An Analysis of the Effect of Common Inflammatory Diseases on Fluid Intelligence and Numeric Memory using UK Biobank

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Abstract

Inflammation is an essential part of human homeostasis, but disruption to normally inflammatory processes can cause inflammation to become chronic. Chronic inflammation is known to be involved in the progression of several diseases in the body and brain, including cancer, non-alcoholic fatty liver disease, Alzheimer's disease, and Parkinson's disease. This study investigates the relationship between chronic inflammatory disease and cognitive outcomes, or more specifically, the effect that having one of five inflammatory conditions (HIV, asthma, diabetes mellitus, obesity, and rheumatoid arthritis) has on cognition and risk of neurodegeneration. These conditions were selected because they are relatively common and known to be chronically inflammatory. Using the epidemiological data from UK Biobank and generalized linear regression models we analyzed the associations between these five inflammatory conditions and performance on fluid intelligence and numeric memory tasks, as well as associations with odds ratios for developing neurodegenerative disease. We found significant associations between the presence of some inflammatory diseases and reduced performance on fluid intelligence and numeric memory tasks, and significant effects of the amount of time spent inflamed. To further understand this relationship we examined the effect that treatment had on the cognitive influences of HIV. We found that individuals with HIV who were receiving antiretroviral therapies were associated with significantly higher scores on fluid intelligence tasks than individuals with HIV who were not receiving antiretroviral treatment. We also found several significant associations between asthma, diabetes, obesity, and rheumatoid arthritis and increased odds ratios for developing neurodegenerative disease. Given these findings, more research is needed to see if reducing chronic low-level inflammation could potentially be incorporated into regimens to reduce the risk of cognitive decline and neurodegeneration.

Introduction

Inflammation is an essential and natural part of everyday functioning. Under normal circumstances, inflammation is the beneficial and normal adaptive response mounted by an individual's body to injury, illness, or other homeostatic insults. It typically resolves once foreign bodies are removed, invaders are handled, and damaged tissues are healed (Medzhitov, 2008). However, in cases where the injury is unable to be resolved, pathogens are unable to be removed, or damage is done to our bodies' innate immune response or mechanisms of anti-inflammatory mediation, inflammation can become chronic (Nathan & Ding, 2010; Pahwa et al., 2022). Chronic inflammation, instead of being beneficial, actually begins to cause harm to the body causing pain, fatigue, insomnia, and even increasing your risk of cancer and infection (Pahwa et al., 2022).

Chronic inflammation is implicated in the etiology and progression of numerous disease states including, chronic kidney disease, non-alcoholic fatty liver disease, cancer, and cardiovascular disease (Furman et al., 2019; Multhoff et al., 2012; Pahwa et al., 2022)**.** Chronic inflammation is also involved in and associated with an increased risk of developing neurodegenerative diseases like Alzheimer's disease (Bettcher & Kramer, 2014; Darweesh et al., 2018; Zotova et al., 2010) and Parkinson’s disease (Przedborski, 2010).

Both chronic inflammatory and neurodegenerative disease rates are rising (Brookmeyer et al., 2018; Lilienfeld & Perl, 1993; Pahwa et al., 2022). As these diseases increase in prevalence, so too increases their impacts. Neurodegeneration is associated with significant years of life lost (Naghavi et al., 2017), reduced quality of life (Chekani et al., 2016; Stites et al., 2018; Wood et al., 2016), and significant financial burdens for sufferers and their families ("2021 Alzheimer's Disease Facts and Figures," 2021; Ahmad et al., 2018; Findley, 2007; Moore et al., 2019; Schenkman et al., 2001; Svendsen et al., 2018).

This thesis aims to begin to understand the complex relationship between inflammation, cognition, and neurodegeneration by examining the correlations present between five common inflammatory diseases (HIV, asthma, diabetes mellitus, obesity, and rheumatoid arthritis) and performance on fluid intelligence and numeric memory tests and odds ratios of developing neurodegenerative diseases.

Methods

1. Subjects

Subjects, demographic information, cognitive measures, diagnoses, and medication information were acquired from UK Biobank under accession number 27412. After excluding participants that withdrew their consent, we were left with 502,414 participants. The mean age of this sample was approximately 70.5 years old, with a standard deviation of 8.1. The sample is made up of 273,328 female participants and 229,085 male participants. We identified several subsets of individuals outlined in *Table 1*, and precise sample sizes and distributions are given for each figure. Demographic distributions for each disease subset have been visualized in *Figure 1,* and diagnosis overlap can be found in *Figure 2.*

2. Cognitive Measures

The two cognitive tests used are a Fluid Intelligence battery and a Numeric Memory Test. These tests were selected as indicators of deficits in fluid intelligence or working memory capacities and short-term memory capacity, both of which are shown to be impaired in cognitive decline (Deary et al., 2009). Each test was administered in person or online, using a touchscreen and accompanying Tactus software at an assessment center (*UK Biobank: Assessment Centre Environment*, 2011) or on an individual's home computer. If they are taking these tests at an assessment center, participants are advised that they may ask for help at any time, and accommodations such as the use of a mouse and keyboard could be provided upon request (*UK Biobank: Touch Screen Questionnaire*, 2011).

The Fluid Intelligence test consisted of 13 questions if taken in person or 14 questions online. In each case, participants had the opportunity to opt out of participation before the test began. If they decided that they would like to stop after starting or that they would not like to answer any particular question, they were able to select 'prefer not to answer' and progress to the next question. Before they begin, the participant is instructed that they have two minutes to answer as many questions as possible, and that time starts as soon as they start the first question. Participants cannot input any new responses once two minutes have elapsed from the start of their first question. The resulting fluid intelligence score is the total number of correct responses given during the two minutes for a maximum score of thirteen for the in-person assessment and fourteen for the online assessment (*UK Biobank: Touch-Screen Fluid Intelligence Test*, 2012). For a complete list of prompts and questions related to both the fluid intelligence task and the numeric memory task, see *Appendix A*.

Data for fluid intelligence scores were retrieved from UK Biobank data fields number 20016 and 20191. In cases where tests were taken more than once across a single modality (e.g. in person or online), the average scores were taken and used for

analysis. Decimal values were not rounded or truncated. The distributions of the data before normalization can be seen in *Figure 3*. Once the data was reduced down to a single score per participant per modality, those scores were normalized using a rank-based inverse normal transformation. After data cleaning, we were left with 123,597 participants with fluid intelligence scores for the online test and 205,311 participants with fluid intelligence scores for the in-person test.

At the beginning of the numeric memory task, participants are shown a two-digit number for 2000 ms + 500 ms for each digit, and then the number is removed. After a period of 3000 ms, the participant is asked to use an onscreen keypad to input the number and press 'Next' to confirm their submission. If their submission is correct, they are shown another number a digit longer up to a maximum length of twelve digits, and the procedure begins again. The test continues until the participant chooses to abandon the test or incorrectly reports a two-digit number five times in succession or a three or more digit number two times in succession (*UK Biobank: Touch-Screen Numeric Memory Test*, 2012). An example of the prompting given at the beginning of the task can be found in *Appendix A*.

Data for the maximum number of digits remembered correctly in a numeric memory task was retrieved from UK Biobank data fields 4282 and 20240. Values indicating the decision to abandon the task were removed. In cases where tests were taken more than once across a single modality, their largest score was taken and used for analysis. The distributions of the data before normalization can be seen in *Figure 4*. Once the data was reduced down to a single score per participant per modality, those scores were normalized using a rank-based inverse normal transformation. After data cleaning, we were left with 111,048 participants with values for a numeric memory task for the online test and 81,100 participants with values for a numeric memory task for the in-person test.

3. Confounds

Several demographic data points were included to correct potential confounds in the analysis. Demographic data on age and sex were retrieved from UK Biobank data fields 34 and 31. Data field 34 codes for a year of birth were converted to age by subtracting the year of birth value from 2022. No changes were made to data field 31. Age is a potential confound because it is strongly associated with cognitive decline (Deary et al., 2009; Murman, 2015) and the risk of developing a neurodegenerative disease (Hou et al., 2019). Sex is also a confound because research has shown sexual dimorphisms in rates of cognitive decline (Lee et al., 2022) and risks for neurodegeneration (Lopez-Lee et al., 2022).

Demographic data about access to income, healthcare, and education were assessed using indices of deprivation. Deprivation measures the general lack of opportunities or resources in an area. It can be evaluated across many domains, including income, health, and education (*English Indices of Deprivation 2010: Guidance Document*, 2011). These analyses do not necessarily indicate an individual's access. Still, by including them in our study, we should be able to account for differences in access to certain services and experiences that could impact results. Income and education deprivation are being used to account for the environmental factors affecting a person's performance on cognitive assessments (Rindermann et al., 2010). The use of the health deprivation should allow us to correct for access to health care in an area as access to healthcare has been shown to impact healthy survival and longevity (Gu et al., 2009). Access to health care is corrected as it could affect health outcomes for any inflammatory diseases or neurodegenerative diseases we examined in this study.

While UK Biobank has separate deprivation measures for England, Scotland, and Wales, only the indices from England were used because differences in health systems, sampling methods, and calculation methods mean that even if the indices were

supposedly measuring the same form of deprivation, they were essentially incomparable. Moreover, examining a single group should prevent variations that result from differences in the structure of public services (Andrews & Martin, 2010) that could impact results. Educational, health, and income deprivation data were retrieved from UK Biobank data fields 26414, 26413, and 2641. No data cleaning or processing was performed.

4. Diseases

We examined five common inflammatory diseases: human immunodeficiency virus (HIV), asthma, diabetes mellitus, obesity, and rheumatoid arthritis. HIV was selected because it causes chronic inflammation of the central nervous system. The establishment of a viral reservoir in the brain and the persistent release of Tat and gp120 viral proteins from HIV-infected monocytes and lymphocytes in the brain causes chronic inflammation of the central nervous system (Ash et al., 2021; Spudich, 2016; Williams et al., 2014). However, HIV is not entirely ideal because of its small and skewed representation in the UK Biobank sample and because HIV is associated with an increased risk of infection and intravenous drug use (Deeks et al., 2015). HIV has been shown to cause significant neurological and cognitive complications even when peripheral immune symptoms are treated using antiretroviral therapies; these effects are known aspects of HIV neuropathogenesis and are often referred to as HIV-Associated Neurocognitive Disorders or NeuroAIDS (Brew et al., 2008; Clifford & Ances, 2013).

Asthma is a heterogeneous inflammatory disease of the airway that typically involves a disproportionate allergic reaction to typically harmless airborne allergens. T-helper type Lymphocytes primarily mediate this reaction but, due to its heterogeneity, several other inflammatory and reactive pathways may also contribute to reactions (Murdoch & Lloyd, 2010). The varied and environment-dependent presentation of asthma makes it an imprecise expression of inflammation (Holgate et al., 2015). The prognosis of asthma also involves changes in the concentration of brain-derived neurotrophic factor (BDNF), which could cause confounding autocrine or paracrine impacts or separately influence changes in cognition or risk of neurodegenerative issues (Freeman et al., 2017). Existing research has found severe asthma is associated with changes in biomarker concentrations and neuroanatomy characteristic of neurodegeneration and proposed neuroinflammatory causes (Rosenkranz et al., 2022).

The inflammation involved in diabetes mellitus consists of releasing inflammatory cytokines, including TNF-α and numerous f interleukins from adipose tissue and the pancreas (Lontchi-Yimagou et al., 2013). An existing body of research has implicated certain forms of diabetes in the progression of neurodegenerative disease (Biessels & Kappelle, 2005; Farhadi et al., 2019; Toth, 2014; Verdile et al., 2015). The use of insulin as a treatment is a potential confound because it is anti-inflammatory (Sun et al., 2014), and current research exists implicating insulin in the progression of Alzheimer's Disease (Biessels & Kappelle, 2005; Ferreira et al., 2018; Gabbouj et al., 2019). Diabetes mellitus is also highly comorbid with obesity (Boles et al., 2017), and obesity has been identified as a risk factor for obesity (Wild & Byrne, 2006). This interrelationship between diabetes mellitus and obesity is borne out in our analysis. There is a 9587-person overlap of individuals having both diseases; this overlap represents approximately 23% of the total population of diabetics and approximately 29% of obese individuals. This overlap can be seen in greater detail in Figure 2.

Because of their interrelationship, the inflammatory profile of obesity is similar to that of diabetes mellitus. Obesity is defined by high adiposity and is associated with many health risks (Bray, 2004). The inflammation related to obesity comes from inflammatory chemical mediators released from adipose tissues called adipokines (Ellulu et al., 2017; Mancuso, 2016; Ouchi et al.,

2011). Obesity has also been linked to the development of insulin resistance (Kim & Reaven, 2010) which could lead to diabetes mellitus and explain the substantial overlap between the diseases.

Rheumatoid arthritis is an autoimmune disease that causes chronic inflammation of the synovial joints (McInnes & Schett, 2011; Nathan & Ding, 2010). The pathogenesis of rheumatoid arthritis involves several proinflammatory cytokines, including TNF-α and various interleukins, all of which contribute to the inflammatory response of the disease (Isomäki & Punnonen, 1997; McInnes & Schett, 2011). Rheumatoid arthritis shows significant differences in presentation related to age and sex (Grassi et al., 1998; Kuiper et al., 2001) that are accounted for during our analysis. Furthermore, individuals with rheumatoid arthritis of the hand have some difficulty with fine motor movements (Kauranen et al., 2000). They may show worsened cognitive scores due to difficulty with the fine motor movements required to complete the touch screen assessments rather than actual deficits in any cognitive processes.

The neurodegeneration categories used in this analysis cover the totality of neurodegenerative diseases. They are grouped based on the type of disease into the following categories: 'Alzheimer's Disease and other dementias', 'Parkinson's Disease,' 'Demyelinating Diseases,' and 'Other Neurodegenerative Diseases.' Specifics of the ICD-10 codes associated with each diagnosis can be found in *Table 2*.

Disease diagnosis was identified using the ICD-10 diagnosis codes in UK Biobank data field 41270 and diagnosis date information from UK biobank data field 41280. An algorithm was used to identify all ICD-10 codes associated with a given diagnosis and find the diagnosis dates. Specifics of the ICD-10 codes related to each diagnosis can be found in *Table 2*.

5. Medications

For some of our analyses, an examination of the effect of medication was done. Data about participant medication and treatment information were retrieved from UK Biobank data field number 20003 and were decoded using UK Biobank data-coding format 4. Information about current medications being used for the treatment of HIV was retrieved from HIVinfo.NIH.gov (FDA-Approved HIV Medicines | NIH, 2022), and a complete list of the search terms used and relevant UK biobank codes can be found in Table 3. An algorithm was used to identify any individuals using any of the identified HIV medications. Any individuals found to be taking any HIV medications were marked with the boolean value "true."

6. Derived Variables

Our analysis included several derived variables related to the length of time an individual has been suffering from inflammation. The first variable measures the amount of time that has passed since the individual was first diagnosed with any of the relevant inflammatory diseases. This variable was made by subtracting the earliest date of any diagnosis across all participants from 2022. The second variable measures the total number of years that an individual has been diagnosed with a relevant inflammatory disease. This variable was calculated by getting the total length of time that a person has had any of the five relevant inflammatory diseases. In cases where there are multiple diagnoses within a single disease category, only the oldest diagnosis is counted. The distributions of these variables can be found in *Figure 5*.

7. Analysis

Generalized linear regression models (GLMs) were fit to predict specific cognitive or neurodegenerative outcomes based on the diagnosis of inflammatory diseases or the amount of time they have been diagnosed with an inflammatory disease.

Non-Boolean independent variables were all normalized using rank-based inverse normal transformation. Each model was corrected for the five potential cofounds (age, sex, income, education, and health). In cases where inflammatory diseases were used, each of the other inflammatory diseases was included as a potential confound to correct for potential overlap between diagnoses. The models used were either gaussian in the cases where the dependent variable was any of the cognitive measures or binomial in cases where the predicted outcomes were diagnosed.

Separate models were used for each test modality and for each neurodegenerative disease because only one dependent variable at a time can be accounted for using a GLM. Multiple models were also used to analyze the impact of the amount of time with an inflammatory diagnosis because those two variables covary so strongly as to remove power from one another. Specifics are listed below.

Results

1. *The Effects of Common Inflammatory Diseases on Fluid Intelligence and Numeric Memory*

Generalized Linear Models (GLMs) were used to predict the effects of inflammatory disease on measures of fluid intelligence and numeric memory. A GLM was generated for each modality for each test for four GLMs. Every model corrected for factors that influence cognition or performance on cognitive assessments (age, sex, education, health, and income). Models included all five disease categories of interest (rheumatoid arthritis, obesity, diabetes mellitus, asthma, and HIV) to account for interplay or overlap between diagnoses and ensure the independence of the effects of any particular disease.

There were significant negitive impacts of all five inflammatory diseases on fluid intelligence in both modalities (Rheumatoid Arthritis Online: Coefficent (Coef) 95% Confidence Interval (CI)=-0.11 (-0.16 to -0.06) p<0.01, pFDR<0.01; Rheumatoid Arthritis In-person: Coef 95% CI=-0.11 (-0.15 to -0.08) p<0.01, pFDR<0.01; Obesity Online: Coef 95% CI=-0.08 (-0.11 to -0.05) p<0.01, pFDR<0.01; Obesity In-person: Coef 95% CI=-0.07 (-0.09 to -0.05) p<0.01, pFDR<0.01; Diabetes Mellitus Online: Coef 95% CI=-0.12 (-0.14 to -0.09) p<0.01, pFDR<0.01; Diabetes Mellitus In-person: Coef 95% CI=-0.19 (-0.21 to -0.17) p<0.01, pFDR<0.01; Asthma Online: Coef 95% CI=-0.05 (-0.07 to -0.03) p<0.01, pFDR<0.01; Asthma In-person: Coef 95% CI=-0.07 (-0.08 to -0.05) p<0.01, pFDR<0.01; HIV Online: Coef 95% CI=-0.29 (-0.53 to -0.04) p=0.02, pFDR<0.05; and HIV In-Person: Coef 95% CI=-0.36 (-0.54 to -0.18) p<0.01, pFDR<0.01).

Performance on the numeric memory test was significantly affected by rheumatoid arthritis (Online: Coef 95% CI=-0.07 (-0.13 to -0.02) p<0.01, pFDR=0.01 and In-person: Coef 95% CI=-0.12 (-0.18 to -0.06) p<0.01, pFDR<0.01), Obesity (Online: Coef 95% CI=-0.08 (-0.11 to -0.05) p<0.01, pFDR<0.01 and In-person: Coef 95% CI=-0.10 (-0.13 to -0.07) p<0.01, pFDR<0.01), Diabetes Mellitus (Online: Coef 95% CI=-0.12 (-0.14 to -0.09) p<0.01, pFDR<0.01 and In-person: Coef 95% CI=-0.17 (-0.20 to -0.14) p<0.01, pFDR<0.01), and HIV but only for the in-person version of the test (Coef 95% CI=-0.48 (-0.87 to -0.09) p=0.02, pFDR=0.02). Asthma showed nominally significant results for the in-person test, but those results fail to withstand FDR correction for multiple comparisons (Coef 95% CI=-0.03 (-0.05 to -0.00) p=0.048, pFDR>0.05). There were no significant results of Asthma or HIV on the online test (Asthma: Coef 95% CI=-0.02 (-0.04 to 0.00) p>0.05, pFDR>0.05 and HIV: Coef 95% CI=-0.18 (-0.43 to 0.08) p>0.05, pFDR>0.05). Forest plots displaying the effects of inflammatory diagnoses on cognitive measures can be found in *Figure 6* and a summary of results can be found in *Table 4*.

These results suggest some interaction between the presence of inflammatory disease and declines in the cognitive processes related to Numeric Memory and Fluid Intelligence. These findings are consistent

with the existing literature surrounding HIV which suggests that HIV infection is associated with deficits in working memory (L. Chang et al., 2001; Hinkin et al., 2002; Martin et al., 2001), episodic memory (Carey et al., 2006; Maki et al., 2009), and cognition in general (Cysique et al., 2010). The existing literature surrounding asthma doesn't indicate a clear positive or negative association being shown across the literature (Dodd, 2015). Diabetes mellitus has been associated with cognitive decline (Saedi et al., 2016; Vijayakumar et al., 2012) and deficits in memory (Kumari et al., 2000) though it is worth noting that these studies primarily cite insulin signaling dysregulation as the main causal factor. Obesity has been found to be associated with impairments in fluid intelligence (Spyridaki et al., 2014) and deficits in working memory in both adults (Gunstad et al., 2006) and children (Wu et al., 2017). There is also existing literature showing associations between rheumatoid arthritis and deficits in cognitive functioning, but these samples struggle to separate their effects from potential confounds like pain (Chaurasia et al., 2020; Meade et al., 2018).

It seems that these findings fit in with the existing literature while adding specificity related to task specifics.

2. *The Effect of Years of Inflammation on Fluid Intelligence and Numeric Memory*

GLMs were used to predict the effect of the amount of time since the diagnosis of inflammation on fluid intelligence and numeric memory. Two different measures of time spent with an inflammatory diagnosis were used: years since their first diagnosis and the total number of years since any inflammatory diagnosis. A GLM was generated for each measure of time for each test in both modalities for eight GLMs. Every model corrected for factors known to influence cognition or performance on cognitive assessments (age, sex, education, health, and income) but did not include corrections based on the presence of an inflammatory diagnosis because the two measures of time are built out of diagnosis data and are necessarily strongly correlated. Separate GLMs were made for each measure of time because they are functions of the same data inputs and are necessarily strongly correlated.

There was a small but significant negative impact of the number of years since an individual's first inflammatory diagnosis on performance on the in-person versions of the numeric memory test (Coef 95% CI=-0.00396 (-0.00679 to -0.00114) $p<0.01$, $pFDR<0.01$) and fluid intelligence test (Coef 95% CI=-0.00416 (-0.00582 to -0.00250) $p<0.01$, $pFDR<0.01$). There were no significant associations between the number of years since an individual's first inflammatory diagnosis and performance on any of the online cognitive tests (Numeric Memory: Coef 95% CI=-0.00041 (-0.00303 to 0.00221) $p>0.05$, $pFDR>0.05$ and Fluid Intelligence: Coef 95% CI=-0.00189 (-0.00430 to 0.00052) $p>0.05$, $pFDR>0.05$). There were small but significant effects of an individual's total years of inflammatory diagnosis on performance in both numeric memory tests and fluid intelligence tests in both modalities (Numeric Memory (in-person): Coef 95% CI=-0.00473 (-0.00681 to -0.00265) $p<0.01$, $pFDR<0.01$; Numeric Memory (online): Coef 95% CI=-0.00223 (-0.00424 to -0.00021) $p=0.03$, $pFDR=0.04$; Fluid Intelligence (in-person): Coef 95% CI=-0.00479 (-0.00600 to -0.00359) $p<0.01$, $pFDR<0.01$; and Fluid Intelligence (in-person): Coef 95% CI=-0.00314 (-0.00599 to -0.00129) $p<0.01$, $pFDR<0.01$). Forest plots displaying the effects of time spent with inflammatory diagnoses on cognitive measures can be found in *Figure 7*. These results suggest that the amount of time spent inflamed may play a small but crucial role in the decline.

3. *The effect of Treated HIV on Fluid Intelligence and Numeric Memory*

GLMs were used to predict treatment's effect on the impairments in performance we see on fluid intelligence and numeric memory tests. We generated four generalized linear regression models, one for each test in each modality. Every model corrected for

factors known to influence cognition or performance on cognitive assessments (age, sex, education, health, and income), and for the other four inflammatory diseases of interest (rheumatoid arthritis, obesity, diabetes mellitus, and asthma) to make sure that the results are the result of the specific aspects of HIV. Each GLM assesses the impact of having a diagnosed HIV infection on its own, being on one or more available HIV treatments, and a factor of the combined effect of having HIV and receiving one or more HIV treatments. HIV was used as opposed to any of the other four inflammatory diseases because there is a relatively small and discreet number of treatments available for HIV.

Moreover, because some HIV treatments are used prophylactically by at-risk populations to lower an individual's risk of contracting HIV infection, there is a contingent of individuals without HIV infection who are taking medications used for HIV treatment (Donnell et al., 2014). This treated but uninfected contingent allows our analysis to better disassociate the effects of medication from the effects driven by HIV infection and lowers covariation between those two factors. Furthermore, very few retroviral infections infect humans (Cloyd, 1996), so the antiretroviral medications used for HIV have few other users that likely account for a negligible amount of our sample. A representation of the subsets and overlap between individuals with HIV and individuals using HIV treatments can be found in *Figure 8a*.

Performance on fluid intelligence tests in both modalities were found to be significantly negatively impacted by only having a diagnosis of HIV (In-person: Coef 95% CI=-0.88 (-1.32 to -0.44) p<0.01, pFDR<0.01, Online: Coef 95% CI=-1.16 (-2.13 to -0.20) p=0.02, pFDR=0.02) or only using HIV treatment (In-person: Coef 95% CI=-0.24 (-0.42 to -0.05) p=0.01, pFDR=0.02, Online: Coef 95% CI=-0.32 (-0.59 to -0.09) p<0.01, pFDR=0.01). Contrarily, the combined presence of both an HIV diagnosis and HIV treatment was found to have a significant positive effect on the performance of the fluid intelligence test in both modalities (In-person: Coef 95% CI=0.86 (0.34 to 1.37) p<0.01, pFDR<0.01, Online: Coef 95% CI=1.27 (0.25 to 2.30) p=0.02, pFDR=0.02). The only significant finding regarding numeric memory was a small significant negative result of being on HIV treatment without having been diagnosed with HIV for only the in-person version of the test (Coef 95% CI=-0.34 (-0.59 to -0.09) p=0.02, pFDR=0.02). No other significant findings were related to the numeric memory task in any modality for the three test conditions. A forest plot displaying the effects of HIV infection and HIV treatment on cognitive measures can be found in *Figure 8b*. A summary of the results can be found in *Table 5*.

These results suggest that medicating the inflammation involved in the pathology of HIV may be associated with protection from the factors that lead to cognitive decline. This result is interesting because existing literature on the neuroinflammation related to HIV suggests that antiretroviral therapies do not stop it (Garvey et al., 2014; Vera et al., 2016). Consistent use of antiretroviral therapies are successful in limiting the HIV viral load present in blood plasma (Gross et al., 2001), limiting transmissibility (Cohen et al., 2016; Montaner et al., 2010), and reducing systemic inflammation in the periphery (Hileman & Funderburg, 2017; Sereti et al., 2017), so it is conceivable that the reduction in the peripheral effects of HIV may be enough to reduce the negative impacts that we see associated with HIV diagnosis.

4. The Effect of Inflammatory Diagnoses on Risk of Developing a Neurodegenerative Disease

GLMs were used to predict an individual's risk of four categories of neurodegenerative diseases (demyelinating diseases (DD), Parkinson's disease (PD), Alzheimer's disease and dementia (AD), and Other neurodegenerative diseases (OND)). Every model corrected for factors that influenced cognition or performance on cognitive assessments (age, sex,

education, health, and income). Models included all five disease categories of interest (rheumatoid arthritis, obesity, diabetes mellitus, asthma, and HIV) to account for interplay or overlap between diagnoses and ensure the independence of the effects of any particular disease. The sample sizes for HIV proved too small for analysis, so no result is shown, but it was still included as a correction for consistency.

An asthma diagnosis increased the risks of developing all four categories of neurodegenerative disease significantly (DD: Odds Ratio (OR) 95% CI=1.16 (1.02 to 1.33) p=0.03, pFDR=0.04; PD: OR 95% CI=1.25 (1.12 to 1.39) p<0.01 pFDR<0.01; AD: OR 95% CI=1.36 (1.26 to 1.47) p<0.01 pFDR<0.01; OTH: OR 95% CI = 1.68 (1.55 to 1.82) p<0.01 pFDR<0.01). These results align with current results suggesting an association between asthma and Parkinson's disease (Cheng et al., 2015; Yeh et al., 2017) and between asthma and Alzheimer's disease and dementia (M.-H. Chen et al., 2014; Peng et al., 2015)**.** Recent findings have also found a relationship between asthma severity and the risk of neuronal injury and neurodegeneration (Rosenkranz et al., 2022). Current literature about the relationship between asthma and demyelinating diseases is mixed, with some studies finding that asthma is associated with reduced odds of developing demyelinating diseases like multiple sclerosis (Tremlett et al., 2002) and some studies reporting an increased prevalence of asthma among individuals with multiple sclerosis (Hill et al., 2019; Ponsonby et al., 2006), and some studies showing no significant association (Hughes et al., 2013)**.** Our analyses suggest that asthma is associated with a higher risk of developing a demyelinating disease, including multiple sclerosis. Still, our analyses don't suggest any directionality of this relationship, nor do they account for the effects of siblings that some of the aforementioned analyses do (Hughes et al., 2013; Ponsonby et al., 2006).

A diabetes mellitus diagnosis increased the odds ratio of developing all four categories of disease significantly (DD: OR 95% CI=1.48 (1.28 to 1.71) p<0.01, pFDR<0.01; PD: OR 95% CI=1.45 (1.32 to 1.60) p<0.01 pFDR<0.01; AD: OR 95% CI=2.22 (2.08 to 2.37) p<0.01 pFDR<0.01; OTH: OR 95% CI = 1.85 (1.68 to 1.99) p<0.01 pFDR<0.01). These findings agree with the current literature, which has found associations between diabetes mellitus and DDs (Barohn et al., 1989; Fatehi et al., 2013), diabetes mellitus and PD (Camargo Maluf et al., 2019; Yang et al., 2017; Yue et al., 2016), and AD (Akomolafe et al., 2006; Arvanitakis et al., 2004; Biessels & Kappelle, 2005; Verdile et al., 2015).

Obesity was only found to significantly increase odds ratios on DD (OR 95% CI=1.31 (1.13 to 1.52) p<0.01, pFDR<0.01) and OTH (OR 95% CI=1.83 (1.68 to 1.99) p<0.01, pFDR<0.01). Obesity is a risk factor for some demyelinating diseases like multiple sclerosis (Guerrero-García et al., 2016; Langer-Gould et al., 2013). Obesity did not have a significant effect on PD (OR 95% CI=1.12 (0.99 to 1.27) p=0.07, pFDR=0.08) or AD (OR 95% CI=1.03 (0.95 to 1.13) p=0.42, pFDR=0.45). This does not align with the literature which has found significant associations between obesity and PD (J. Chen et al., 2014) and obesity and AD (Letra et al., 2014); however, the suggested mechanism for these associations often implicate insulin dysregulation, which is likely to be separately categorized as diabetes mellitus. The correction for diabetes mellitus could be causing a loss of power and a loss of significance.

Rheumatoid arthritis significantly increased the odds of developing PD (OR 95% CI=1.56 (1.29 to 1.88) p<0.01, pFDR<0.01), AD (OR 95% CI=1.46 (1.27 to 1.66) p<0.01, pFDR<0.01), and OTH (OR 95% CI=2.02 (1.73 to 2.31) p<0.01, pFDR<0.01). Previous research has found that rheumatoid arthritis is associated with a significantly reduced risk of developing Alzheimer's disease (Bae & Lee, 2019; Cai et al., 2018; Kao et al., 2016; Policicchio et al., 2017) and Parkinson's disease (Bacelis et al., 2021, 2021; Sung et al., 2016), which is in direct contradiction to our findings. However, population studies of autoimmune rheumatic disease, a category that encompasses rheumatoid arthritis, found that the inflammation associated with the disease was

associated with a significantly higher risk of developing PD (C.-C. Chang et al., 2018) and dementia (Lin et al., 2018). In contrast, other studies have found that several autoimmune diseases, but specifically not rheumatoid arthritis, (which had no significant effect in this study), increased the risk of AD (X. Li et al., 2018). The more genetic approach of some of the papers mentioned above may account for different factors than our analyses (Cai et al., 2018; C. Li et al., 2021; Policicchio et al., 2017; Suzuki et al., 2011), which could account for our diametrically opposed results. Alternatively, research has found that the immunoglobulins that cause autoimmune diseases like rheumatoid arthritis are implicated in the pathology of AD and PD and might exert a protective effect (Sim et al., 2020). Rheumatoid arthritis is related to peripheral neurodegeneration in the enteric nervous system (Piovezana Bossolani et al., 2019), and translational research suggests that perhaps instead of arthritis predisposing subjects to developing neurodegeneration, it might be that certain neurodegenerative profiles may predispose subjects to develop arthritis (Lang et al., 2017). Overall, it is clear that more research into the specific profile of rheumatoid arthritis is needed before the true mechanisms or direction of this effect become clear.

Rheumatoid arthritis had no significant effect on the odds ratio related to DD (OR 95% CI=1.11 (0.83 to 1.47) p=0.49, pFDR=0.51), which is consistent with existing literature which shows no significant association between Rheumatoid Arthritis and DD (Hughes et al., 2013; Tremlett et al., 2002) despite genetic analyses showing some overlap in genetic susceptibility to rheumatoid arthritis and the demyelinating autoimmune disease, multiple sclerosis (Suzuki et al., 2011). These effects are displayed in *Figure 9* and summarized in *Table 6*.

5. The Effect of Years of Inflammation on Risk of Developing a Neurodegenerative Disease

GLMs were used to predict the effect of the amount of time since the diagnosis of inflammation on the risk of developing a neurodegenerative disease. Two different measures of time spent with an inflammatory diagnosis were used: Years since their first diagnosis and the total number of years since any inflammatory diagnosis. A GLM was generated for each measure of time for each test in both modalities for eight GLMs. Every model corrected for factors known to influence cognition or performance on cognitive assessments (age, sex, education, health, and income) but did not include corrections based on the presence of an inflammatory diagnosis because the two measures of time are built out of diagnosis data and are necessarily strongly correlated. Separate GLMs were made for each measure of time because they are functions of the same data inputs and are necessarily strongly correlated.

There were small but significant effects of total years of inflammation on all four categories of neurodegenerative disease (DD: OR 95% CI=1.011 (1.002 to 1.021) p=0.01, pFDR=0.02; PD: OR 95% CI=1.009 (1.003 to 1.017) p<0.01, pFDR<0.01; AD: OR 95% CI=1.020 (1.016 to 1.025) p<0.01, pFDR<0.01; OTH: OR 95% CI=1.026 (1.021 to 1.030) p<0.01, pFDR<0.01). While there is little literature that has specifically found an association between the amount of time spent inflamed and the odds of developing neurodegenerative diseases, there is a well-documented relationship between inflammation and neurodegeneration (Amor et al., 2014), the etiology and progression of which often involves glial expression of an inflammatory phenotype in glial cells (Cunningham, 2013; Perry & Teeling, 2013). This phenotype can arise as a result of systemic inflammation or due to the high presence of pro-inflammatory chemical mediators in the brain (Jang et al., 2013; Perry & Teeling, 2013; Varnum & Ikezu, 2012). These results may add to our current understanding by suggesting that these phenotype-switching effects are worsened or increased due to

prolonged exposure to inflammation. More research is needed to understand the precise mechanisms driving this association. Forest plots of these results can be found in *Figure 10*.

Discussion

Our results suggest significant associations between having been diagnosed with one of the five inflammatory diseases of interest and performance on fluid intelligence tasks and some numeric memory tasks. There are also significant increases in odds ratios for neurodegenerative diseases in several categories. The most significant results were related to a diabetes mellitus diagnosis. These results might suggest a possible implication of inflammation or inflammatory diseases in the etiology or progression of cognitive decline or neurodegeneration. The effects of fluid intelligence, numeric memory, and neurodegeneration are significantly negatively affected by time, suggesting that the amount of time spent inflamed is associated with worse cognitive and disease outcomes.

More research is needed to elucidate the directionality and mechanisms of these relationships. Still, should they prove causal, these findings have important implications for treating these inflammatory diseases and the potential avoidance of cognitive decline. This is especially relevant as treatment methods have shifted towards delaying the onset of neurodegeneration and cognitive decline rather than treating symptoms once they arise (Young, 2009).

If the early treatment or alleviation of chronic low-level inflammation could reduce risk, lessen the severity, or delay the onset of cognitive decline or neurodegeneration, there would be sweeping implications for treatment at large, mainly because simple lifestyle modifications like increased exercise (Bruunsgaard, 2005) or changes in diet (Bulló et al., 2007) have shown effectiveness in modulating and improving systemic inflammation.

However, these findings also align indirectly with interpretations of cognition related to allostatic load that find that long-term dysregulation of allostasis, or the body's ability to adapt to stressors, influences age-related disease progression and cognitive decline (Juster et al., 2010; Karlamangla et al., 2002). Even at low levels, persistent inflammation represents a significant enough disruption to allostasis to drive maladaptive and longitudinally detrimental effects on the body and the brain. Perhaps understanding these diseases' outcomes as disruptions to allostasis could lead to new avenues of research into the mechanisms underpinning them or potential treatments or strategies to avoid adverse neural outcomes.

In the case of HIV, it appears that in fluid intelligence tasks, the negative effects discussed above seem to be modulated by treatment and may be able to increase the effects we see related to HIV significantly. As mentioned earlier, this outcome is surprising in terms of the literature. Current understandings of HIV and HIV-Associated Neurocognitive Disorders find that HIV treatments are not enough to avoid cognitive decline (Garvey et al., 2014; Vera et al., 2016). More research is needed to understand if this association is specific to the particular types of cognitive processes used to complete a fluid intelligence task or if something particular to the sample of HIV-infected individuals in UK Biobank may be driving this effect. Either way, any amount of behavioral symptom alleviation is encouraging.

The effects related to time are interesting because they suggest that the amount of time spent inflamed may play a small but crucial role in the decline and neurodegeneration, especially when accounting for potential overlap in inflammatory diseases. The results strengthen the insulation that it is not the presence of inflammation, in general, driving these effects but the prolonged presence of chronic inflammation that is related to the impact we see, which aligns with existing research that has

linked inflammation and cognitive decline (Bettcher & Kramer, 2014; Gorelick, 2010).

Additional research may also focus on evaluating how subsets of inflammatory mediators such as cytokines, white blood cells, and biomarkers are related to these effects to provide greater clarity into which factors may specifically be related to the associations we see — moreover an investigation into imaging methods may illustrate if and how the effects mentioned above might correlate with changes in neural architecture. A greater understanding of the changes in brain structure could provide greater insight into how inflammation impacts the brain, into the specific functions we expect to be affected, and test modalities that could better show the effects of these changes.

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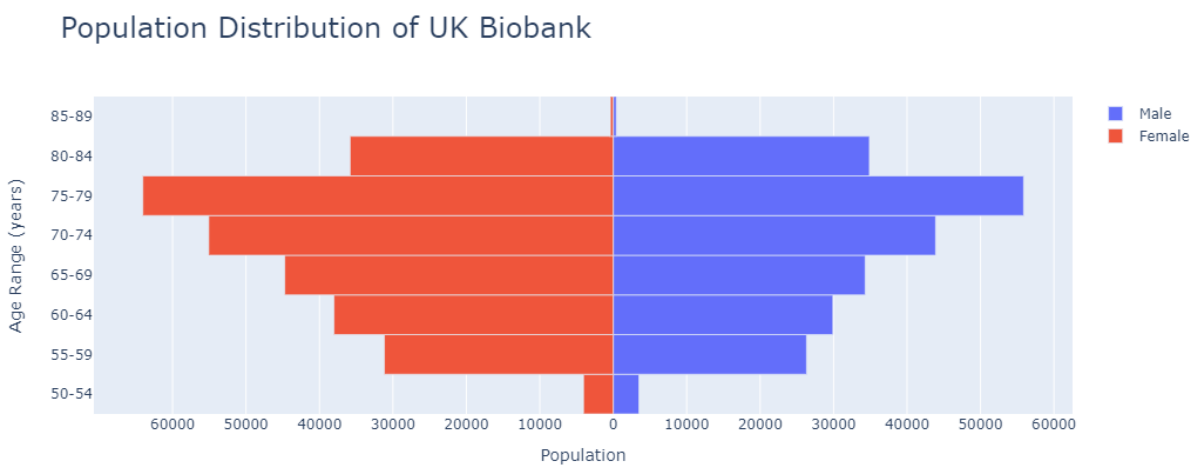
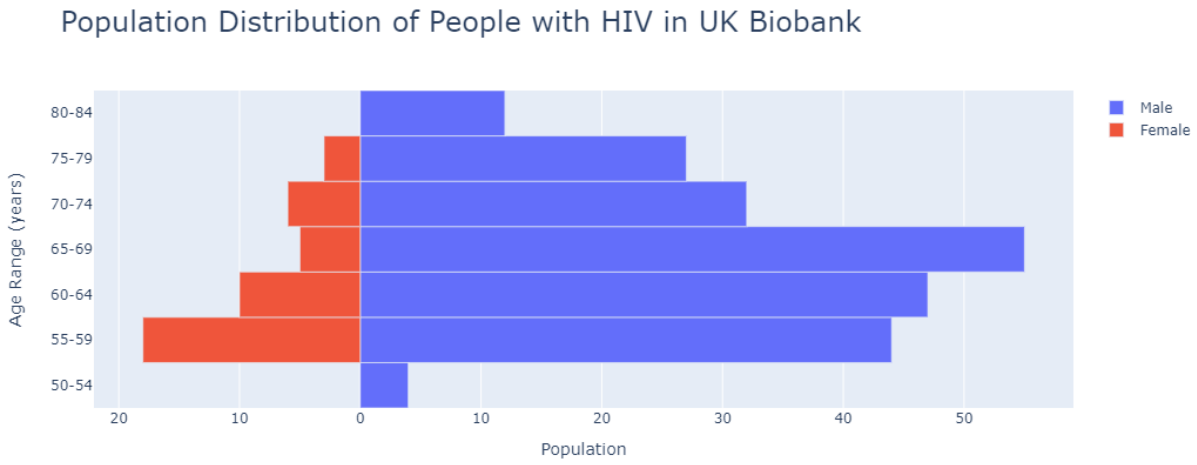
Figure 1: Population Distributions

a)



b)



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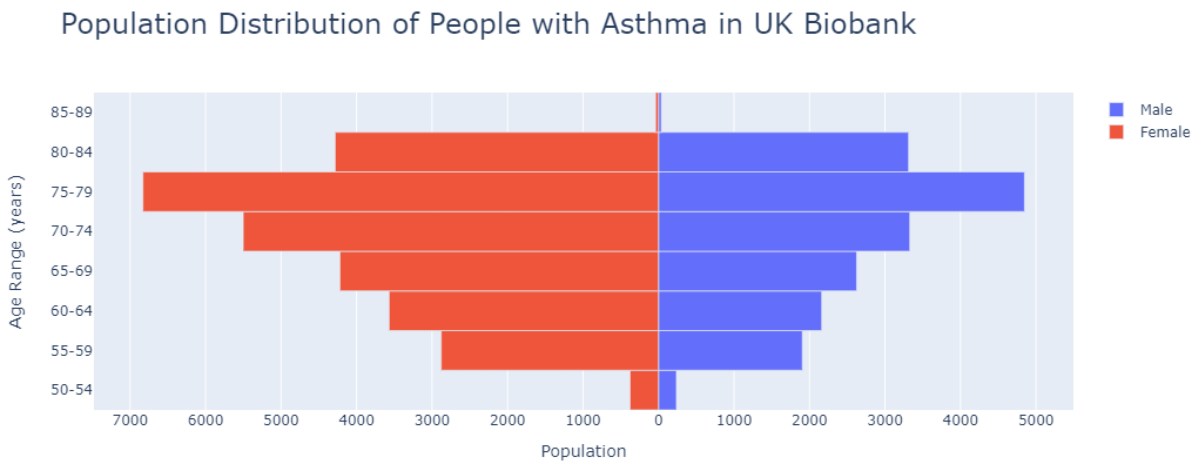
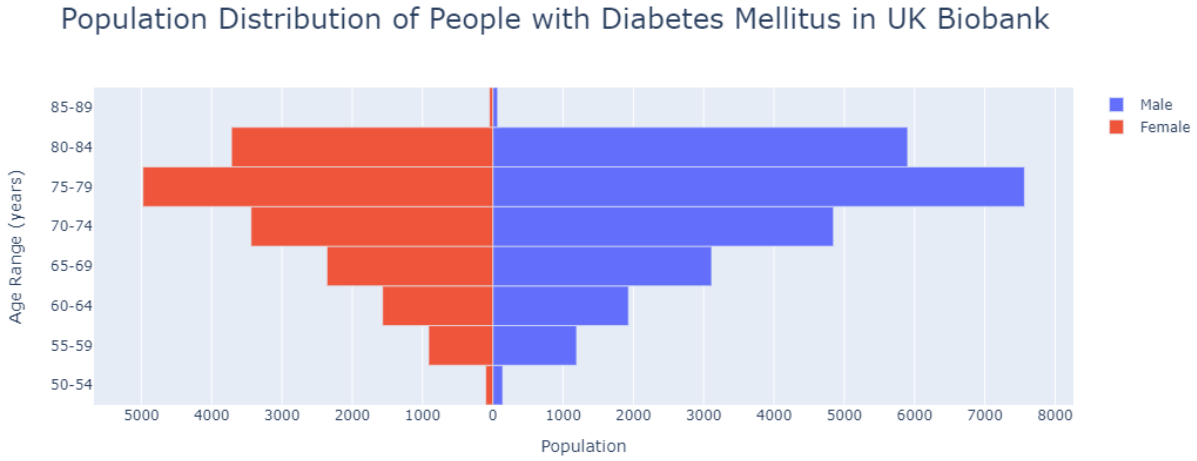
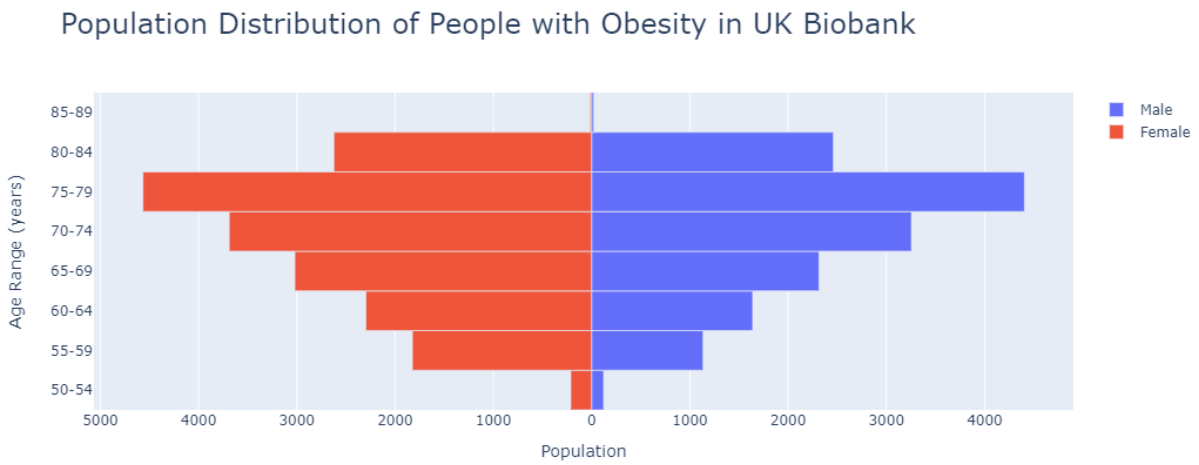

Population Distribution of People with Asthma in UK Biobank
Age Range (years)
85-89
80-84
75-79
70-74
65-69
60-64
55-59
50-54
7000
6000
5000
4000
3000
2000
1000
0
1000
2000
3000
4000
5000
Population
Male
Female

d)


Population Distribution of People with Diabetes Mellitus in UK Biobank
Age Range (years)
85-89
80-84
75-79
70-74
65-69
60-64
55-59
50-54
5000
4000
3000
2000
1000
0
1000
2000
3000
4000
5000
6000
7000
8000
Population
Male
Female

e)



f)

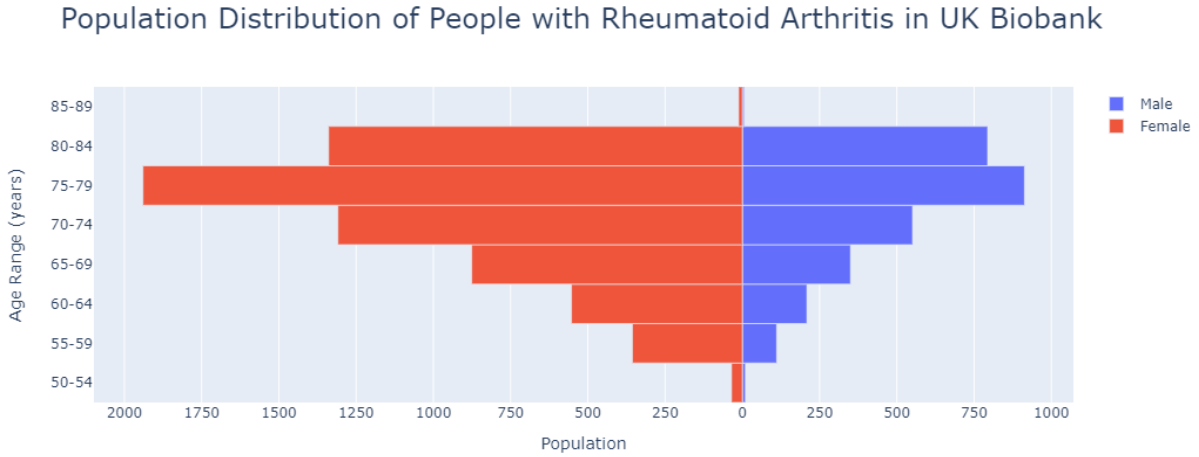


Figure 1: Pyramid plots of the age and sex distribution of the populations and subpopulations of our samples. a) Pyramid plot of the population distribution of the total population of UK biobank. n=502413. b) Pyramid plot of the population distribution of the subset of individuals in UK biobank with HIV. n=263. c) Pyramid plot of the population distribution of the subset of individuals in UK biobank with asthma. n=46,156. d) Pyramid plot of the population distribution of the subset of individuals in UK biobank with Diabetes Mellitus. n=41,883. e) Pyramid plot of the population distribution of the subset of obese individuals in UK biobank. n=33,604. f) Pyramid plot of the population distribution of the subset of individuals in UK biobank with Rheumatoid Arthritis in UK Biobank. n=9364.

Figure 2: Venn Diagram of Inflammatory Diagnosis Overlap

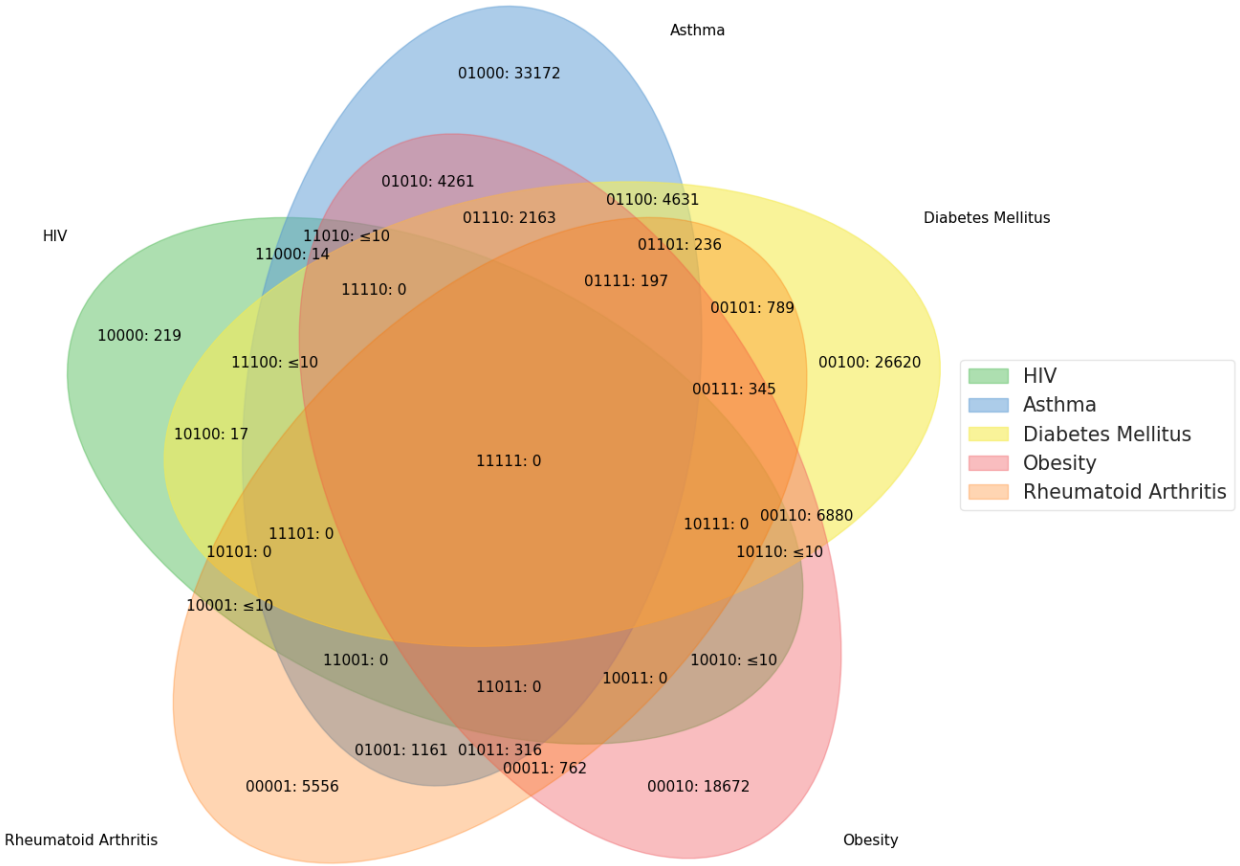


Figure 2: Five-way Venn diagram showing the overlap of individuals with any of the five diagnoses of interest. The five-digit identifier before each number represents whether or not any individual has been diagnosed with a given disease. A one in any of the five positions represents a diagnosis of HIV, asthma, diabetes mellitus, obesity, or rheumatoid arthritis respectively based on position. Very small non-zero values are recorded as '≤10' to ensure participant anonymity.

Figure 3: Pre-Normalized Fluid Intelligence Score Distributions

a) **b)**

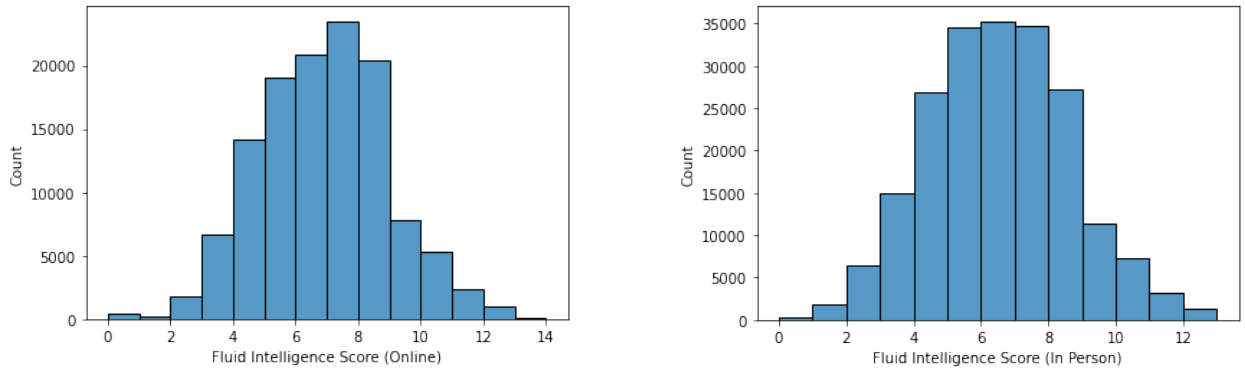


Figure 3: Histograms of the pre-normalized recorded fluid intelligence scores used in this study. Shows the approximate count for each score. a) shows the distribution of scores for the online version of the test. b) shows the scores for the in-person version of the test. If any participant took a test more than once, the mean of their scores was taken and recorded.

Figure 4: Pre-Normalized Numeric Memory Task Distributions

a) **b)**

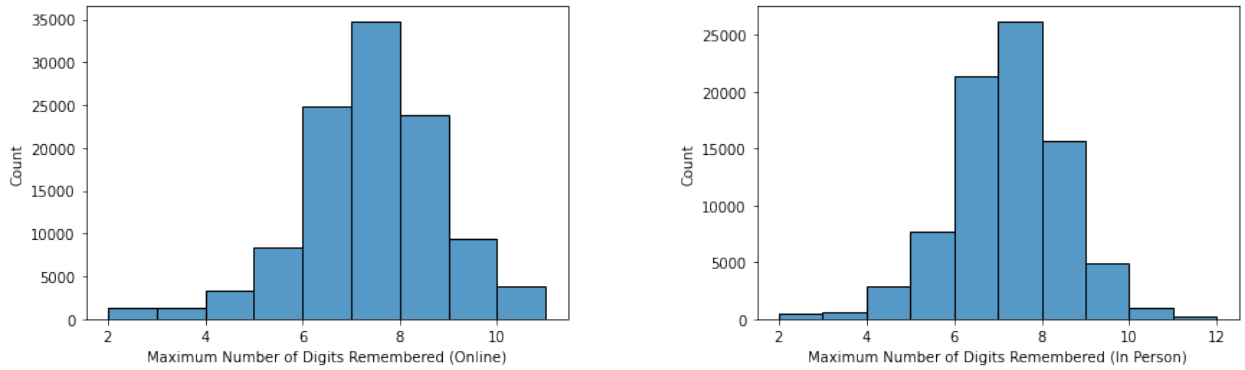
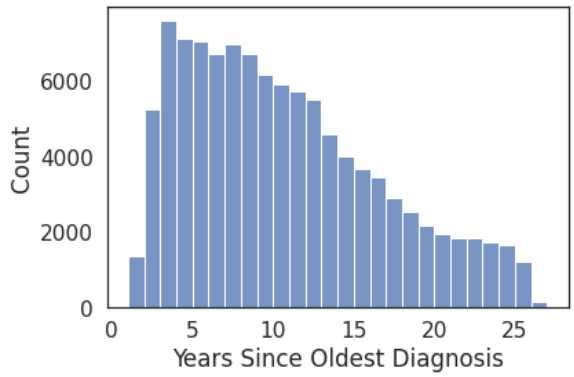


Figure 4: Histograms of the pre-normalized recorded maximum number of digits remembered on a numeric memory task used in this study. Shows the approximate count for each maximum number of digits remembered. a) shows the distribution of the maximum number of digits remembered for the online version of the test. b) shows the maximum number of digits remembered for the in-person version of the test. If any participant took a test more than once, their largest maximum was recorded.

Figure 5: Distribution of Time Variables Related to inflammatory Diagnoses

a)



b)

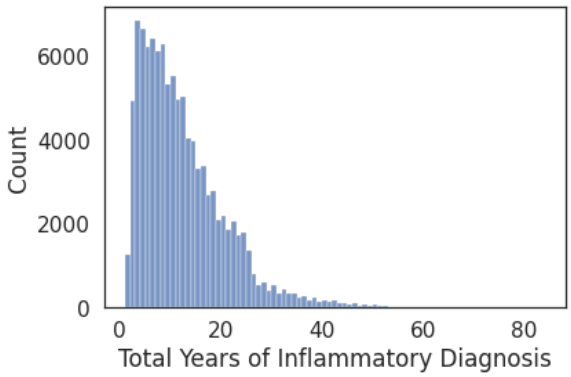
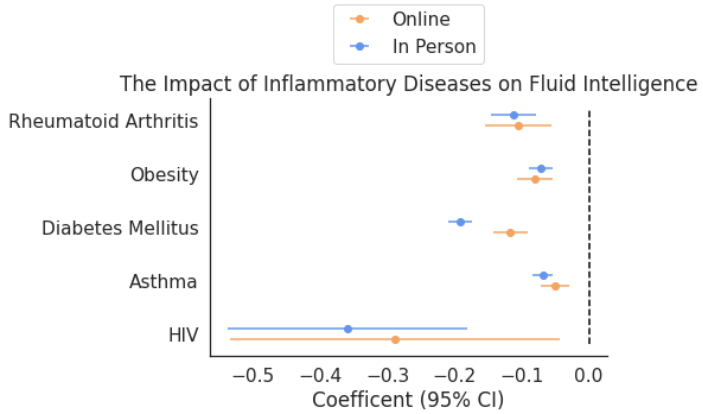


Figure 5:

Figure 6: The Effect of Inflammatory Diagnosis on Fluid Intelligence and Numeric Memory

a)



	Online Coefficent (95% CI)	In Person Coefficent (95% CI)
Rheumatoid Arthritis	-0.11 (-0.16 to -0.06)	-0.11 (-0.15 to -0.08)
Obesity	-0.08 (-0.11 to -0.05)	-0.07 (-0.09 to -0.05)
Diabetes Mellitus	-0.12 (-0.14 to -0.09)	-0.19 (-0.21 to -0.17)
Asthma	-0.05 (-0.07 to -0.03)	-0.07 (-0.08 to -0.05)
HIV	-0.29 (-0.53 to -0.04)	-0.36 (-0.54 to -0.18)

b)

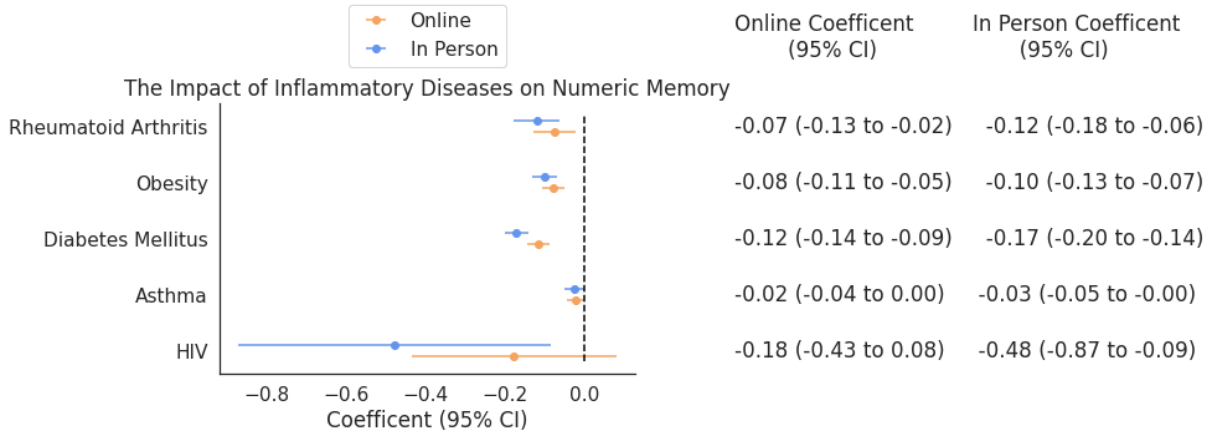
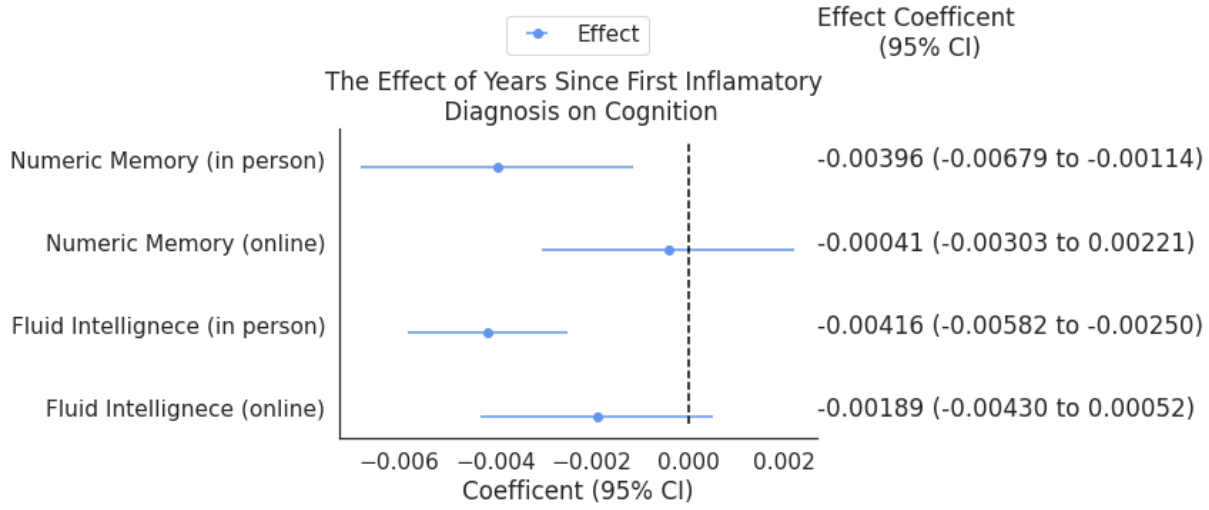


Figure 6: Forest plots of the impact of the presence of the inflammatory diagnoses of interest on fluid intelligence scores and the maximum number of digits remembered on a numeric memory test. Details of the number of participants and the number of diagnoses can be found in Table 1. a) show the effect of five common inflammatory diseases on the results of fluid intelligence tests in two modalities: online or in-person. b) show the effect of five common inflammatory diseases on the results of numeric memory tests in two modalities: online or in-person.

Figure 7: The Effect of Years of Inflammation on Fluid Intelligence and Numeric Memory

a)



b)

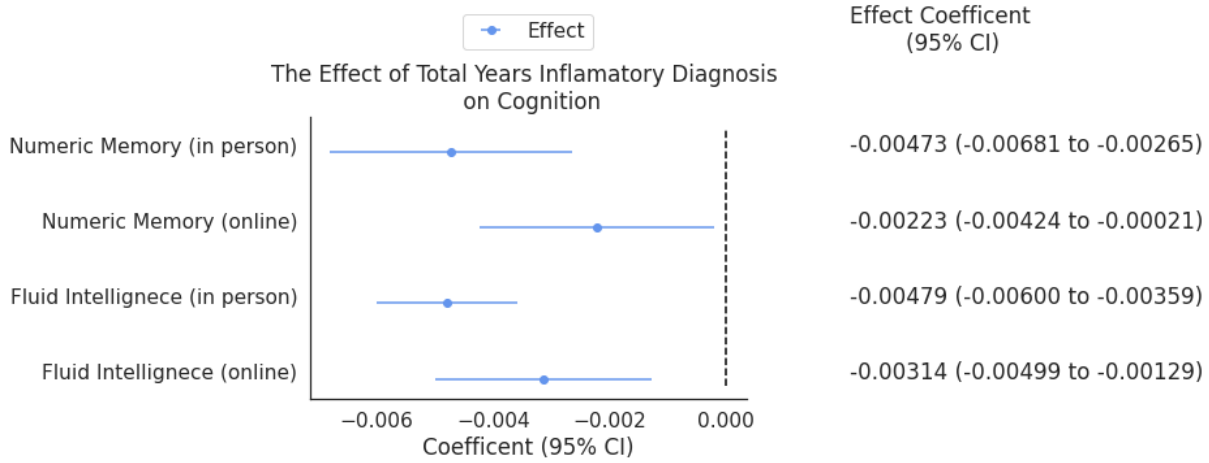
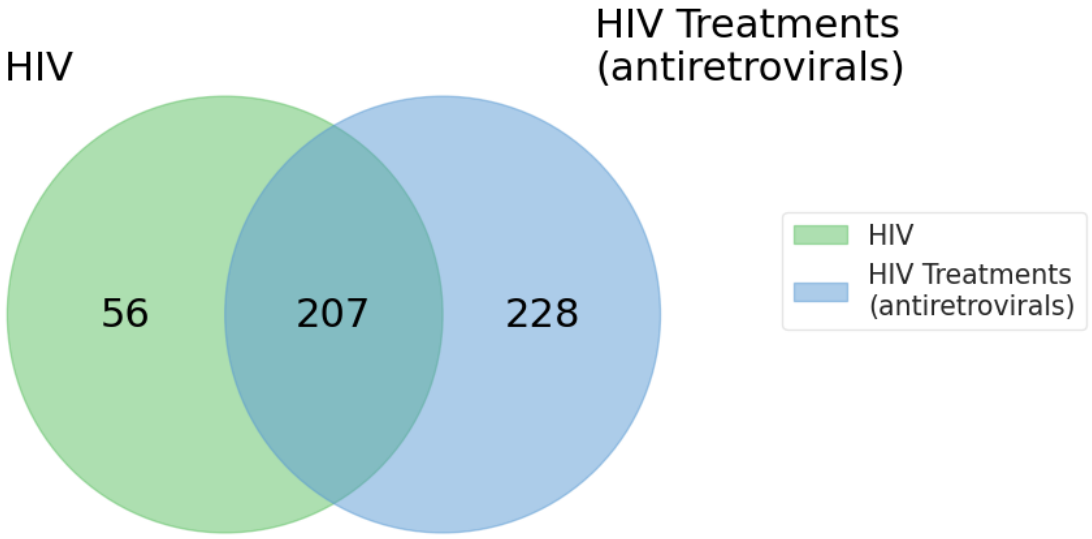


Figure 7: Forest plots of the impact of the amount of time spent with one or more inflammatory diseases on fluid intelligence and numeric memory. The number of participants is as follows: Numeric Memory (in-person) n=14,066, Numeric Memory (online) n=16,666, Fluid Intelligence (in-person) n=39,326, Fluid Intelligence (online) n=18,905. a) shows the impact of the amount of time that has passed since their first inflammatory diagnosis on performance on fluid intelligence tests and numeric memory tests both taken online and in person. b) shows the impact of the amount of time that has passed since the diagnosis of each inflammatory disease category on performance on fluid intelligence tests and numeric memory tests both taken online and in person.

Figure 8: The Distribution and effects of HIV and HIV treatment on Fluid Intelligence and Numeric Memory

a)



b)

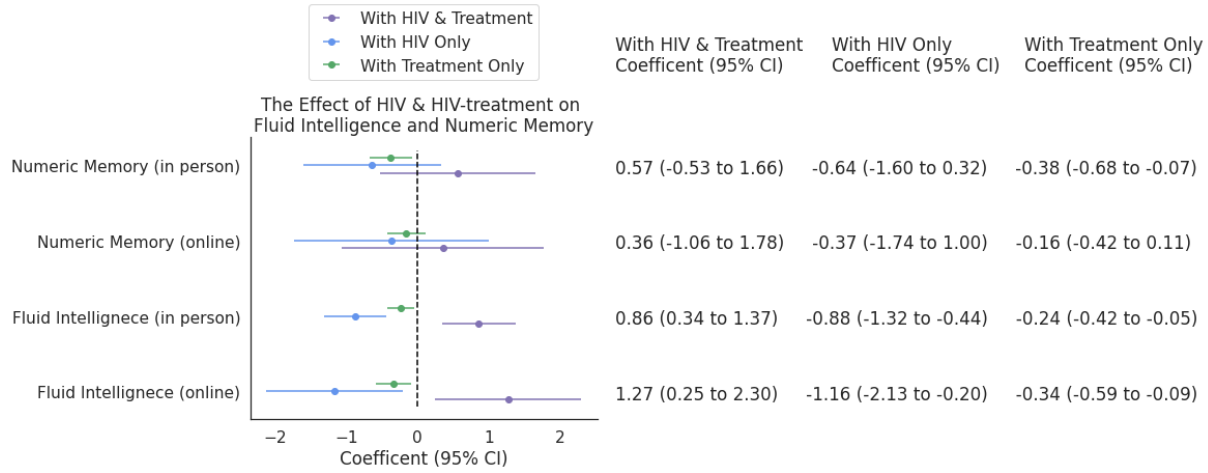
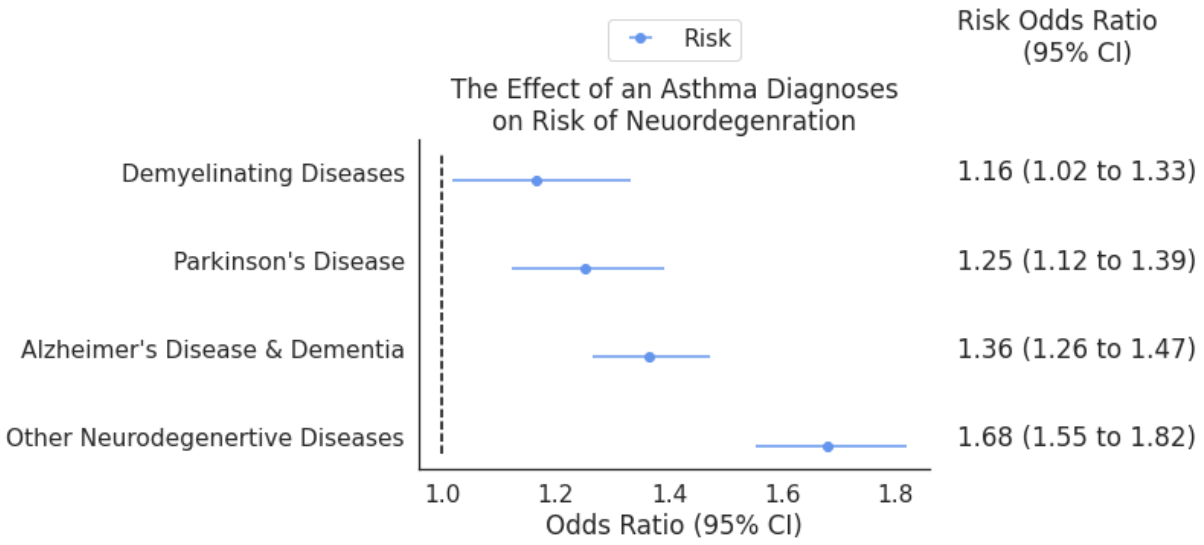


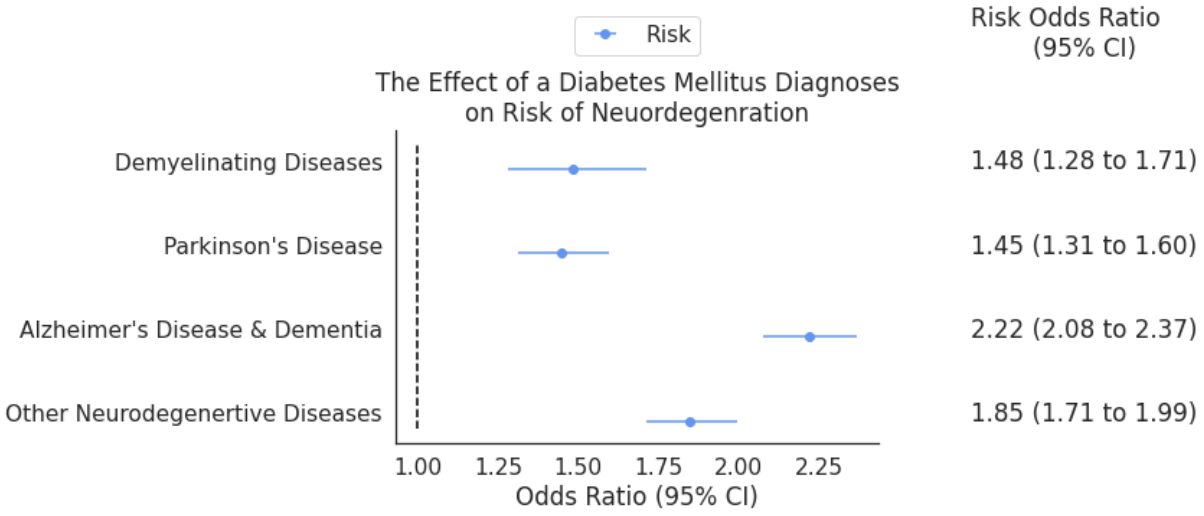
Figure 8: Representation of the population with and effects of HIV and HIV treatment on cognition. a) shows the sample sizes and amount of overlap of individuals with HIV and individuals using HIV treatments. b) forest plot showing the separate and combined influences of HIV and HIV treatment on performance on fluid intelligence tests and numeric memory tests both taken online and in person.

Figure 9: The Effect of Inflammatory Diagnosis on Odds Ratio of Developing a Neurodegenerative Disease

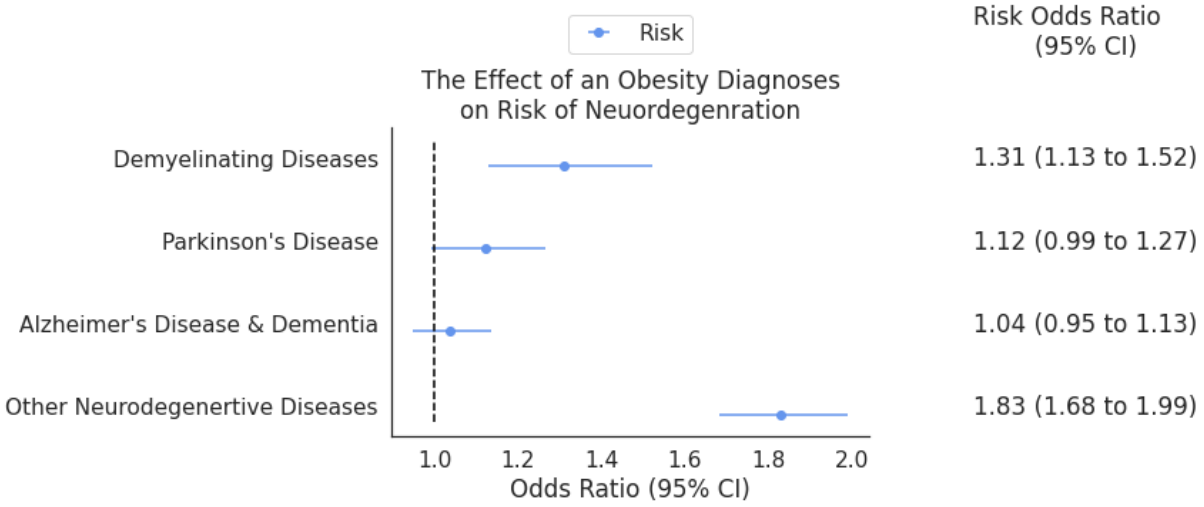
a)



b)


Risk
Risk Odds Ratio
(95% CI)
The Effect of a Diabetes Mellitus Diagnoses
on Risk of Neuordegenration
Demyelinating Diseases
Parkinson's Disease
Alzheimer's Disease & Dementia
Other Neurodegenertive Diseases
1.48 (1.28 to 1.71)
1.45 (1.31 to 1.60)
2.22 (2.08 to 2.37)
1.85 (1.71 to 1.99)
1.00
1.25
1.50
1.75
2.00
2.25
Odds Ratio (95% CI)

c)


Risk
Risk Odds Ratio
(95% CI)
The Effect of an Obesity Diagnoses
on Risk of Neuordegenration
Demyelinating Diseases
Parkinson's Disease
Alzheimer's Disease & Dementia
Other Neurodegenertive Diseases
1.31 (1.13 to 1.52)
1.12 (0.99 to 1.27)
1.04 (0.95 to 1.13)
1.83 (1.68 to 1.99)
1.0
1.2
1.4
1.6
1.8
2.0
Odds Ratio (95% CI)

d)

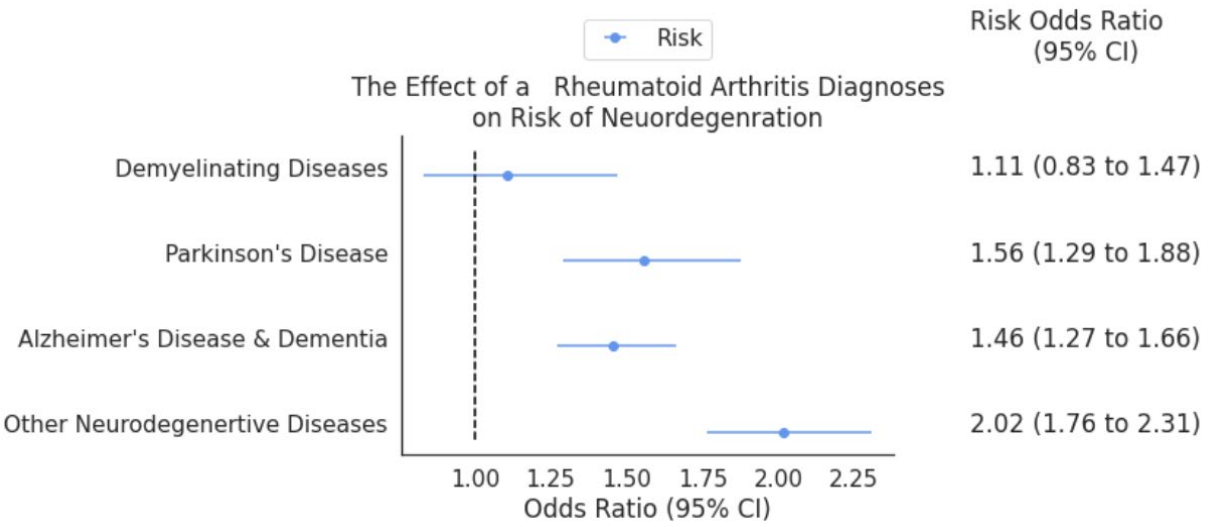


Figure 9: Forest plots of the impact of the presence of the inflammatory diagnoses of interest on odds of developing neurodegenerative diseases. a) depicts the risks associated with asthma. b) depicts the risks associated with diabetes mellitus c) depicts the risks associated with obesity. d) depicts the risks associated with rheumatoid arthritis.

Figure 10: The Effect of Total Years of Inflammation on Risk of Developing a Neurodegenerative Disease

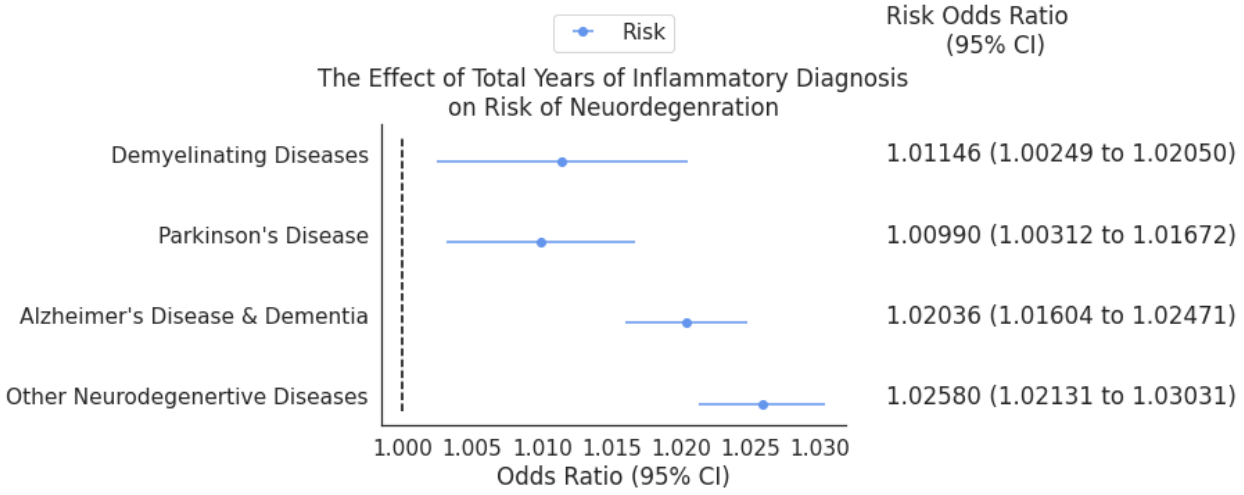


Figure 10: The effect of Total years of inflammation on the odds ratio of developing four categories of neurodegenerative disease. n=96171.

Table 1: Sets and Subsets

Fluid Intelligence (online) n=107,487	HIV: n=71 asthma: n=9,773 diabetes mellitus: n=6,594 obesity: n=6,216 rheumatoid arthritis: n=1,684
Fluid Intelligence (in-person) n=193,762	HIV: n=122 asthma: n=18,341 diabetes mellitus: n=15,513 obesity: n=12,770 rheumatoid arthritis: n=3,468
Numeric Memory (online) n=96,666	HIV: n=65 asthma: n=8,664 diabetes mellitus: n=5,736 obesity: n=5,470 rheumatoid arthritis: n=1,457
Numeric Memory (in-person) n=74,754	HIV: n=27 asthma: n=6,969 diabetes mellitus: n=5,273 obesity: n=4,367 rheumatoid arthritis: n=1,197

Table 1: Breakdown of the number of participants with a given diagnosis in each for each test in each modality.

Table 2: ICD-10 Codes Used in a Diagnosis

Category	ICD-10 Codes	ICD-10 Description	Number of Diagnoses	
HIV	B20 (all)	Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases	**75**	
	B21 (all)	Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms	**17**	
	B22 (all)	Human immunodeficiency virus [HIV] disease resulting in other specified diseases	**12**	
	B23 (all)	Human immunodeficiency virus [HIV] disease resulting in other conditions	**39**	
	B24 (all)	Unspecified human immunodeficiency virus [HIV] disease	**166**	
	Z21 (all)	Asymptomatic human immunodeficiency virus [HIV] infection status	**118**	**427**
Rheumatoid Arthritis	M05 (all)	Seropositive rheumatoid arthritis	**1953**	
	M06 (all)	Other rheumatoid arthritis	**15867**	
	M08.0 (all)	Juvenile rheumatoid arthritis	**51**	**17871**
Asthma	J45 (all)	Asthma	**48672**	**48672**

Diabetes Mellitus	E10 (all)	Insulin-dependent diabetes mellitus	**6894**	
	E11 (all)	Non-insulin-dependent diabetes mellitus	**48125**	
	E12 (all)	Malnutrition-related diabetes mellitus	**7**	
	E13 (all)	Other specified diabetes mellitus	**522**	
	E14 (all)	Unspecified diabetes mellitus	**5907**	**61455**
Obesity	E66 (all)	Obesity	**38496**	**38496**
Alzheimer's Disease and other dementias	F00 (all)	Dementia in Alzheimer's disease	**2634**	
	F01 (all)	Vascular Dementia	**1664**	
	F02 *	Dementia in other diseases classified elsewhere	**1024**	
	F03 (all)	Unspecified dementia	**3657**	
	G30 (all)	Alzheimer's disease	**3409**	**12388**
Parkinson's Disease	G20 (all)	Parkinson's disease	**3675**	**3675**
Demyelinating Diseases	G35 (all)	Multiple sclerosis	**2089**	
	G36 (all)	Other acute disseminated demyelination	**30**	
	G37 (all)	Other demyelinating diseases of central nervous system	**482**	**2601**
Other Neurodegenerative Diseases	G23 (all)	Other degenerative diseases of basal ganglia	**269**	
	G25 (all)	Other extrapyramidal and movement disorders	**2520**	
	G31 (all)	Other degenerative diseases of nervous system, not elsewhere classified	**2760**	**5549**

* Excluding F02.4 Dementia in human immunodeficiency virus [HIV] disease

Table 2: Breakdown of the disease categories used in this analysis and their associated ICD-10 codes. Shows the number of diagnoses for each code and category. It is worth noting that each instance of a diagnosis does not represent a unique individual; it is possible for one individual to have more than one diagnosis within a category and more than one category of diagnosis.

Table 3: Medication Search Terms and Coding

SEARCH TERMS: abacavir, aptivus, atazanavir, atripla, bictegravir, biktarvy, cabenuva, cabotegravir, cimduo, cobicistat, combivir, complera, darunavir, delstrigo, descovy, didanosine, dolutegravir, doravirine, dovato, edurant, efavirenz, emtricitabine, emtriva, enfuvirtide, epivir, epzicom, etravirine, evotaz, fosamprenavir, fostemsavir, fuzeon, genvoya, ibalizumab, indinavir, intelence, invirase, isentress, juluca, kaletra, lamivudine, lexiva, lopinavir, maraviroc, nevirapine, norvir, odefsey, pifeltro, prezcobix, raltegravir, retrovir, reyataz, rilpivirine, ritonavir, rukobia, saquinavir, stavudine, stribild, sustiva, symfi, symtuza, tenofovir, tipranavir, tivicay, triumeq, trizivir, trogarzo, truvada, tybost, videx, viramune, viread, vocabria, ziagen

UK Biobank Coding	Description
1140874454	zidovudine
1140874456	retrovir 100mg capsule
1140874460	retrovir 250mg capsule

1140874466	retrovir 200mg/10ml intravenous infusion concentrate
1140874468	retrovir 50mg/5ml s/f oral solution
1140888928	didanosine
1140888934	videx 25mg tablet
1140888936	videx 100mg tablet
1140909574	retrovir 200mg/20ml intravenous infusion
1140927000	retrovir 300mg tablet
1140928142	lamivudine
1140928146	epivir 150mg tablet
1140928202	epivir 10mg/ml oral solution
1140928248	stavudine
1140928384	ritonavir
1140928392	norvir 100mg capsule
1140928396	norvir 80mg/ml oral solution
1141145612	saquinavir
1141145618	invirase 200mg capsule
1141145924	indinavir
1141156956	videx 150mg tablet
1141157274	saquinavir product
1141157370	zidovudine product
1141165518	efavirenz
1141165526	sustiva 50mg capsule
1141165528	sustiva 100mg capsule
1141165530	sustiva 200mg capsule
1141165852	abacavir
1141165858	ziagen 300mg tablet
1141165860	ziagen 20mg/ml oral solution
1141166356	viramune 50mg/5ml oral suspension
1141166768	lamivudine+zidovudine
1141166772	combivir tablet
1141167014	nevirapine
1141167020	viramune 200mg tablet
1141171600	videx ec 125mg e/c capsule
1141171602	videx ec 200mg e/c capsule
1141171656	videx ec 250mg e/c capsule
1141171658	videx ec 400mg e/c capsule

1141172702	abacavir+lamivudine+zidovudine
1141172704	trizivir tablet
1141173910	lopinavir+ritonavir
1141173916	kaletra 133.3mg/33.3mg capsule
1141173918	kaletra 400mg/100mg/5ml oral solution
1141175926	videx 200mg tablet
1141179764	tenofovir
1141179768	viread 245mg tablet
1141182636	sustiva 30mg/ml oral solution
1141186178	epivir 300mg tablet
1141187568	sustiva 600mg tablet
1141189380	emtricitabine
1141189384	emtriva 200mg capsule
1141189662	abacavir 300mg / lamivudine 150mg / zidovudine 300mg tablet
1141190554	atazanavir
1141190558	atazanavir 200mg capsule
1141190560	atazanavir 150mg capsule
1141190566	reyataz 200mg capsule
1141190570	reyataz 150mg capsule
1141194026	fuzeon 90mg/ml injection (pdr for recon)+solvent
1141194062	enfuvirtide
1141195570	reyataz 100mg capsule
1141195572	atazanavir 100mg capsule
1141200344	fosamprenavir
1141200354	fosamprenavir 700mg tablet
1141201514	fosamprenavir 50mg/ml oral suspension

Table 3: List of all of the search terms used to identify HIV treatments given to the UK Biobank population. A total of 73 search terms were identified representing both the generic and brand names of all FDA approved HIV treatments (*FDA-Approved HIV Medicines | NIH*, 2022). A total of 65 unique UK biobank treatment codes were identified and used in our analysis.

Table 4: The Effect of Inflammatory Diagnosis on Fluid Intelligence and Numeric Memory Supplement

a)

FI_score_o_norm ~ age + sex + edu + health + income + HIV + asthma + DM + obesity + RA

Diagnosis	Total Controls	Total Cases	Coef	CI Lower	CI Upper	p	pFDR
HIV	107416	71	-0.28903	-0.53382	-0.04424	0.020658	0.027544
Asthma	97714	9773	-0.05018	-0.07157	-0.02879	4.26E-06	1.02E-05
Diabetes Mellitus	100893	6594	-0.11681	-0.143	-0.09063	2.23E-18	1.22E-17
Obesity	101271	6216	-0.08021	-0.10653	-0.05388	2.35E-09	7.43E-09
Rheumatoid Arthritis	105803	1684	-0.10512	-0.15506	-0.05517	3.70E-05	8.23E-05

b)

FI_score_i_norm ~ age + sex + edu + health + income + HIV + asthma + DM + obesity + RA

Diagnosis	Total Controls	Total Cases	Coef	CI Lower	CI Upper	p	pFDR
HIV	193640	122	-0.35909	-0.5368	-0.18137	7.49E-05	0.00015
Asthma	175421	18341	-0.06893	-0.08425	-0.05361	1.17E-18	6.99E-18
Diabetes Mellitus	178249	15513	-0.19171	-0.20857	-0.17485	4.67E-110	1.40E-108
Obesity	180992	12770	-0.07164	-0.08989	-0.0534	1.40E-14	5.61E-14
Rheumatoid Arthritis	190294	3468	-0.11281	-0.14637	-0.07925	4.45E-11	1.57E-10

c)

max_mem_o_norm ~ age + sex + edu + health + income + HIV + asthma + DM + obesity + RA

Diagnosis	Total Controls	Total Cases	Coef	CI Lower	CI Upper	p	pFDR
HIV	96601	65	-0.17672	-0.43336	0.079916	0.177132	0.204384
Asthma	88002	8664	-0.02172	-0.04454	0.001093	0.062032	0.075958
Diabetes Mellitus	90930	5736	-0.11655	-0.1447	-0.0884	4.83E-16	2.42E-15
Obesity	91196	5470	-0.07697	-0.10516	-0.04878	8.71E-08	2.49E-07
Rheumatoid Arthritis	95209	1457	-0.07453	-0.12825	-0.02081	0.006544	0.010612

d)

max_mem_i_norm ~ age + sex + edu + health + income + HIV + asthma + DM + obesity + RA

Diagnosis	Total Controls	Total Cases	Coef	CI Lower	CI Upper	p	pFDR
HIV	74727	27	-0.47798	-0.8704	-0.08555	0.016975	0.023686
Asthma	67785	6969	-0.02524	-0.0503	-0.00018	0.048333	0.060416
Diabetes Mellitus	69481	5273	-0.171	-0.19997	-0.14204	5.73E-31	5.73E-30
Obesity	70387	4367	-0.10032	-0.1316	-0.06905	3.23E-10	1.08E-09
Rheumatoid Arthritis	73557	1197	-0.12039	-0.17784	-0.06295	3.99E-05	8.56E-05

Table 4: Breakdown of the effects and significance of a variety of inflammatory diseases on fluid intelligence and numeric memory measures as well as the formula used for each linear regression model. a) shows the effects of a variety of inflammatory diseases on the online fluid intelligence test. b) shows the effects of a variety of inflammatory diseases on the in-person fluid intelligence test. c) shows the effects of a variety of inflammatory diseases on the online numeric memory test. d) shows the effects of a variety of inflammatory diseases on the in-person numeric memory test.

Table 5: The effect of Treated HIV on Fluid Intelligence and Numeric Memory Supplement

a)

fI_score_o_norm ~ age + sex + edu + health + income + on_HIV_meds * HIV

Condition	Total Controls	Total Cases	Coef	CI Lower	CI Upper	p	pFDR
on_HIV_meds	107360	127	-0.33854	-0.59155	-0.08552	0.008729	0.013783
HIV	107416	71	-1.16425	-2.12695	-0.20155	0.017773	0.024236
on_HIV_meds:HIV	107422	65	1.27346	0.246527	2.300393	0.015079	0.021942

b)

fI_score_i_norm ~ age + sex + edu + health + income + on_HIV_meds * HIV

Condition	Total Controls	Total Cases	Coef	CI Lower	CI Upper	p	pFDR
on_HIV_meds	193546	216	-0.23618	-0.42114	-0.05122	0.012326	0.018488
HIV	193640	122	-0.87971	-1.31846	-0.44096	8.50E-05	0.000165
on_HIV_meds:HIV	193660	102	0.858357	0.344211	1.372502	0.001067	0.001884

c)

max_mem_o_norm ~ age + sex + edu + health + income + on_HIV_meds * HIV

Condition	Total Controls	Total Cases	Coef	CI Lower	CI Upper	p	pFDR
on_HIV_meds	96548	118	-0.15894	-0.42498	0.107092	0.241605	0.26845
HIV	96601	65	-0.36972	-1.73815	0.998696	0.596424	0.61699
on_HIV_meds:HIV	96605	61	0.358623	-1.05957	1.77682	0.620162	0.630673

d)

max_mem_i_norm ~ age + sex + edu + health + income + on_HIV_meds * HIV

Condition	Total Controls	Total Cases	Coef	CI Lower	CI Upper	p	pFDR
on_HIV_meds	74690	64	-0.37589	-0.67986	-0.07193	0.015359	0.021942
HIV	74727	27	-0.63694	-1.59787	0.32398	0.193892	0.2195
on_HIV_meds:HIV	74732	22	0.566112	-0.52941	1.661634	0.31115	0.339436

Table 5: Breakdown of the effects and significance of having HIV, being on HIV treatment, and having HIV and being treated together of performance on fluid intelligence and numeric memory measures as well as the accompanying formula used in the relevant linear regression model. a) shows the effect of each test condition on the online fluid intelligence test. b) shows the effect of each test condition on the in-person fluid intelligence test. c) shows the effect of each test condition on the online numeric memory test. d) show the effect of each test condition on the in-person numeric memory test.

Table 6: The Effect of Inflammatory Diagnosis on Odds Ratio of Developing a Neurodegenerative Disease

a)

AD ~ age + sex + edu + health + income + asthma + DM + obesity + RA + HIV

Condition	Total Controls	Total Cases	With AD & Condition	Coef	CI Lower	CI Upper	p	pFDR
Asthma	386494	46156	915	1.363959	1.264237	1.471548	1.12E-15	5.18E-15
Diabetes Mellitus	390767	41883	1592	2.216483	2.076578	2.365814	1.65E-126	9.90E-125
Obesity	399046	33604	639	1.037698	0.948966	1.134727	0.417144	0.44694
Rheumatoid Arthritis	423286	9364	267	1.455109	1.271925	1.664675	4.66E-08	1.40E-07

b)

PD ~ age + sex + edu + health + income + asthma + DM + obesity + RA + HIV

Condition	Total Controls	Total Cases	With PD & Condition	Coef	CI Lower	CI Upper	p	pFDR
Asthma	386494	46156	439	1.250906	1.123824	1.392358	4.21E-05	8.71E-05
Diabetes Mellitus	390767	41883	589	1.447279	1.312748	1.595596	1.11E-13	4.17E-13
Obesity	399046	33604	324	1.120744	0.991511	1.26682	0.068215	0.081858
Rheumatoid Arthritis	423286	9364	127	1.556052	1.290912	1.875649	3.50E-06	8.75E-06

c)

DD ~ age + sex + edu + health + income + asthma + DM + obesity + RA + HIV

Condition	Total Controls	Total Cases	With DD & Condition	Coef	CI Lower	CI Upper	p	pFDR
Asthma	386494	46156	284	1.164762	1.017495	1.333342	0.027005	0.035224
Diabetes Mellitus	390767	41883	258	1.481045	1.281827	1.711226	9.90E-08	2.70E-07
Obesity	399046	33604	219	1.311484	1.129622	1.522624	0.00037	0.000695
Rheumatoid Arthritis	423286	9364	59	1.105605	0.832421	1.468443	0.48812	0.51381

d)

other_neurodegenertive_disorders ~ age + sex + edu + health + income + asthma + DM + obesity + RA

Condition	Total Controls	Total Cases	With OTH & Condition	Coef	CI Lower	CI Upper	p	pFDR
Asthma	386494	46156	865	1.680181	1.551911	1.819053	1.51E-37	1.81E-36
Diabetes Mellitus	390767	41883	1046	1.846732	1.710108	1.99427	3.75E-55	7.50E-54
Obesity	399046	33604	786	1.830085	1.682707	1.990372	3.37E-45	5.05E-44
Rheumatoid Arthritis	423286	9364	255	2.016457	1.76355	2.305633	1.10E-24	8.24E-24

e)

Asthma

Model	Coef	CI Lower	CI Upper	P	pFDR
AD	1.363959	1.264237	1.471548	1.12E-15	5.18E-15
PD	1.250906	1.123824	1.392358	4.21E-05	8.71E-05
DD	1.164762	1.017495	1.333342	0.027005	0.035224
OTH	1.680181	1.551911	1.819053	1.51E-37	1.81E-36

f)

Diabetes Mellitus

Model	Coef	CI Lower	CI Upper	P	pFDR
AD	2.216483	2.076578	2.365814	1.65E-126	9.90E-125
PD	1.447279	1.312748	1.595596	1.11E-13	4.17E-13
DD	1.481045	1.281827	1.711226	9.90E-08	2.70E-07
OTH	1.846732	1.710108	1.99427	3.75E-55	7.50E-54

g)

Obesity

Model	Coef	CI Lower	CI Upper	P	pFDR
AD	1.037698	0.948966	1.134727	0.417144	0.44694
PD	1.120744	0.991511	1.26682	0.068215	0.081858
DD	1.311484	1.129622	1.522624	0.00037	0.000695
OTH	1.830085	1.682707	1.990372	3.37E-45	5.05E-44

h)

Rheumatoid Arthritis

Model	Coef	CI Lower	CI Upper	P	pFDR
AD	1.455108994	1.271925203	1.664675075	4.66E-08	1.40E-07
PD	1.55605203	1.290912314	1.875648636	3.50E-06	8.75E-06
DD	1.105605027	0.832420807	1.468442962	0.48811974	0.513810253
OTH	2.016456962	1.763549747	2.305633106	1.10E-24	8.24E-24

Table 6: Summary tables of the Effect of Inflammatory Diagnosis on Odds Ratio of Developing a Neurodegenerative Disease. Tables 7a-7d display the model and the results from each model and Tables 7e-7h display the same results but instead are organized by each of the four inflammatory diseases examined in this analysis to align better with the forest plots. a) summary table of the model and results of the effects of inflammatory diagnosis on risk of developing Alzheimer's disease and dementia. b) summary table of the model and results of the effects of inflammatory diagnosis on risk of developing Parkinson's disease. c) summary table of the model and results of the effects of inflammatory diagnosis on risk of developing demyelinating diseases. d) summary table of the model and results of the effects of inflammatory diagnosis on risk of developing other neurodegenerative diseases not accounted for in the other three categories. e) summary table of the results of asthma on the four categories of neurodegenerative disease. f) summary table of the results of diabetes mellitus on the four categories of neurodegenerative disease. g) summary table of the results of obesity on the four categories of neurodegenerative disease. h) summary table of the results of rheumatoid arthritis on the four categories of neurodegenerative disease.

Appendix A: Prompts and Questions

Fluid Intelligence Test

Test Start Prompt:

"In this next test you will have a maximum of two minutes to answer as many questions as possible. Don't spend too long on any one question and you can skip any question if you wish"

Options:

- "1 Begin check"
- "2 I am unable to try this"

Selecting "1 Begin check" will progress the participant to the first question and start the clock.
Selecting "2 I am unable to try this" will progress the participant to the next test and skip the fluid intelligence test.

Question 1: "Add the following numbers together: 1 2 3 4 5 – is the answer?"

Options:

- 13
- 14
- 15
- 16
- 17
- Do not know
- Prefer not to answer

Question 2: "Which number is the largest?"

Options:

- 642
- 308
- 987
- 714
- 253
- Do not know
- Prefer not to answer

Question 3: "Bud is to flower as child is to?"

Options:

- Grow
- Develop
- Improve
- Adult
- Old
- Do not know
- Prefer not to answer

Question 4: "11 12 13 14 15 16 17 18 Divide the sixth number to the right of twelve by three. Is the answer?"

Options:

- 5
- 6

- 7
- 8
- Do not know
- Prefer not to answer

Question 5: “If Truda’s mother’s brother is Tim’s sister’s father, what relation is Truda to Tim?”
Options:

- Aunt
- Sister
- Niece
- Cousin
- No relation
- Do not know
- Prefer not to answer

Question 6: “If sixty is more than half of seventy-five, multiply twenty-three by three. If not subtract 15 from eighty-five. Is the answer?”
Options:

- 68
- 69
- 70
- 71
- 72
- Do not know
- Prefer not to answer

Question 7: “Stop means the same as?”
Options:

- Pause
- Close
- Cease
- Break
- Rest
- Do not know
- Prefer not to answer

Question 8: “If David is twenty-one and Owen is nineteen and Daniel is nine years younger than David, what is half their combined age? ”
Options:

- 25
- 26
- 27
- 28
- 29
- Do not know
- Prefer not to answer

Question 9: “Age is to years as height is to? ”
Options:

- Long
- Deep
- Top
- Meters
- Tall
- Do not know
- Prefer not to answer

Question 10: “150…137…125…114…104… What comes next?”
Options:

- 96
- 95
- 94
- 93
- 92
- Do not know
- Prefer not to answer

Question 11: “Relaxed means the opposite of?”
Options:

- Calm
- Anxious
- Cool
- Worried
- Tense
- Do not know
- Prefer not to answer

Question 12: “100…99…95…86…70… What comes next?”
Options:

- 50
- 49
- 48
- 47
- 46
- 45
- Do not know
- Prefer not to answer

Question 13: “If some flinks are plinks and some plinks are stinks then some flinks are definitely stinks?”
Options:

- False
- True
- Neither true nor false
- Not sure

- Do not know
- Prefer not to answer

Question 14: "If 'Anne' is thirty-four and 'John' is forty-seven, what number is 'that'?"
Options:

- 49
- 50
- 51
- 52
- 53

Note: Question 14 was only given in the online version. The "Do not know" and "Prefer not to answer" options are only present for the in-person version of the test. (*Data-Field 20193*, n.d.; *UK Biobank: Touch-Screen Fluid Intelligence Test*, 2012)

Numeric Memory Test
Test Start Prompt: "In the next game you will be shown a number to remember. The number will then disappear and after a short while, you will be asked to enter it into the number pad on the screen. The number will become longer each time you remember correctly. Press 'Next' for a short video demonstration. The first number will be 2 digits long. When you're ready to begin, touch the 'Next;' button"
Options:

- "Next"
- "Abandon"

Selecting "Next" starts a short video demonstration and then starts the numeric memory task.
Selecting "Abandon" stops the task and proceeds to the next task.

Note: Also present on the screen is a 10-digit keypad but said keypad is only active after the 3000 ms waiting period. The "Next" button is present for the entire task and is used to confirm numeric submission. The "Abandon" button is present for the entire task and can be used to stop the task and proceed to the next at any time.(*Category 100029*, n.d.; *UK Biobank: Touch-Screen Numeric Memory Test*, 2012)