.9 kg/m<sup>2</sup>
- Average sleep per week: 65.1 hours

# STUDY RESULTS – CYTOKINE DATA (CONTEXT)

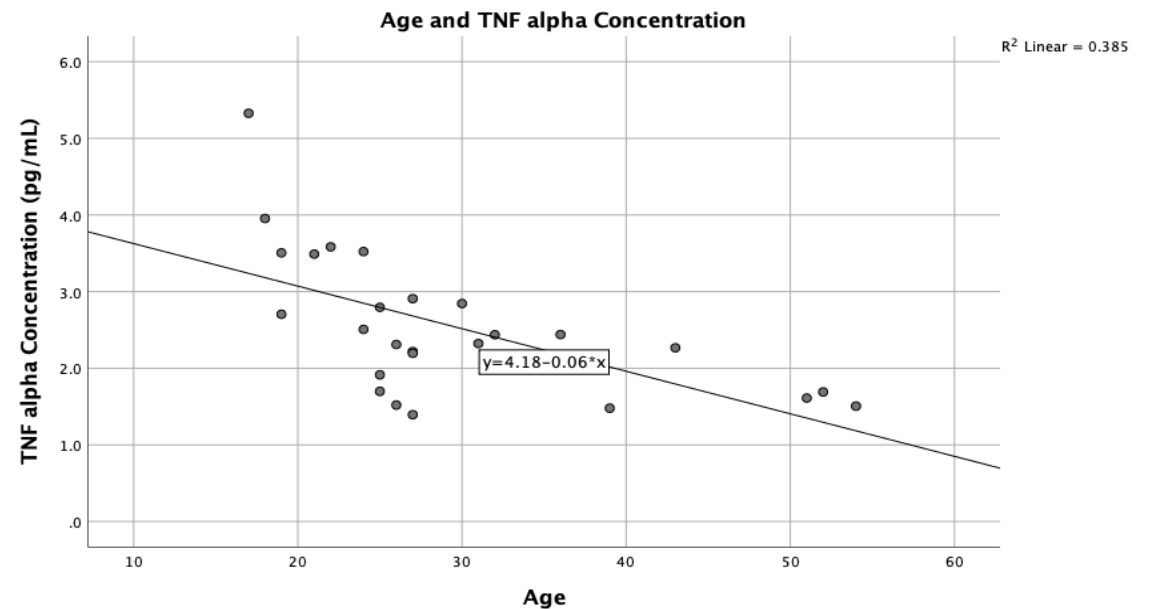
- Age can affect cytokine levels
- BMI can affect cytokines levels
- Gender can affect cytokine levels
- Interestingly, the effect of these factors was not consistent across our groups of patients

# AGE AND CYTOKINE LEVELS

- Controls: Age did not correlate with any cytokines
- IH: Age did not correlate with any cytokine
- EDS: Age was negatively correlated with TNF alpha and IL-10 concentration
- NT2: Age negatively correlated with TNF alpha concentration



NT2



EDS

## **BMI AND CYTOKINE LEVELS**

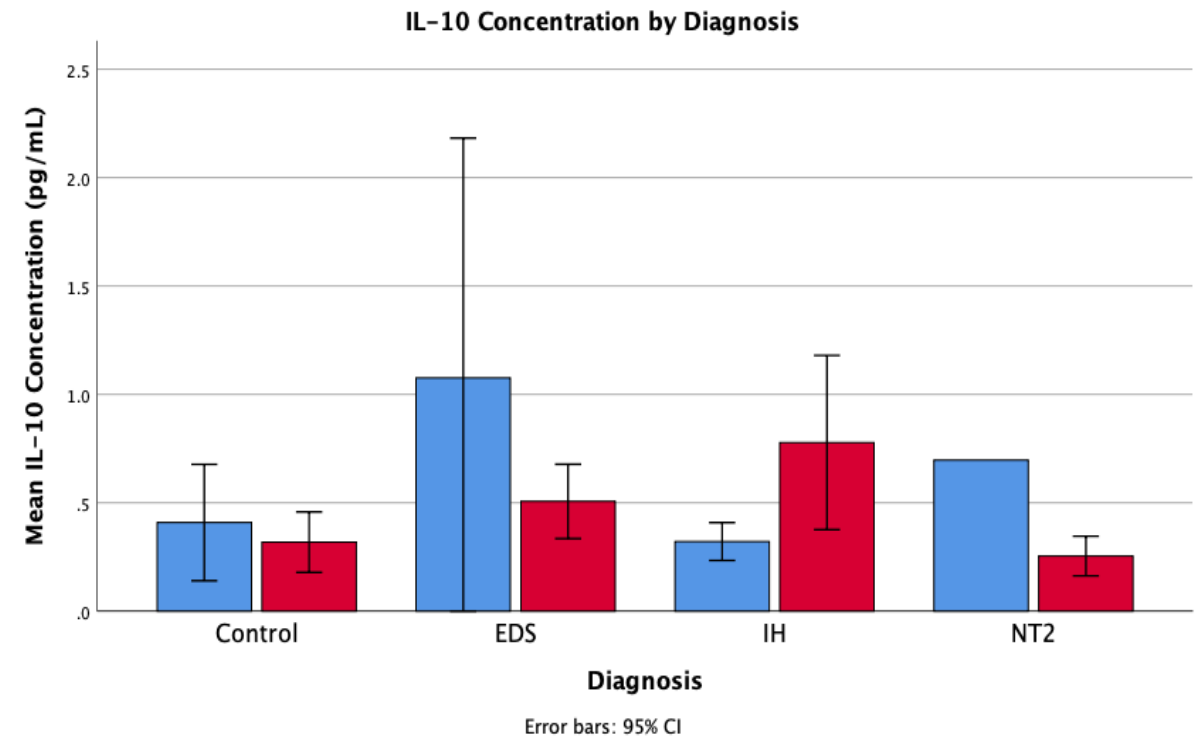
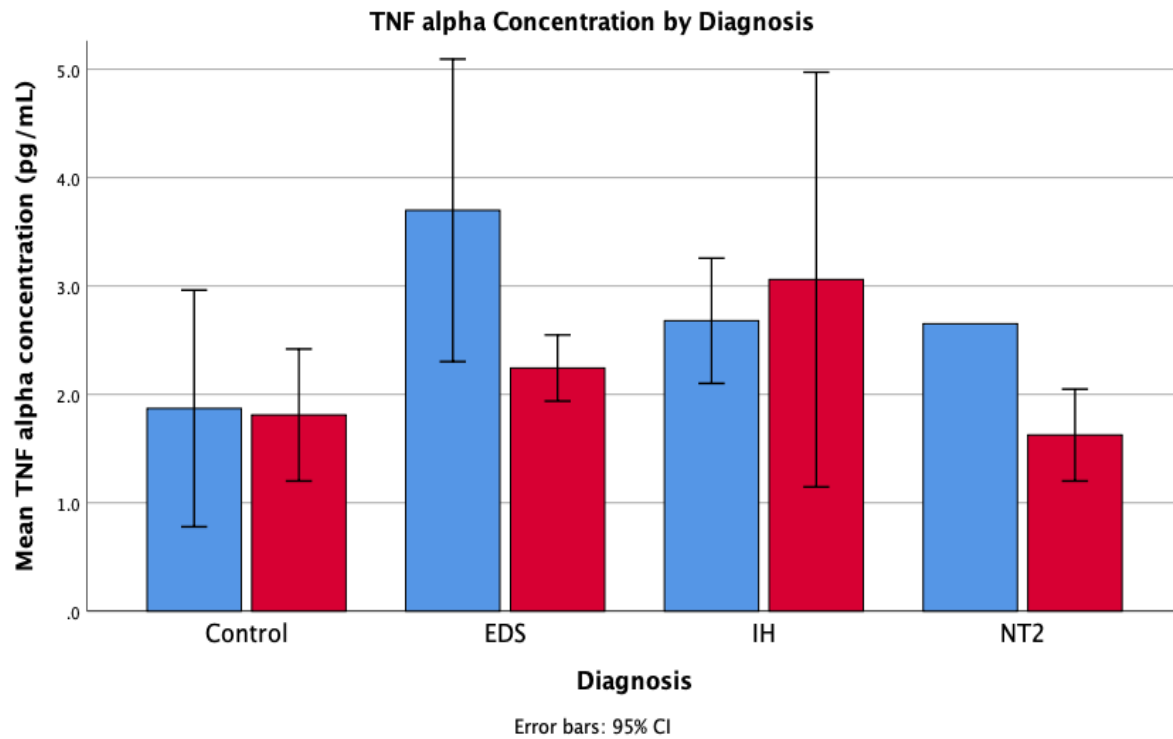
Controls: Significant positive correlation with IFN G, IL6, IL8

IH: Significant positive correlation with IL-6

EDS: Negative correlation with IL-4 and TNF-alpha

NT2: No significant correlations with BMI

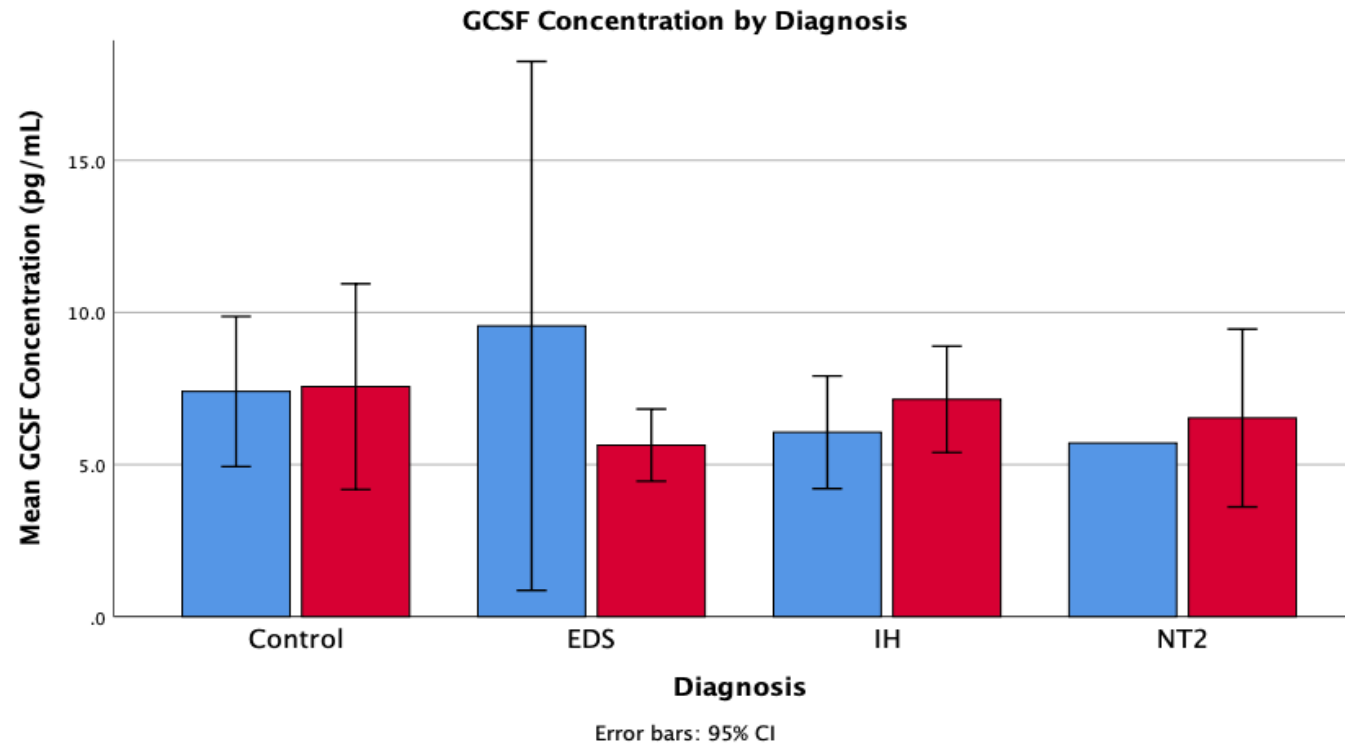
# GENDER AND CYTOKINE LEVELS



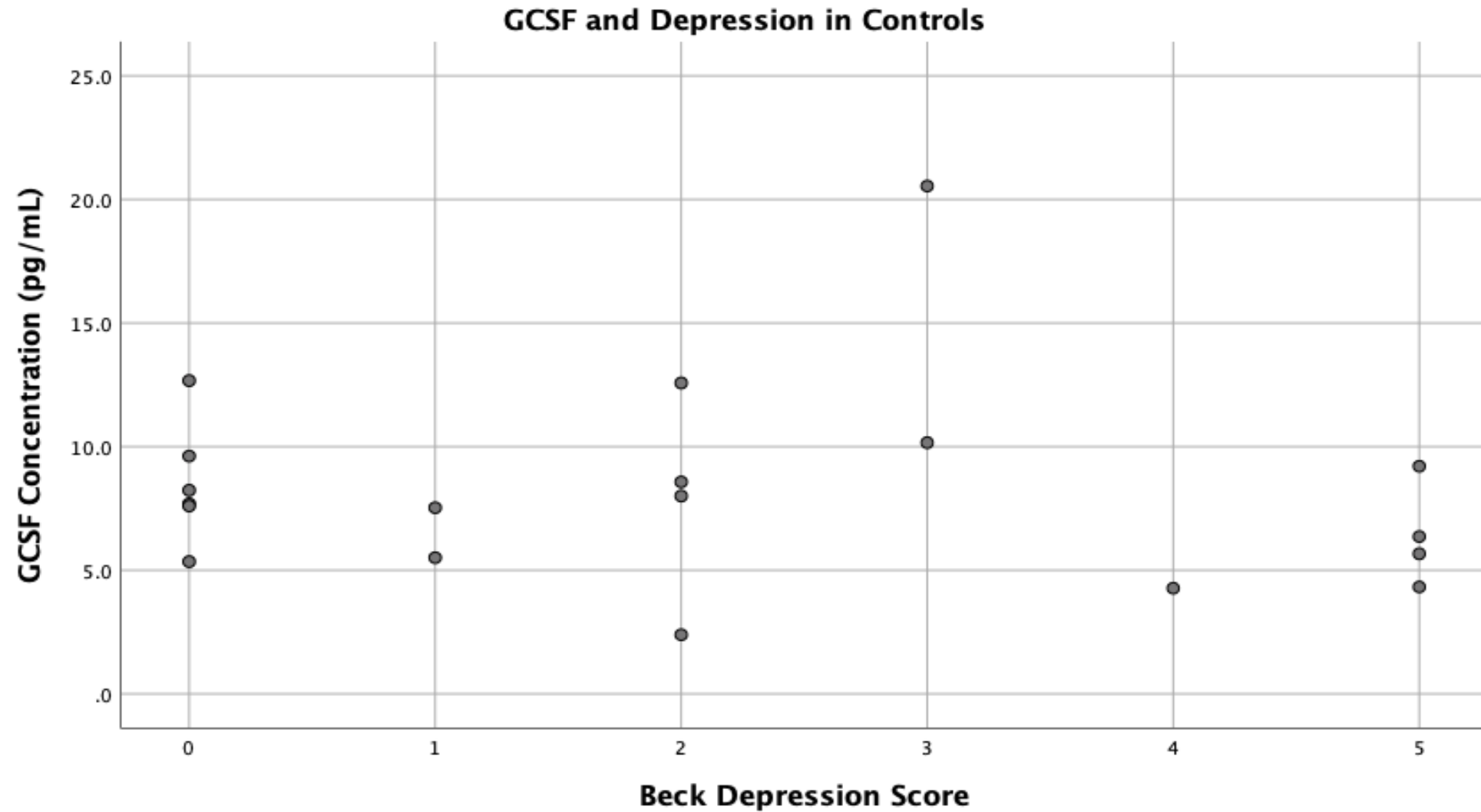
**Red = Female**  
**Blue = Male**



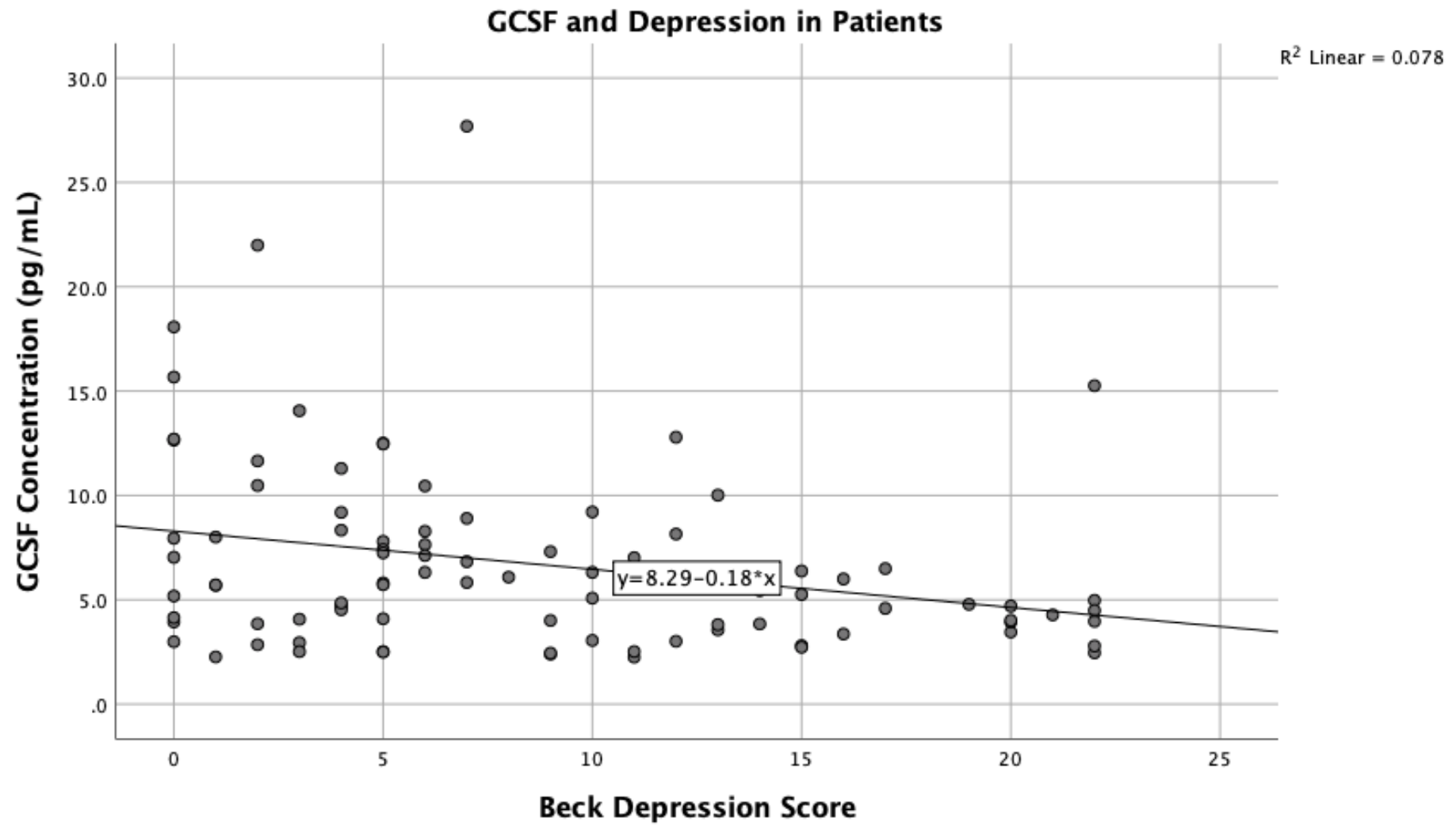
**Red = Female**  
**Blue = Male**



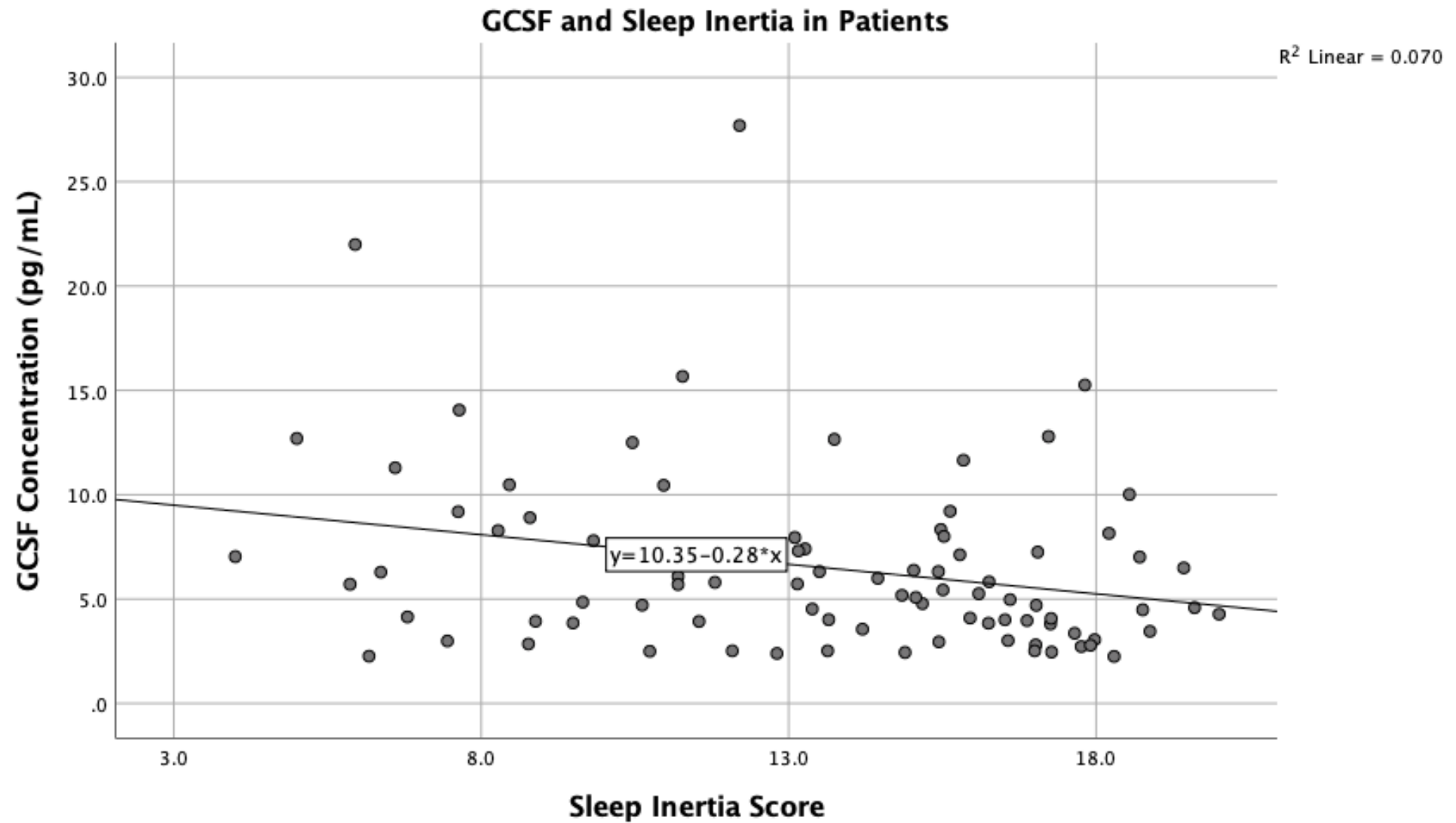
# GENDER AND CYTOKINE LEVELS



**CYTOKINES AND SYMPTOMS IN SLEEPINESS  
DISORDERS**

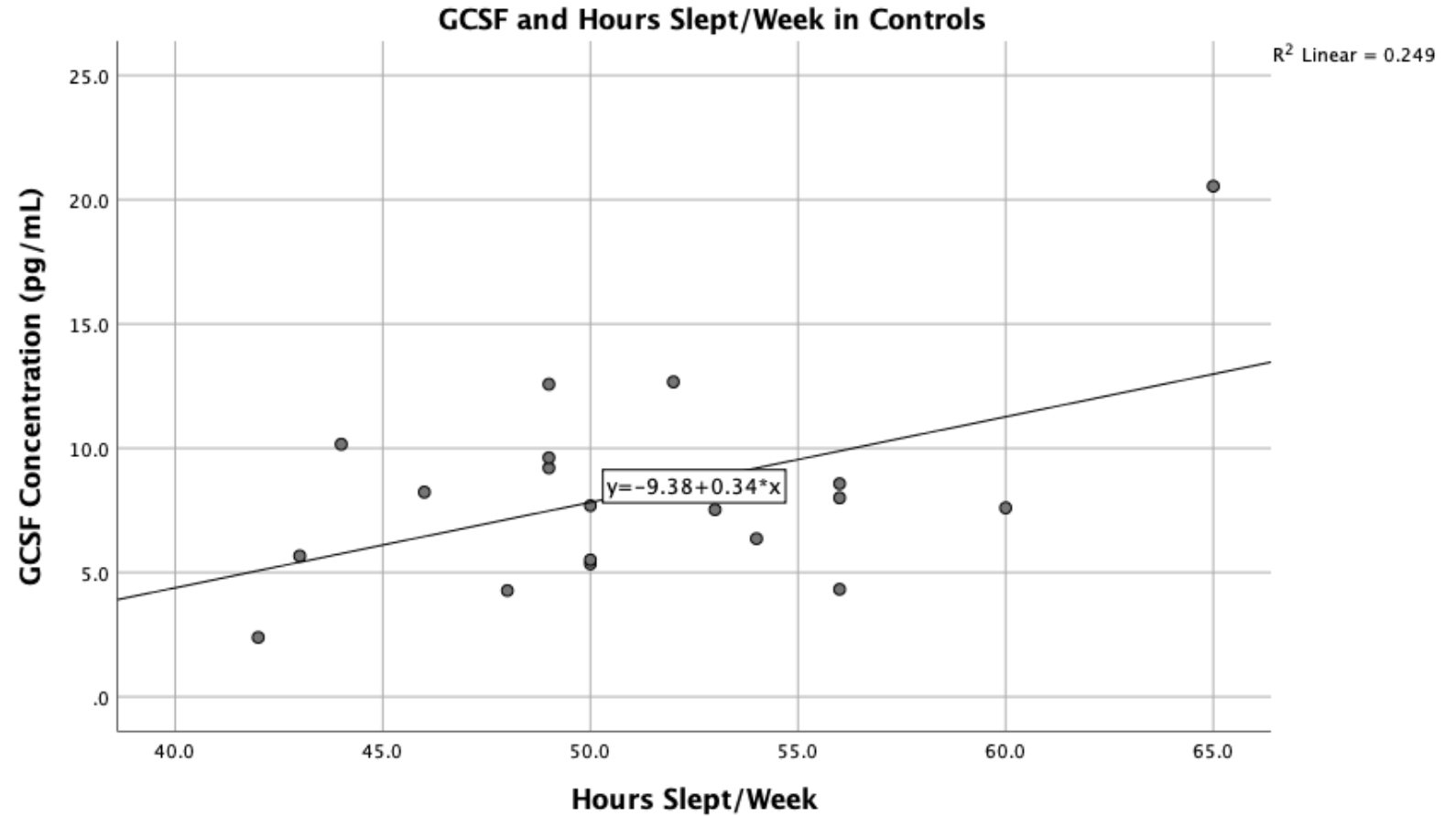


**CYTOKINES AND SYMPTOMS IN SLEEPINESS  
DISORDERS**

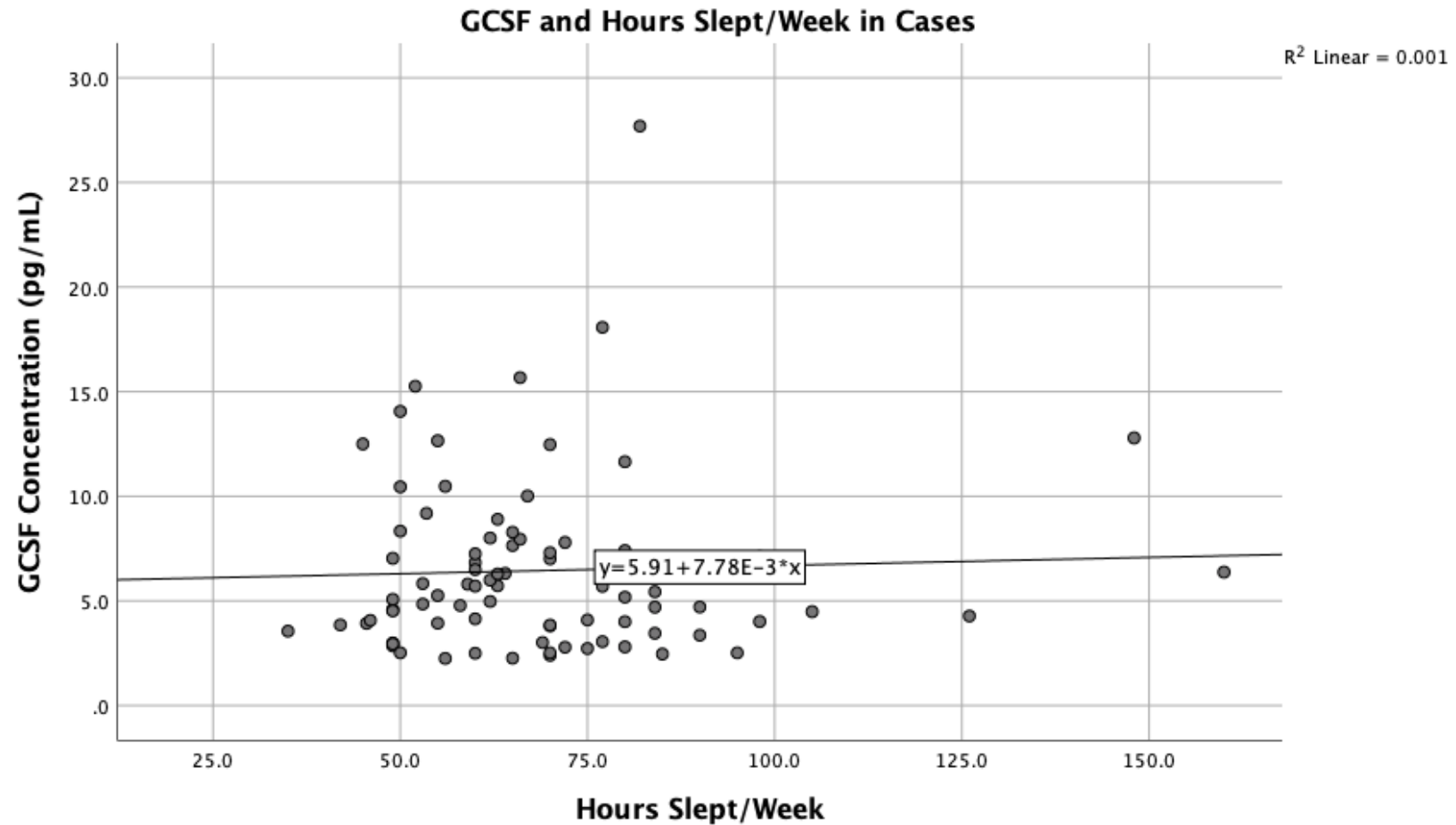


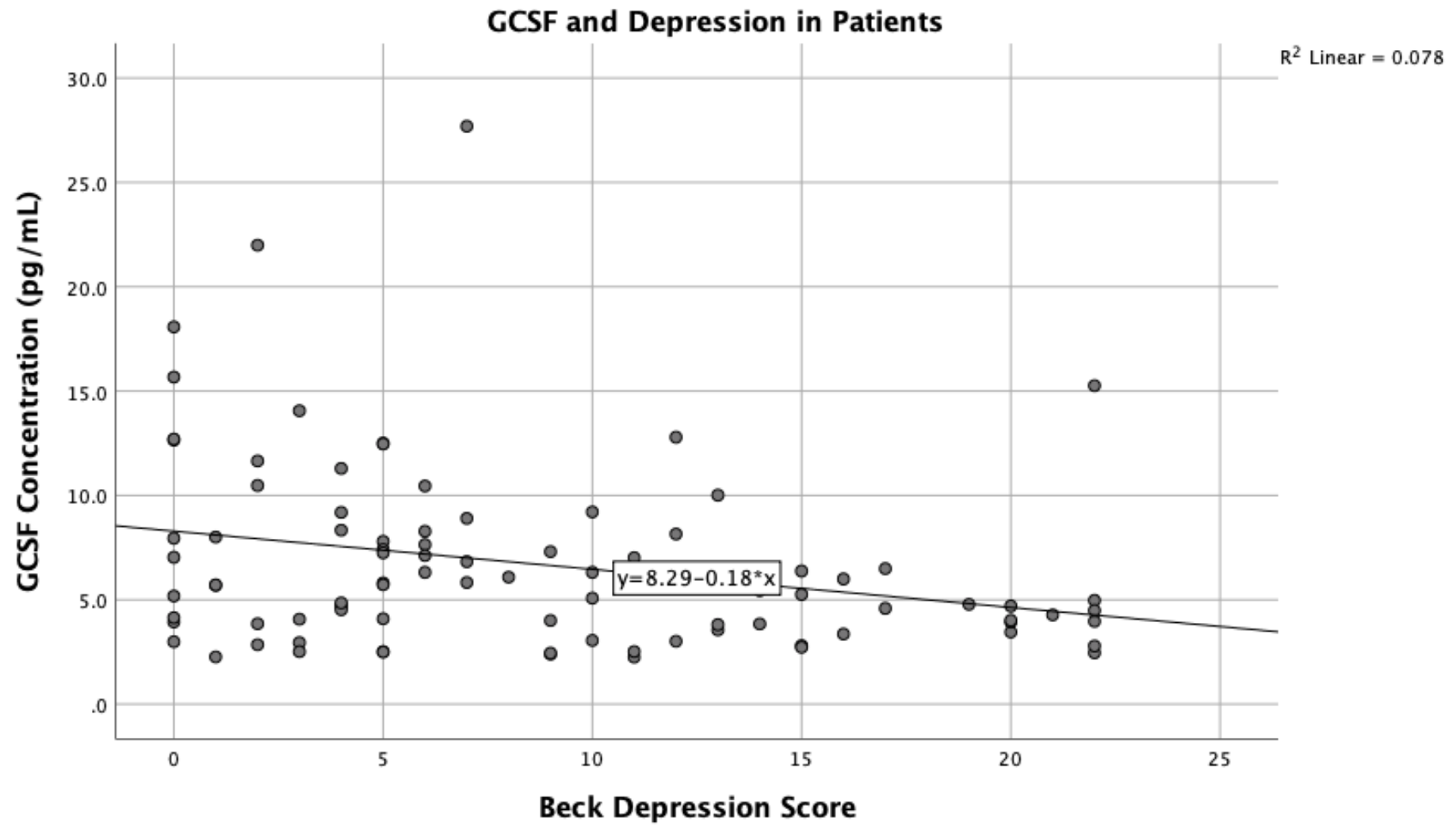
**CYTOKINES AND SYMPTOMS IN SLEEPINESS  
DISORDERS**

WHAT IS  
GOING  
WRONG TO  
CAUSE THIS?  
IN  
CONTROLS,  
MORE SLEEP  
= HIGHER  
GCSF



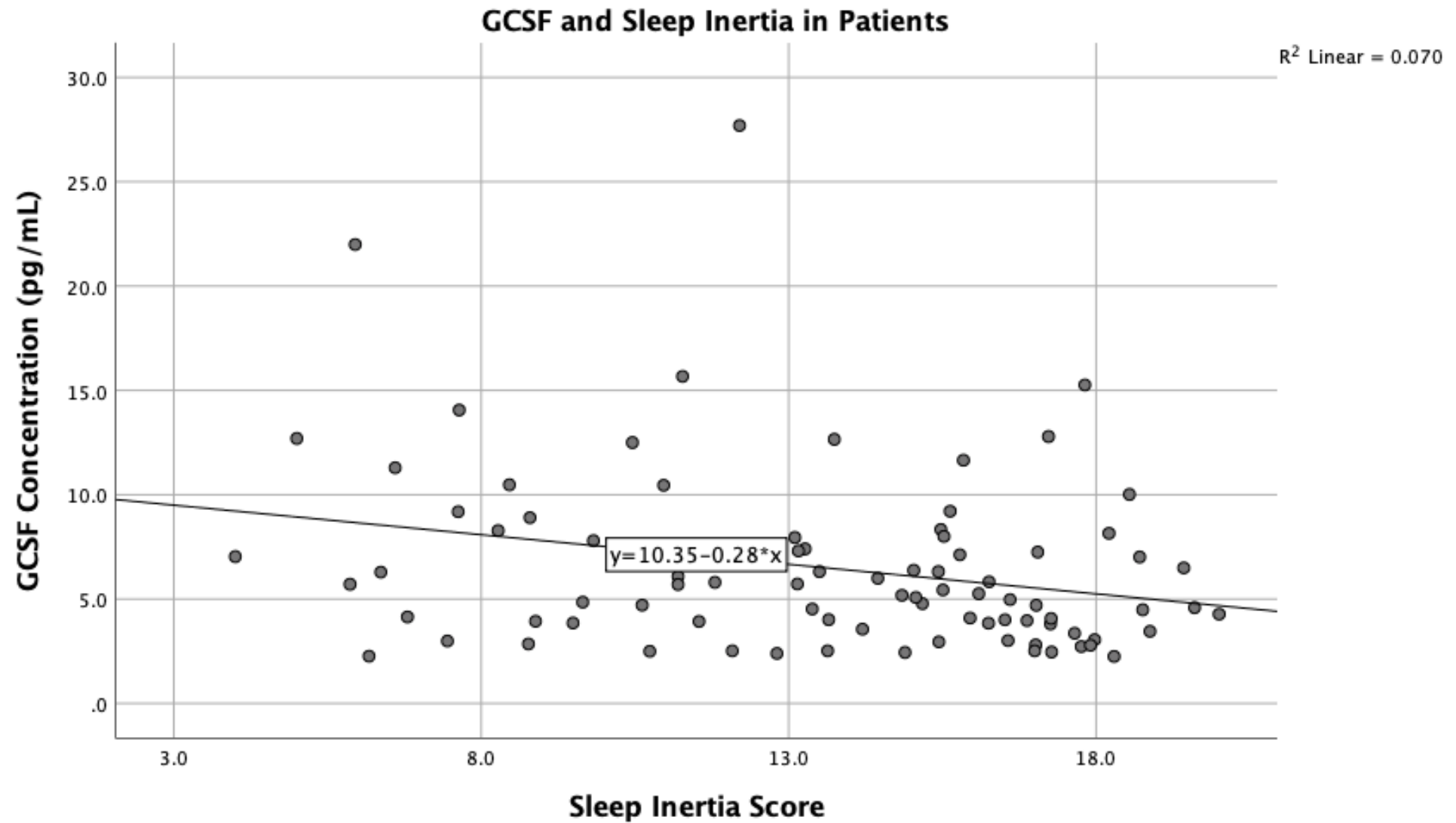
IN SLEEPY  
PATIENTS,  
GCSF DOESN'T  
NECESSARY  
INCREASE  
WITH MORE  
SLEEP.





**CYTOKINES AND SYMPTOMS IN SLEEPINESS  
DISORDERS**





**CYTOKINES AND SYMPTOMS IN SLEEPINESS  
DISORDERS**

# LUMPERS AND SPLITTERS

Utility of lumping: If certain symptoms of sleepiness disorders are correlated with certain cytokines (ex. GCSF), therapies that target that cytokines can be used to treat symptoms

Utility of splitting: Levels of cytokines varied for each of the four diagnoses we covered (controls, IH, NT2, and EDS) and between men and women. Could we use cytokines help tell us what disorder a patient has? Or could we use similar cytokines levels to create new diagnosis “clusters”?

# NEXT STEPS

- Use similar cytokines profiles to create “clusters” of patient diagnoses and compare those to current diagnoses as defined by sleep study results
  - What can we learn from these differences and similarities as to the causes and characteristics of disorders of sleepiness?
- Many cytokines fluctuate on a circadian schedule, and even over weeks-months. Future studies will quantify these fluctuations and see if diagnosis also has an effect.
- Etanercept (TNF alpha blocker) has been used by prior authors (Vgontzas et al., 2004), to treat symptoms of sleepiness in sleep apnea, could this or other cytokine mimics/blockers be used to treatment symptoms of IH, NT2, or EDS?



# REFERENCES

- Kapsimalis, F., Basta, M., Varouchakis, G., Gourgoulialis, K., Vgontzas, A., & Kryger, M. (2008). Cytokines and pathological sleep. *Sleep Medicine*, 9(6), 603–614. <https://doi.org/10.1016/j.sleep.2007.08.019>
- Miller, A. V., & Ranatunga, S. K. M. (2012). Immunotherapies in Rheumatologic Disorders. *Medical Clinics of North America*, 96(3), 475–496. <https://doi.org/10.1016/j.mcna.2012.04.003>
- Soy, M., Keser, G., Atagündüz, P., Tabak, F., Atagündüz, I., & Kayhan, S. (2020). Cytokine storm in COVID-19: Pathogenesis and overview of anti-inflammatory agents used in treatment. *Clinical Rheumatology*, 1–10. <https://doi.org/10.1007/s10067-020-05190-5>
- Trotti, L. M., Staab, B. A., & Rye, D. B. (2013). Test-retest reliability of the multiple sleep latency test in narcolepsy without cataplexy and idiopathic hypersomnia. *Journal of Clinical Sleep Medicine: JCSM: Official Publication of the American Academy of Sleep Medicine*, 9(8), 789–795. <https://doi.org/10.5664/jcsm.2922>
- Vgontzas, A. N., Bixler, E. O., Lin, H.-M., Prolo, P., Trakada, G., & Chrousos, G. P. (2005). IL-6 and its circadian secretion in humans. *Neuroimmunomodulation*, 12(3), 131–140. <https://doi.org/10.1159/000084844>
- Vgontzas, A. N., Zoumakis, E., Lin, H.-M., Bixler, E. O., Trakada, G., & Chrousos, G. P. (2004). Marked Decrease in Sleepiness in Patients with Sleep Apnea by Etanercept, a Tumor Necrosis Factor- $\alpha$  Antagonist. *The Journal of Clinical Endocrinology & Metabolism*, 89(9), 4409–4413. <https://doi.org/10.1210/jc.2003-031929>
- Vgontzas, Alexandros N., Papanicolaou, D. A., Bixler, E. O., Kales, A., Tyson, K., & Chrousos, G. P. (1997). Elevation of Plasma Cytokines in Disorders of Excessive Daytime Sleepiness: Role of Sleep Disturbance and Obesity. *The Journal of Clinical Endocrinology & Metabolism*, 82(5), 1313–1316. <https://doi.org/10.1210/jcem.82.5.3950>

# ACKNOWLEDGEMENTS

- Hypersomnia Foundation
- Dr. Lynn Marie Trotti
- Dr. David Rye
- Danielle Moron
- Victoria Olvera, DNP
- Erin Bremer, NP
- Emory Department of Neurology
- Emory Sleep Center

