Module_1:

Team Members:

Stella Perini and Grace lee

Project Title:

Identifying Relationships Between Head Injury and the Progression of Alzheimer's Disease Symptomology.

Project Goal:

This project seeks understand the coorleation between the effect of Tramatic Brain Injury on Alzheimers patients:

1. Does a history of head injury influence the age at which cognitive symptoms first appear in patients with Alzheimer's disease? and
2. Does experiencing a head injury accelerate the progression of dementia symptoms in individuals with Alzheimer's disease?

Disease Background:

Fill in information about 11 bullets:

- Prevalence & incidence: (7.2 million Americans age 65 and older/ 56 million) x 100 = 11% --> specifically for Americans 65 and older
- Economic burden "In the US in 2022, the estimated healthcare costs associated with AD treatment were $321billion, withcostsprojectedtoexceed$1 trillion by 2050." The progressive nature of Ad and lack of disease-modifying therapies contributes to the economic and societal burden of illness on the US healthcare system. Two-thirds are cost-of-care data from Medicare and Medicaid and the remaining costs include out-of-pocket costs by the patient and their families or other payment sources such as private insurance, and uncompensated care. https://www.ajmc.com/view/the-economic-and-societal-burden-of-alzheimer-disease-managed-care-considerations
- Risk factors (genetic, lifestyle)

- Age is the greatest known risk factor, most people with the disease are 65 and older and the risk of Alzheimers doubles every 5 years after that
- Family history --> those who have a brother, sister, or parent are more likely to develop the disease -Genetics (heredity) --> scientists know genes are involved in Alzheimer
- Head injury --> there is a noticable link between head injury and future risk of dementia
- Certain Medical Conditions --> brain health and heart heath https://www.alz.org/alzheimers-dementia/what-is-alzheimers/causes-and-risk-factors?utm_source=google-grant&utm_medium=paidsearch&utm_campaign=google_grant&gad_source=1&gad_caMJcaAsINEALw_wcB

- Societal determinants --> non medical factors

- Edication Access and Quality --> Lower levels of education are associated with poorer brain health and higher risk of Alzheimers disease and related dementias
- Economic Stability --> lower socioeconomic status is linked to a higher incidence of AD, as poverty can limit access to resources and increase chronic stress
- Healthcare Access and Quality --> poor access to healthcare can delay diagnosis and treatment which can further worsen those outcomes https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.70279

- Symptoms

1. Difficulty completing tasks --> Peolpe facing AD may behin to have trouble completeing daily tasks that were once very familiar to them such as driving to the grocery store and not knowing how to get home
2. New problems with words --> May have trouble even engaging in conversation, may stop in the middle of a conversation and not know how to continue, they may also repeat themselves or use the wrong word to describe something
3. misplacing things --> those with AD may lose things by putting objects in unusual places. They lose the ability to retrace their steps and find the object again. They may lose the ability to identify the object as their own or realize that they need the object.
4. Difficulty with Visual Perception --> The individual may have vision problems causing them to have uneven balance, have trouble reading, or have difficulty judging spatial relationships
5. Memory Loss that Affects Daily life --> This is the most common symtom of AD and is often one of the first signs. Memory loss can occur with recently learned information. The individual may begin forgetting important dates or asking the same questions over and over again. https://www.snydervillage.com/normal-aging-and-alzheimers/?

gad_source=1&gad_campaignid=12405224311&gbraid=0AAAACidTC0_26A7_KhPhQ6y&gclid=Cj0KCQjwrJTGBhCbARIsANFBfgvXSm2Av4bTV_BIxOQfgK_wxThGVhlZ3ed3lgo

- Diagnosis The diagnosis of Alzheimers disease involes a combination of components analyzed about a patient. This includes medical history, physical and neurological exams, lab tests, brain scans, functional assessments and more. It can be difficult to diagnose Alzheimers disease and catch it before the age of at least 65, but 90% of cases are based on recent history of mental and behavioral symtoms, physical exams, imaging, labratory tests, neuropsychological tests and more. https://www.brightfocus.org/alzheimers/diagnosis/?utm_campaign=fy26-googlegrant-adr&gad_source=1&gad_campaignid=20033238172&gbraid=0AAAAAD751rH5RbGV2BS0HqbE5Q0s_S3jocrazvlBQWYzdjSmWkbR9FL30r2uyufohAs5caAgRZEALw_wcB

Mental status testing --> this test focuses on your thinking skills, known as cognitive skills, and memory. These scores on these tests can reveal the degree of cognitive impairment. Neuropsychological tests --> You may see a specialist trained in brain conditions and mental health conditions. Interviews with friends and family --> Doctors and healthcare professionsals may ask your family members or friends questions about you and your behavior Brain imaging tests --> Alzheimers dementia results from the loss of brain cells overtime, this is known as degeneration that may appear in a variety of ways in a brain scan. however, these scans alone aren't enough to make a diagnosis. Brain imaging technologies --> MIR, CT scan, PET scan

Future of diagnosis: researchers are working on new mechanisms to diagnose Alzheimers patients earlier on in their life such as measuring amyloid or tau in the blood. In addition to biomarkers of genes and proteins, including tau. New imaging tests are also being developed, this could also help determine how much of the disease has progressed. More research is necessary. https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers/art-20048075 Standard of care treatments (& reimbursement) https://pmc.ncbi.nlm.nih.gov/articles/PMC9258577/ reviewing of patient's current medications and prescription of antidementia drug. Cholinesterase inhibitors are prescripbed for mild-moderate Alzheimer's disease. Memantine is used for moderate-severe stages. https://www.standardsofcare.org/understanding-care/types/dementia-alzheimers/ in-home caregiver provides personal and support services for daily tasks. Nursing homes or memory care units. Memory care units - specialized facilities or wings in nursing homes with secure environments and trained staff to handle wandering, aggression, and advanced dementia needs.

- Disease progression & prognosis https://www.mayoclinic.org/diseases-conditions/alzheimers-disease/in-depth/alzheimers-stages/art-20048448 There are 5 stages associated with Alzheimer's disease. They are preclinical Alzheimer's disease, mild cognitive impairment, mild dementia, moderate dementia, and severe

dementia. Preclinical Alzheimer's disease are usually identified only in research settings. This stage could last for years, but no one would notice any symptoms during this stage. People with mild cognitive impairment have mild changes in their memory and thinking ability. They have trouble judgining amount of time needed for a task or ability to make good decisions. Alzheimer's disease often is diagnosed in the mild dementia stage. The symptoms affect daily functioning such as memory loss of recent events, trouble with problem-solving, changes in personality, getting lost or misplacing belongings. People grow more confused and forgetful during the moderate dementia stage. They show increasingly poor judgement and experience even greater memory loss. It is more severe than mild dementia. In the last stage of the disease, mental function continues to decline. People generally lose the ability to communicate and require daily assistance with personal care.

- Continuum of care providers https://www.alz.org/help-support/caregiving/care-options Primary care, geriatricians, neurologists, geriatric psychiatrists, neuropsychologists, social workers, home health/in-home aides, adult day centers, long-term care/memory units, palliative/hospice teams, and caregiver support organizations
- Biological mechanisms (anatomy, organ physiology, cell & molecular physiology) https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/what-happens-brain-alzheimers-disease The disease first damages the hippocampus and entorhinal cortex, which are essential for memory and learning. As Alzheimer’s progresses, it spreads to other cortical regions, leading to loss of language, reasoning, and behavior control. Neurons lose their ability to communicate, metabolize, and repair themselves. Eventually, these neurons die, causing brain shrinkage (atrophy), especially in memory-related areas.
- Clinical Trials/next-gen therapies https://www.leqembi.com/en/how-does-leqembi-work?cid=PPC-accountype:MICROSOFT-campaign:Treatment%253BS%253BPH%253BBR%253BNER%253BCO%253BTRE-searchterm:early+alzheimers+disease+therapy-adgroup:UB+Treatment_Therapy_Phrase-keywordid:p81132716513&gclsrc=3p.ds&&us_privacy=$%7Bus_privacy%7D Disease modifying therapies include leqembi, which is a monoclonal antibody that binds to soluble amyloid-B protofibrils, helping the immune system clear them before they form large plaques. It has been approved for early Alzheimer's around July 2023. There are also other tau-targeted therapies such as antisense oligonucleotides, which lowers tau production by reducing MAPT mRNA.

Data-Set:

For this project we’re using two datasets from the Integrated multimodal cell atlas of Alzheimer’s disease (Mathys et al., 2024, Nature Neuroscience, https://doi.org/10.1038/s41593-024-01774-5). The first, UpdatedLuminex.csv, includes

measurements of Alzheimer's-related proteins (Aβ40, Aβ42, total tau, and phosphorylated tau) taken from brain tissue using Luminex multiplex immunoassays, reported in picograms per microgram of protein. The second, UpdatedMetaData.csv, provides background information on the same 84 donors, such as age, sex, APOE genotype, diagnosis, and standardized pathology scores (Braak, Thal, CERAD), as well as cognitive test results and post-mortem tissue quality measures. Clinical and cognitive data were collected during life, while genetic and pathology measures came from DNA testing and post-mortem analysis. Together, these files make it possible to study how protein biomarkers relate to both symptoms and brain changes in Alzheimer's disease.

The data set given represents various Alzheimers patients and their results to numerous tests. This includes many factors that contribute to the progression of their symtoms, information about their behavior, physical attributes and more. The data set includes, sex, race, age, education, APOE genotype, age of dementia diagnosis, neuroimaging status, head injury, if they have done certain behavioral or physical tests such as Brrak score, CERAD score, CAA score, etc. It also includes other diseases this patient is diagnosed with. All of this informaiton is important when comparing patients, and analyzing which symtoms have caused the most harm, and patterns within patients.

Some techniques that were used include

Data Analysis:

In [ ]:
```python
import csv
import warnings
import matplotlib.pyplot as plt

class Patient:

    all_patients = []

    death_age = []

    education_lvl = {}

    def __init__(self, DonorID, ABeta40: float , ABeta42: float, tTau: float

        self.DonorID = DonorID
        self.ABeta40 = ABeta40
        self.ABeta42 = ABeta42
        self.tTau = tTau
        self.pTau = pTau
        self.sex = None
        self.death_age = None
        self.ed_lvl = None
        self.cog_stat = None
        self.age_symp_on = None
        self.age_diag = None
        self.head_inj = None
```

```
        self.thal_score = None
        self.MMSE = MMSE
        Patient.all_patients.append(self)

    def __repr__(self):
        return f"{self.DonorID} | sex: {self.sex} | ABeta40 {self.ABeta40} |

    def get_id(self):
        return self.DonorID

    def get_ABeta42(self):
        return self.ABeta42

    def get_thal(self):
        return self.thal_score

    def get_death_age(self):
        return self.death_age


    @classmethod
    def combine_data(cls, filename: str):
            with open(filename, encoding="utf8") as f:
                reader = csv.DictReader(f)
                rows_of_patients = list(reader)
                #for line in csv create object
                for row in range(len(rows_of_patients)):
                    if Patient.all_patients[row].DonorID == rows_of_patients
                        if rows_of_patients[row]["Sex"] != "":
                            Patient.all_patients[row].sex = rows_of_patients

                        if rows_of_patients[row]["Age at Death"] != "":
                            Patient.all_patients[row].death_age = int(rows_o

                        if rows_of_patients[row]["Highest level of educatior
                            Patient.all_patients[row].ed_lvl = rows_of_patie

                        if rows_of_patients[row]["Cognitive Status"] != "":
                            Patient.all_patients[row].cog_stat = rows_of_pat

                        if rows_of_patients[row]["Age of onset cognitive sym
                            Patient.all_patients[row].age_symp_on = int(rows

                        if rows_of_patients[row]["Age of Dementia diagnosis"
                            Patient.all_patients[row].age_diag = int(rows_of

                        if rows_of_patients[row]["Known head injury"] != "":
                            Patient.all_patients[row].head_inj = rows_of_pat

                        if rows_of_patients[row]["Thal"] != "":
                            Patient.all_patients[row].thal_score = int(rows_
                        if rows_of_patients[row]["Last MMSE Score"] != "":
                            try:
                                Patient.all_patients[row].MMSE = float(rows_
                            except ValueError:
                                Patient.all_patients[row].MMSE = None
```

```
                else:
                    warnings.warn("IDs do not match.")

    @classmethod
    def sort_ed(cls):
        for patient in Patient.all_patients:
            Patient.education_lvl.update({patient.ed_lvl: []})
        for patient in Patient.all_patients:
            Patient.education_lvl[patient.ed_lvl].append(patient)

    @classmethod
    def subsort_thal(cls):
        for key in Patient.education_lvl:
            values = Patient.education_lvl.get(key)
            values.sort(key = Patient.get_thal)
            Patient.education_lvl.update({key: values})

    @classmethod
    def instantiate_from_csv(cls, filename: str, other_file: str):
    #open csv and create list of all rows
        with open(filename, encoding="utf8") as f:
            reader = csv.DictReader(f)
            rows_of_patients = list(reader)
            #for line in csv create object
            for row in rows_of_patients:
                Patient(
                    DonorID = row['Donor ID'],
                    ABeta40 = float(row['ABeta40 pg/ug']),
                    ABeta42 = float(row['ABeta42 pg/ug']),
                    tTau = float(row['tTAU pg/ug']),
                    pTau = float(row['pTAU pg/ug']),

                )
            Patient.all_patients.sort(key = Patient.get_id)
            Patient.combine_data(other_file)

    @classmethod
    def filter(cls, patients, **criteria):
        """
        Return all patients from the list that match the given keyword argum
        Example: Patient.filter(Patient.all_patients, sex="Female", cog_stat
        """
        results = patients
        for attr, value in criteria.items():
            results = [p for p in results if getattr(p, attr) == value]
        return results
```

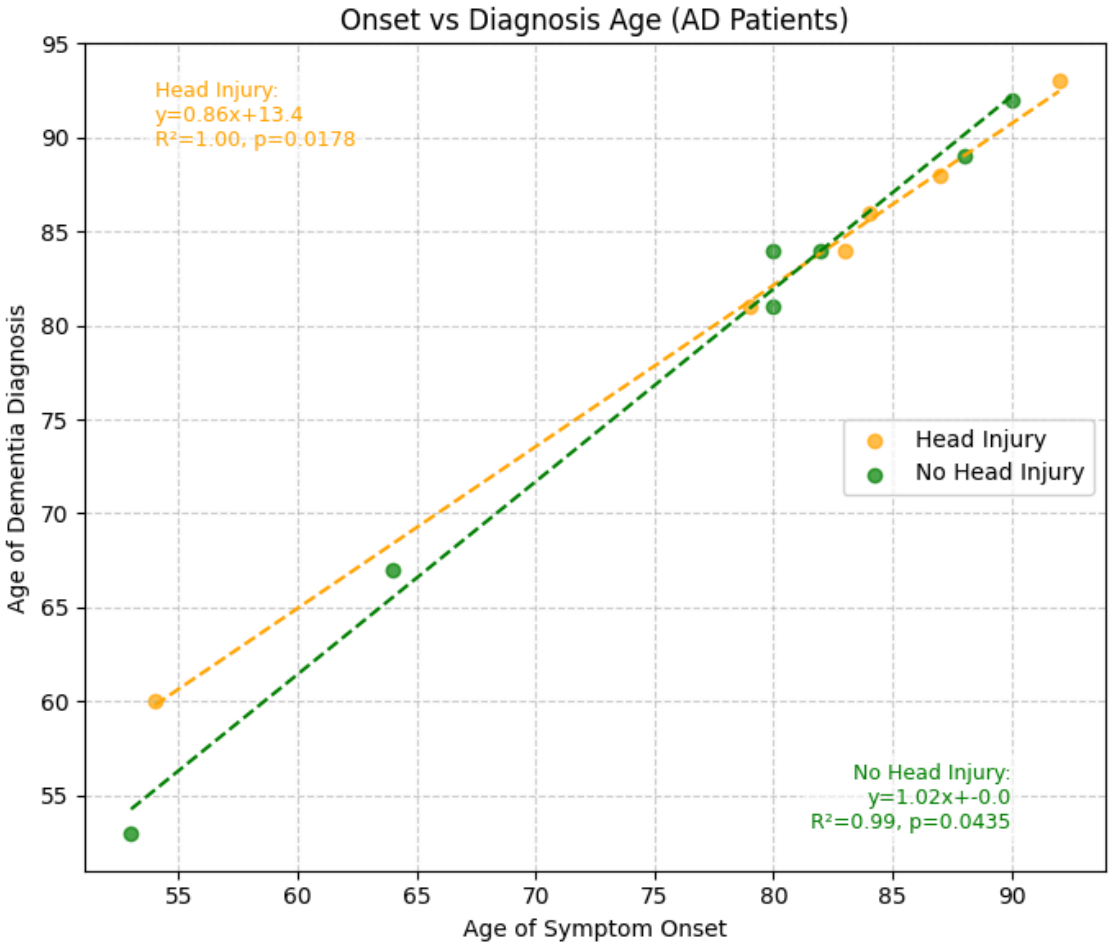
In [ ]:
```
import matplotlib.pyplot as plt
import statistics
from scipy import stats
import numpy as np
from patient import Patient
from sklearn.linear_model import LinearRegression
from sklearn.metrics import r2_score
```

```
# --- Load Data ---
Patient.all_patients.clear()
Patient.instantiate_from_csv("UpdatedLuminex.csv", "UpdatedMetaData.csv")

# --- Alzheimer's patients only ---
alz_patients = [p for p in Patient.all_patients if p.cog_stat in ["Dementia"

# Groups
alz_with_injury = [p for p in alz_patients if p.head_inj == "Yes" and p.age_
alz_no_injury   = [p for p in alz_patients if p.head_inj == "No" and p.age_s

# Data
x_yes = [p.age_symp_on for p in alz_with_injury]
y_yes = [p.age_diag for p in alz_with_injury]
x_no  = [p.age_symp_on for p in alz_no_injury]
y_no  = [p.age_diag for p in alz_no_injury]

# --- T-tests ---
# Onset
onset_yes = [p.age_symp_on for p in alz_with_injury]
onset_no  = [p.age_symp_on for p in alz_no_injury]
t_onset, p_onset = stats.ttest_ind(onset_yes, onset_no, equal_var=False)

# Progression
prog_yes = [p.age_diag - p.age_symp_on for p in alz_with_injury]
prog_no  = [p.age_diag - p.age_symp_on for p in alz_no_injury]
t_prog, p_prog = stats.ttest_ind(prog_yes, prog_no, equal_var=False)
```

In [ ]:

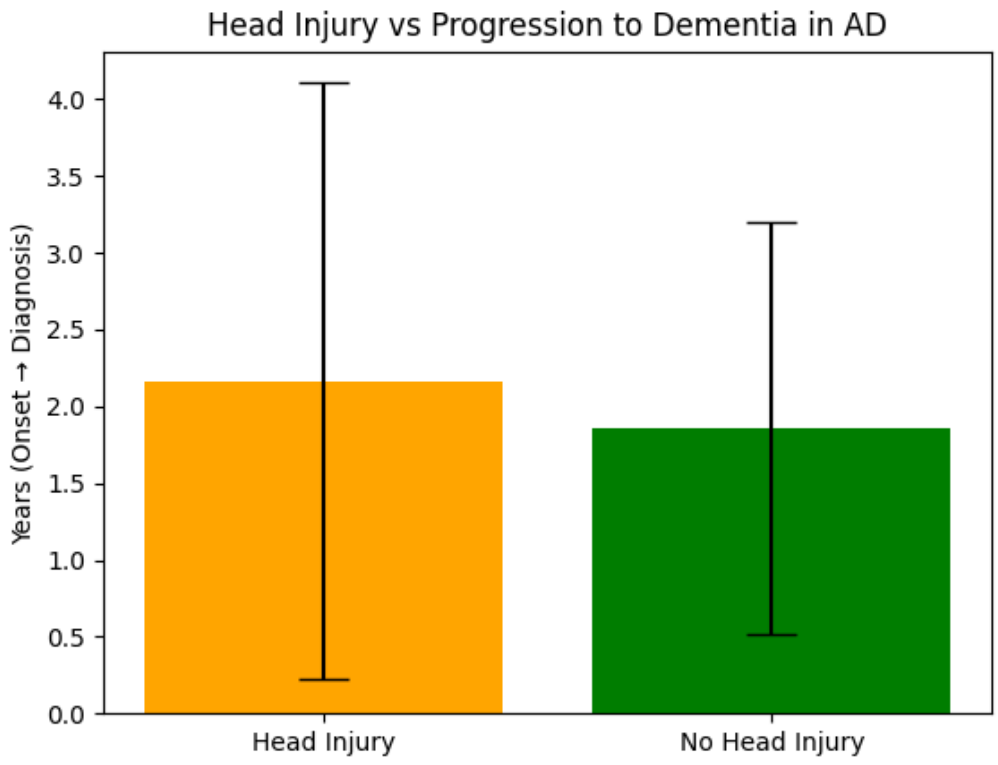
```
# --- Scatter Plot with Regression ---
plt.figure(figsize=(7,6))
plt.scatter(x_yes, y_yes, color="orange", alpha=0.7, label="Head Injury")
plt.scatter(x_no, y_no, color="green", alpha=0.7, label="No Head Injury")

def add_regression(x, y, color, anchor, label):
    if len(x) > 2:
        X = np.array(x).reshape(-1,1)
        model = LinearRegression().fit(X, y)
        slope = model.coef_[0]
        intercept = model.intercept_
        r2 = r2_score(y, model.predict(X))
        _, _, r_val, _, p_val = stats.linregress(x, y)

        # Regression line
        x_line = np.linspace(min(x), max(x), 100).reshape(-1,1)
        plt.plot(x_line, model.predict(x_line), color=color, linestyle="--")

        # Place annotation
        if anchor == "topleft":
            xpos, ypos, va, ha = min(x), max(y), "top", "left"
        elif anchor == "bottomright":
            xpos, ypos, va, ha = max(x), min(y), "bottom", "right"
        else:
            xpos, ypos, va, ha = min(x), max(y), "top", "left"

        plt.text(xpos, ypos,
                 f"{label}\ny={slope:.2f}x+{intercept:.1f}\nR²={r2:.2f}, p={
```

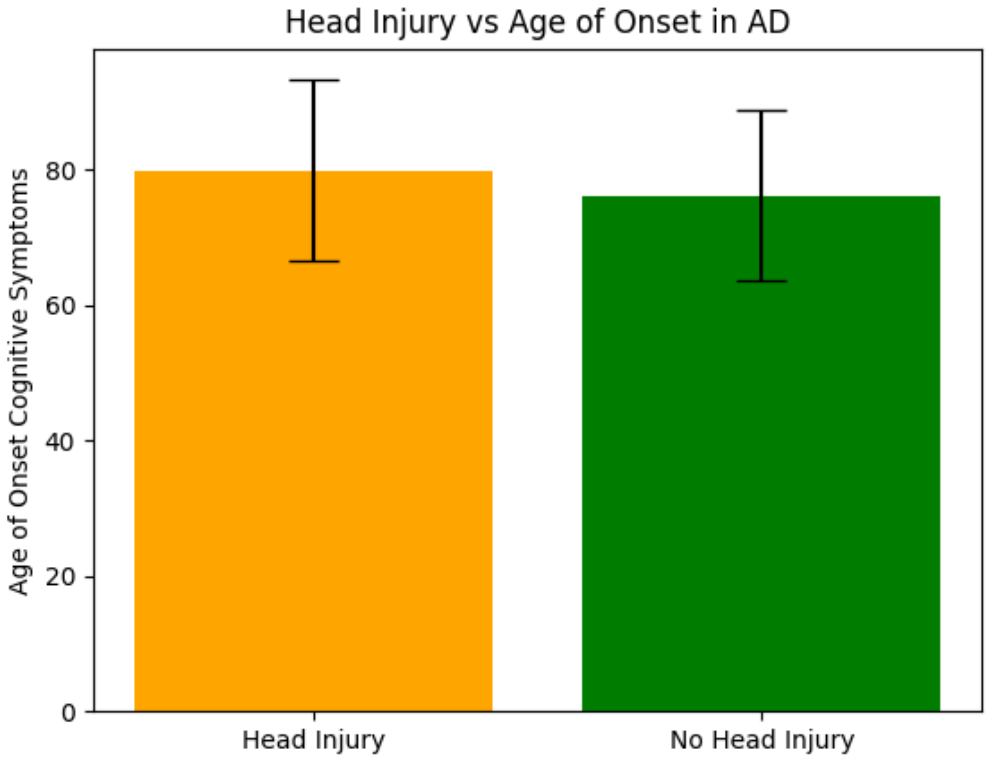
```
                color=color, fontsize=9,
                verticalalignment=va, horizontalalignment=ha,
                bbox=dict(facecolor="white", alpha=0.6, edgecolor="none"))

# Add regressions
add_regression(x_yes, y_yes, "orange", "topleft", "Head Injury")
add_regression(x_no, y_no, "green", "bottomright", "No Head Injury")


plt.xlabel("Age of Symptom Onset")
plt.ylabel("Age of Dementia Diagnosis")
plt.title("Onset vs Diagnosis Age (AD Patients)")
plt.legend()
plt.grid(True, linestyle="--", alpha=0.6)
plt.tight_layout()
plt.show()
```



In [ ]:
```
# Helper plotting function
def plot_with_ttest(data1, data2, labels, title, ylabel):
    means = [statistics.mean(data1), statistics.mean(data2)]
    stdevs = [statistics.stdev(data1), statistics.stdev(data2)]
    ns = [len(data1), len(data2)]

    # t-test
    t, p = stats.ttest_ind(data1, data2, equal_var=False)
```

```
    # Bar graph
    plt.figure(figsize=(6,5))
    bars = plt.bar(labels, means, yerr=stdevs, capsize=10, color=["orange","

    plt.title(title)
    plt.ylabel(ylabel)
    plt.tight_layout()
    plt.show()

   # Print results
    print(f"{title}")
    print(f" {labels[0]} (n={ns[0]}): mean={means[0]:.1f}, stdev={stdevs[0]:
    print(f" {labels[1]} (n={ns[1]}): mean={means[1]:.1f}, stdev={stdevs[1]:
    print(f" t={t:.2f}, p={p:.4f}\n")

# --- Plot 1: Age of Onset ---
plot_with_ttest(onset_yes, onset_no,
                labels=["Head Injury", "No Head Injury"],
                title="Head Injury vs Age of Onset (AD Patients)",
                ylabel="Age at Onset (years)")

# --- Plot 2: Progression Duration ---
plot_with_ttest(prog_yes, prog_no,
                labels=["Head Injury", "No Head Injury"],
                title="Head Injury vs Progression Duration (AD Patients)",
                ylabel="Years from Onset → Diagnosis")
```





Verify and Validate your analysis:

Regression Analysis: Strong linear relationships in both groups ($R^2 \approx 1$, $p < 0.05$). Head injury: $R^2 = 0.99$ No head injury: $R^2 = 1.00$ ≣ Strong relationship between onset and dementia (as predicted)

T-Test Analysis Dementia: $t = 0.33$, $p = 0.75$ → no significant difference in age of onset. Early Onset Cognitive symptoms: $t = 0.53$, $p = 0.608$ → no significant difference in progression speed.

Interpretation:

- Presence of head injury does not significantly change onset age or progression timeline.
- Regression slope trend hints at quicker progression in head injury group, but t-tests show this is not statistically significant.

Verification (Do the results make sense?):

- Regression suggested a faster trajectory with head injury, but t- tests showed no significant differences in onset or progression. This conflicts with expectations.

Validation (Compare to external sources):

- Prior studies (e.g., PubMed-indexed TBI research) consistently report earlier onset and faster progression of Alzheimer's in patients with head injury and our findings do not reflect this, suggesting possible sample limitations or statistics

Conclusions and Ethical Implications:

Conclusions:

- Results do not align with established research. While data trends hinted at faster progression, lack of statistical significance weakens support.

Ethical Implications:

- Patients: earlier monitoring & intervention. --> yearly check ins to ensure AD symptomology is caught as early as possible.
- Clinicians: screen for head injury history. --> make this very important and essential in all check ups.
- Public health: emphasize injury prevention insports, military,and workplace. --> potentially changing rules and regulations within sports games such as football to prevent these trauamtic injuries

Limitations and Future Work:

Next Steps:

- Expand dataset for stronger analysis.
- Examine impact of severity/frequency of head injury.
- Explore biological mechanisms (e.g.,tau,inflammation).
- Investigate interventions to reduce risk or slow progression. --> this may include new medical technologies that can prevent head injury or simply advandly engineered helmets for football players/contact port athletes

NOTES FOR MY TA CLass 1:

Thought proccess for the 6 questions:

1. When comparing the data set based on differences in race/ethnicity, are there certain demographics that are more prone to Alzheimers disease? and at what age? How do their CERAD scores differ?
2. Does having a past record of playing contact sports, especially that can cause head injury such as football and soccer, increase the progression of the symptoms of Alzheimers disease? Does this progression show a difference in their neuroimaging?
3. Does having mental disorders such as anxiety and depression throughout the patients life previous to the diagnosis of Alzheimers corrolate to the progression of

Alzheimers disease symtoms at a certain age? How do their Braak scores compare?
4. Does having certain genetic factors such as the APOE Genotype affect the pH of the brain, therefore leading to a more progressive affect of the disease?
5. To what extent does gender and hormonal level affect the build up of tau in the brain? No questions for my TA! Overall--> Decided to go with question #2 because we are interested in the corrolation between alzheimers and record of head injury. Through research, we will figure out what tests are used on Alzheimers patients to analyze the effect of head injury in their past, and if this lead to progressive Alzheimers/more severe.

Our groups roles: Grace --> Will focus on the code, understanding how to manipulate it and creating different graphs Stella --> Understanding the data we are given and then doing other research on it. Understanding the graphs created and writing the notebooks on our progress. She will note trends in the graphs and in the data.

Class #2/#3: During these classes we are working on manipulating the code in order to create our own scatter plot that will give us information on specific patients that will help lead us to answering our over-arching question. We had trouble with the code and ultimately created a couple different graphs. Since our question is based off of head injury, which only has two possible varibles: has head injury and doesn't have record of head injury, running a scatter plot is difficult. Because of this, we created two bar graphs.

1. The first one was just comparing TAU build up vs. Sex (male vs. female), we created this to test our code and incorperate the effect of gender on our data considering men and females suffer through different amounts of head injury on record.
2. The second bar graph we created compared record of head injury vs. MMSE score. Through research we found that the MMSE score is a good test to compare to record of head injury, considering a bad MMSE score indicates "An MMSE (Mini-Mental State Examination) score is a number between 0 and 30 indicating cognitive function, with higher scores generally meaning better cognition. A score of 25 or higher is considered normal cognition, while scores between 21-24 often indicate mild impairment, 10-20 suggest moderate impairment, and scores under 10 signal severe impairment" (https://muhc.ca/sites/default/files/micro/m-PT-OT/OT/Mini-Mental-State-Exam-(MMSE).pdf) This graph showed abnormal results
3. We then decided that we should make a scatter plot as well. On this graph, we compared MMSE score to age of diagnosed dementia. We created this graph because it will help us understand if this MMSE score is affected by age and progression of dementia. This will help us answer our question because we can then analyze the corrolation between head injury record and age of diagnosed dementia, assuming those with record of head injury were diagnosed with dementia earlier than those without head injiury.

(The bar graphs and scatter plot are under data analysis sectoin)

Class #4: Focused on age of dementia diagnosis and early onset cognitive impairment compared to head injury and no head injury During this class, Grace and I continued to create more graphs and analyze different data sets in order to find the best comparison to use in our presentation. She continued to work on the code and formualitng T-test tests while I started creating the presentaiton and putting our conclusions into words. We were confused about a lot of our results because most of the results went against our hypothesis. This included when we compared head injury to age of Dementia diagnosis and to early onset cognitive impairment because they both relate to head injury and is constant in our research.

- found T-two tailed one way test was statistically insignificant t = 0.33 for early onset cognitive damange and t = 0.53 for dementia
- linear regression line comparing dementia vs. early onset cognitive damage to be R^2 = 0.99 which is almost perfect, and very rare in data analysis. This is as expected through our research because those with dementia are most likely to of had early onset cognitive damage.
- Overall, we found no statsitical significance between head injury and Alzheimers Disease which was very shocking.

Class #5:

- Presenting our project!

In [ ]:
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No further notes for my TA!
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In [ ]:
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Citations:

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Eisai Inc. (n.d.). How does LEQEMBI® (lecanemab-irmb) work? https://www.leqe