Dietary and Lifestyle Factors of Brain Iron Accumulation and Parkinson's Disease Risk

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Abstract

Purpose: Iron is an essential nutrient which can only be absorbed through an individual's diet. Excess iron accumulates in organs throughout the body including the brain. Iron dysregulation in the brain is commonly associated with neurodegenerative diseases like Alzheimer's disease and Parkinson's Disease (PD). Our previous research has shown that a pattern of iron accumulation in motor regions of the brain related to a genetic iron-storage disorder called hemochromatosis is associated with an increased risk of PD. To understand how diet and lifestyle factors relate to this brain endophenotype and risk of PD we analyzed the relationship between these measures, estimates of nutrient intake, and diet and lifestyle preference using data from UK Biobank.

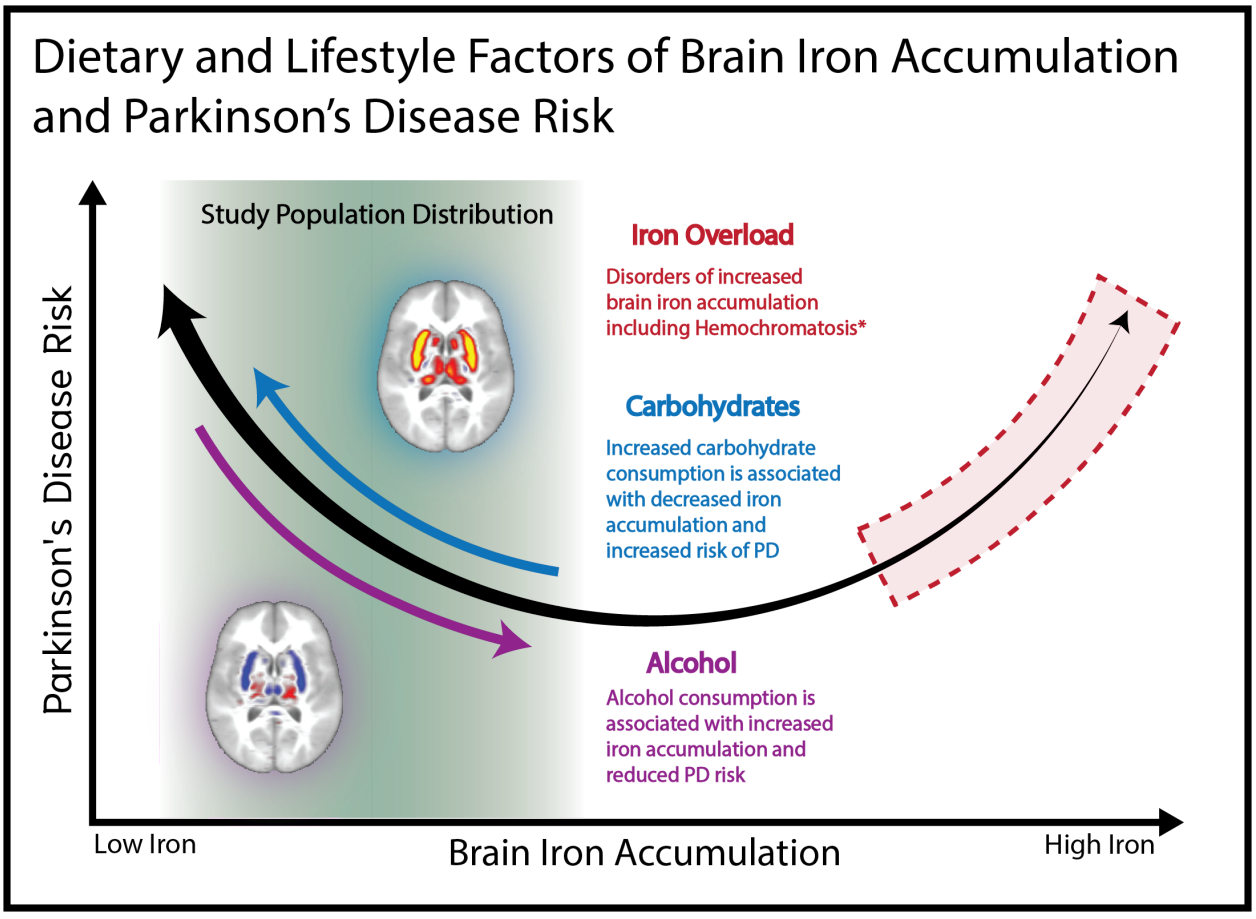
Methods: Using distinct imaging and non-imaging samples (20,477 to 28,388 and 132,023 to 150,603 participants, respectively), we performed linear and logistic regression analyses using estimated dietary nutrient intake and food preferences to predict a) brain iron accumulation score (derived from T2-Weighted Magnetic Resonance Imaging) and b) PD risk. In addition, we performed a factor analysis of diet and lifestyle preferences to investigate if latent lifestyle factors explained significant associations. Finally, we performed an instrumental variable regression of our results related to iron accumulation and PD risk to identify if there were common dietary and lifestyle factors that were jointly associated with differences in brain iron accumulation and PD risk.

Results: We found multiple highly significant associations with measures of brain iron accumulation and preferences for alcohol (factor 7: $t=4.02$, $p_{FDR}=0.0003$), exercise (factor 11: $t=-4.31$, $p_{FDR}=0.0001$), and high-sugar foods (factor 2: $t=-3.73$, $p_{FDR}=0.0007$). Preference for

alcohol (factor 7: t=-5.83, $p_{FDR}<1x10^{-8}$), exercise (factor 11: t=-7.66, $p_{FDR}<1x10^{-13}$), and high sugar foods (factor 2: t=6.03, $p_{FDR}<1x10^{-8}$) were also associated with PD risk. Instrumental variable regression of individual preferences revealed a significant relationship in which dietary preferences associated with higher brain iron levels also appeared to be linked to a lower risk for PD (p=0.004). A similar relationship was observed for estimates of nutrient intake (p=0.0006). Voxel-wise analysis of i) high-sugar and ii) alcohol factors confirmed T2-weighted signal differences consistent with iron accumulation patterns in motor regions of the brain including the cerebellum and basal ganglia.

Conclusion: Dietary and lifestyle factors and preferences, especially those related to carbohydrates, alcohol, and exercise, are related to detectable differences in brain iron accumulation and alterations in risk of PD, suggesting a potential avenue for lifestyle interventions that could influence risk.

Graphical Abstract



*Previous research has established that iron overload in the brain is associated with increased risk of movement disorder[1–3].

Introduction

Nutrition and Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder in the world and is characterized by progressive and potentially disabling difficulties with movement including bradykinesia, resting tremor, and rigidity[4], and causes significant reduction in quality of life[5]. It has a global prevalence of 425:100,000 in individuals 65-75 years old and that prevalence increases to 1,903:100,000 in individuals over 80 years old[6]. Current trends in PD incidence, prevalence, and disease burden show that the global burden of PD has increased[7]

Current understandings suggest that PD is likely caused by an interaction between genetic predisposition and the presence of environmental factors that can accumulate throughout a lifetime[4]. Environmental factors that have been shown to be related to PD risk include: cigarette smoking[8], alcohol consumption[9,10], and caffeine consumption[11–13] which are associated with reduced PD risk, and pesticide or herbicide exposure[8,13,14] and head injuries[13,15,16] which are associated with increased PD risk. In addition to alcohol and caffeine consumption, there is a large body of research into other nutritional and dietary factors that may affect PD risk including vitamin E[17–19], flavinoids[17,20,21], and β-carotene[17,18,22]. It has also been suggested that dairy may increase risk for PD[13]. In general, a high-quality diet is associated with a lower risk of PD[23] and the avoidance of undernutrition and malnutrition has been shown to improve outcomes related to PD[24] including PD mortality[25]. Furthermore, whole dietary patterns like the Mediterranean diet, a diet characterized by a high intake of fresh fruits, vegetables, and whole grains, the use of olive oil as the primary source of fat, moderate consumption of fish and poultry, and low consumption of red meat[26], have been shown to improve outcomes related to PD[27,28].

Dietary preferences can potentially have a significant impact on the gut microbiome. An individual's microbiome is known to be associated with human health[29,30], diet selection[31], nutrient absorption (including iron)[32], and behavior[33]. There is a well-established relationship between the gut microbiome and the pathogenesis of PD as multiple meta-analyses have found significant differences between microbiota demographics between individuals with PD and healthy controls[34,35]. Some developed theories of PD etiology, such as Braak's Hypothesis, state that PD may start in the gut's enteric nervous system before ascending to the brain[36]. These theories are supported by known associations between prodromal gastrointestinal issues and the hallmark PD biomarker, α-synuclein, in the enteric nervous system before PD diagnosis[37].

Iron and Parkinson's Disease

Increased iron accumulation in regions like the substantia nigra and the basal ganglia and dyshomeostasis of iron metabolism are common findings in PD patients[38,39]. Despite this, investigations of dietary iron have yielded mixed results. Overall, dietary iron intake appears not to be associated with the risk of PD, but subgroup analyses in western and in male subpopulations found that dietary iron was associated with a significant increase in PD risk[40]. Furthermore, research related to anemia, a disease that can be caused by low iron intake, has

also found mixed results with some reporting anemia is associated with increased risk of PD[41–44], some reporting the opposite[45], and a recent systematic review reporting a non-significant increase in PD risk and high heterogeneity between studies[46]. On the other end of the spectrum, there is research supporting the idea that iron overload at the cellular level may play a role in the etiology of PD[47]. These seemingly contradictory results may suggest a hormetic relationship and our previous research has identified a hormetic signal[2] - in which both low and high levels of brain iron in motor circuits are associated with increased PD risk when compared with intermediate brain iron levels (see Graphical Abstract).

Motivation

Although previous work has investigated the dietary patterns of PD patients, this does not provide a mechanistic understanding of how dietary differences may be causing differential PD risk profiles. Such an understanding is important for not only developing targeted effective treatment but may also provide insight as to potential pharmaceutical avenues for therapies. To bridge this gap, in the current study, we aim to investigate brain iron differences related to dietary and lifestyle factors linked to PD risk. We aim to achieve this by building upon previous work which identified a brain iron-specific biomarker of PD which we refer to as the *hemochromatosis brain PVS*. This biomarker aggregates iron accumulation signals from T2-w brain MRI scans from motor regions including the cerebellum, thalamus, caudate, and putamen (Supplementary Figure 1). Our analysis of this novel biomarker revealed that it is strongly influenced by genetic mutations and that lower brain iron levels are related to higher PD risk[2]. In the current study, we aimed to understand how dietary and lifestyle factors are related to this iron-specific biomarker and how this is jointly related to PD risk. This can help uncover how modifiable dietary and lifestyle preferences are related to PD risk and how detected associations appear to be mediated by central iron levels as captured by the hemochromatosis brain PVS.

Methods

The Hemochromatosis Brain PolyVoxel Score

C282Y homozygosity is responsible for 95% of cases of hemochromatosis[48] - a disorder of iron metabolism that can eventually lead to iron overload and other complications[49]. The primary imaging measure in this analysis is a PolyVoxel Score (PVS) based on a classifier trained in UK Biobank to distinguish between individuals with and without C282Y homozygosity from T2-weighted MRI brain scans, which is known to be sensitive to iron in the brain[50]. This process is described in greater detail by Loughnan et. al. 2022[2]. Broadly, this PVS captures a univariate continuum of iron accumulation in brain regions including the cerebellum, thalamus, caudate, putamen, pallidum, red nucleus, substantia nigra, and the subthalamic nucleus. Contributions to the PVS vary based on classifier weightings and the area of the brain region (Supplementary Figure 1). Previous research has shown that this Hemochromatosis Brain PVS

is strongly associated with genes related to iron metabolism and predicts PD risk in independent data[2], with lower brain iron being related to greater PD risk in the general population.

UKBiobank Measures

Genotypes, MRI scans, demographics, diagnoses, and diet and lifestyle measures were obtained from the UK Biobank (URLs) under accession number 27412, excluding 206 participants who withdrew their consent. All participants provided electronically signed informed consent and the study was approved by the UK Biobank Ethics and Governance Council. The recruitment period for participants was from 2006 to 2010, and participants had to be 40-69 years old during this period to be included in the sample. Analyses were run in September 2023. Demographics on the cohorts used in these analyses can be found in Table 1.

Table 1: Sample Demographics

			Imaging			Non Imaging	
Preferences	**Sample Size:**		28,388	**Sample Size:**		132,023
	Mean Age (SD)		64.13 (7.45)	**Mean Age (SD)**		66.65 (7.70)
	# Female (%)		14,871 (52.38)	**# Female (%)**		74,360 (56.32)
	# PD Cases (%)		45 (0.16)	**# PD Cases (%)**		456 (0.35)
	Max Income	**Category**	**%**	**Max Income**	**Category**	**%**
		<£18,000	6.47		<£18,000	13.29
		£18,000-£30,999	18.86		£18,000-£30,999	23.29
		£31,000-£51,999	30.22		£31,000-£51,999	28.97
		£52,000-£100,000	33.40		£52,000-£100,000	26.23
		>£100,000	11.05		>£100,000	8.22
Nutrients	**Sample Size:**		20,477	**Sample Size:**		150,603
	Mean Age (SD)		64.06 (7.56)	**Mean Age (SD)**		58.63 (8.05)
	# Female (%)		10,545 (51.50)	**# Female (%)**		80,595 (53.51)
	# PD Cases (%)		37 (0.18)	**# PD Cases (%)**		979 (0.65)
	Max Income	**Category**	**%**	**Max Income**	**Category**	**%**
		<£18,000	5.97		<£18,000	15.88
		£18,000-£30,999	18.83		£18,000-£30,999	24.79
		£31,000-£51,999	30.52		£31,000-£51,999	28.37
		£52,000-£100,000	33.31		£52,000-£100,000	23.81
		>£100,000	11.38		>£100,000	7.15

Table 1: Demographic distributions of test samples separated into four groups based on whether they are in the imaging or non-imaging cohort and the preference or nutrient analyses.

Nutrient and Preference Data

Nutrient data (Category 100117) consisted of 63 estimates of nutritional food components based on responses to Oxford WebQ dietary assessment[51–53]. For participants with more than one instance of nutritional estimates, the mean value of nutritional estimates was used in our analysis. All values were z-score normalized before analysis.

The preferences data (Category 1039) used in this study were gathered from a web-based questionnaire developed and designed to reflect preferences for many foods and activities. The questionnaire included 150 items measured on a nine-point scale from 'extreme dislike' to 'extreme like' designed to cover a range of sensory aspects as well as variable food groups[54]. After noninformative values ('Never tried' or 'Prefer not to answer') were removed, 6 columns were removed for having greater than 10% missingness across the population (preferences for bell peppers, capers, globe artichoke, going to the gym, pollock, and soy milk), and 3,459 participants were removed for having individual missingness of greater than 10%, any additional missing values from the remaining data were imputed from the median value for that variable, and the data was z-score normalized.

Parkinson's Disease Diagnosis

PD and related parkinsonism diagnosis were extracted from ICD10 diagnosis data (Data-Field 41270) and included the following diagnosis codes: F02.3, G20, G21.0, G21.1, G21.2, G21.3, G21.4, G21.8, G21.9, G22. Individuals with any one or more of these diagnoses were categorized as having been diagnosed with PD.

Statistical Analyses

Analyses were performed using generalized linear regressions in Python using statsmodels version 0.14.0. All analyses were controlled for sex (Data-Field 31), the maximum reported pre-tax income category (Data-Field 738), and the top 10 genetic principal components (Data-Field 22009) to account for ancestral and global genetic factors. Analyses that involve the Hemochromatosis Brain PVS additionally controlled scanner for MRI study site (Data-Field 54) to account for differences in imaging equipment. All analyses controlled for age; imaging analyses controlled for the age at the time of the scan (retrieved from Data-Field 20216), disease analyses of nutrition and preferences were corrected for age which was calculated from when the surveys were completed (Data-Field 105010 and 20750 respectively). P-values within each analysis were corrected using the multitest correction from stats models version 0.14.0 using Benjamini/Hochberg FDR and Bonferroni correction methods.

Lower dimensional factors were generated in Python using Educational Testing Service's Factor_Analyzer package (version 0.5.0) which calculates factors by minimizing residuals[55,56]. Factors were varimax rotated for interpretability. All other parameters were set to their default.

To calculate robust standard errors across our data we performed 10,000 bootstrap iterations[57] of our regression analyses for the relationships between estimated nutrient intake and the Hemochromatosis Brain PVS, estimated nutrient intake and odds ratio for PD, food and

lifestyle preferences and the Hemochromatosis Brain PVS, food and lifestyle preferences and odds ratio for PD, the lower-dimensional preference space and the Hemochromatosis Brain PVS, and the lower-dimensional preference space and the odds ratio for PD.

Brain Association Maps of Dietary Factors

Brain association maps derived from T2-weighted imaging, an imaging measure known to be sensitive to iron[50], were created to visualize the dietary factors that were significantly associated with PD risk and the hemochromatosis brain PVS. To achieve this, we performed voxel-wise univariate regression using all 28,388 individuals from our preference imaging subsample (Table 1), predicting T2-weighted signal from dietary factors 2 (sweets) and 7 (alcohol), separately. All images were pre-processed and registered to a standard space using methods described elsewhere, Loughnan et. al. 2022[58]. Covariates of age at scan, sex, scanner, and top 10 principal components of genetic ancestry were corrected for by pre-residualizing images before model fitting. For visualization purposes we plotted voxel-wise beta effects from these models after passing a smoothing kernel with a full width at half maximum of 2.82 units. Additionally, we restricted plotting beta values to those that were used to compute the hemochromatosis brain PVS and we show the PVS weights for reference.

Results

Nutrient Analyses

Estimated Nutrient Intake and Brain Iron

To understand how estimated nutrient intake might be associated with the pattern of iron accumulation captured by the hemochromatosis brain PVS we performed linear regressions in our imaging sample (N=20,477). We identified several FDR-corrected significant negative associations between the hemochromatosis brain PVS and starch (t=-3.21, p_{FDR}=0.018), carbohydrates (t=-3.27, p_{FDR}=0.013), riboflavin (t=-3.27, p_{FDR}=0.013), vegetable protein (t=-3.31, p_{FDR}=0.013), lactose (t=-3.36, p_{FDR}=0.013), and maltose (t=-3.74, p_{FDR}=0.012) (Figure 1A) - indicating higher consumption of these nutrients is linked with lower levels of brain iron in motor regions captured by the PVS. A full numeric summary of these results can be found in Supplementary Table 1.

Estimated Nutrient Intake and Parkinson's Disease Risk

To examine the relationship between estimated nutrient intake and risk of developing PD we performed a linear regression in our non-imaging sample (N_{Case}=979 and $N_{Control}$=149,624). We found estimated intake of energy beverages (t=-2.87, p_{FDR}=0.037) and alcohol (t=-4.56, p_{FDR}<0.001) were negatively associated with PD risk. Estimated higher consumption of free sugar (t=2.73, p_{FDR}=0.044), fructose (t=2.82, p_{FDR}=0.038), sucrose (t=3.06, p_{FDR}=0.023), non-milk extrinsic sugars (t=3.19, p_{FDR}=0.018), glucose (t=3.26, p_{FDR}=0.017), total sugar (t=3.45,

p_{FDR}=0.012), and carbohydrates (t=3.46, p_{FDR}=0.012) were all positively associated with PD risk (Figure 1B). A full numeric summary of these results can be found in Supplementary Table 2.

Estimated Nutrient Intake, Brain Iron and Parkinson's Disease Instrumental Variable Regression

To understand the joint effect of nutrients on brain iron accumulation, as captured by the PVS, and PD risk we performed instrumental variable regression on the analyses described above. This instrumental variable regression was performed on statistics that were generated in non-overlapping samples (see Table 1). As Figure 2C shows we identified a significant negative association (r=-0.421, p=0.0006) between a) nutrient intake and brain iron accumulation and b) nutrient intake and PD risk. This suggests that nutrient mediated increases in brain iron are linked with lower PD risk - the direction of this effect is in line with previous findings in normative aging individuals[2]. We note that many high sugar related items simultaneously display a pattern of increased PD risk and decreased brain iron accumulation (as captured by the PVS) - see upper left quadrant of Figure 1C.

Figure 1: Nutrient Analysis

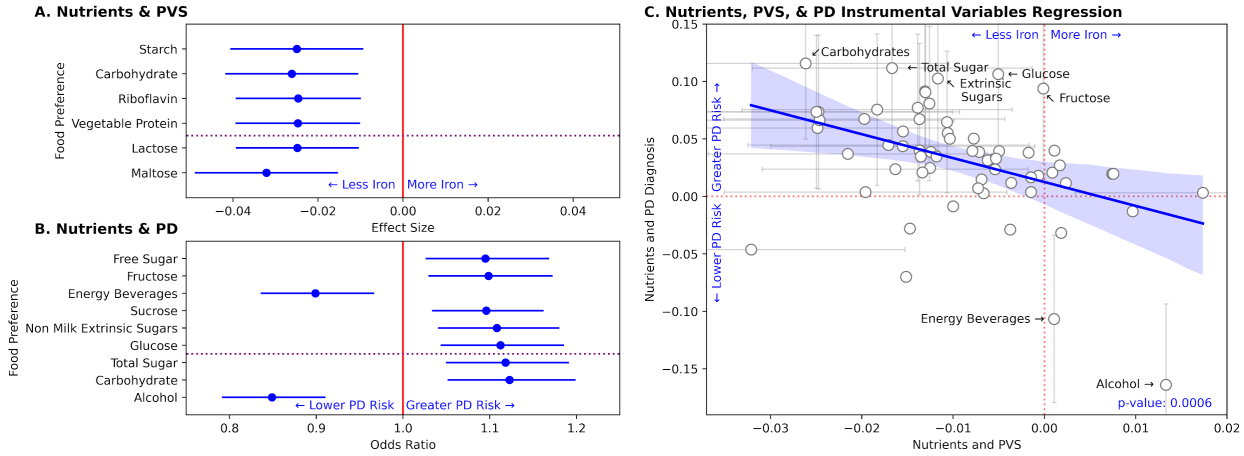


Figure 1: (A) Forest plot showing the FDR significant associations between estimated nutrient intake and the hemochromatosis brain PVS. Results below the dotted line are additionally Bonferoni Significant. A full numeric summary of all the results analyzed can be found in Supplementary Table 1. (B) Forest plot showing the FDR significant associations between estimated nutrient intake and odds ratio for developing PD. Results below the dotted line are additionally Bonferoni Significant. A full numeric summary of all the results analyzed can be found in Supplementary Table 2. (C) Scatter plot of the instrumental variable regression between a) estimated nutrient intake and the hemochromatosis brain PVS and b) estimated nutrient intake and PD risk. The top seven nutrients furthest from the origin are annotated. Instrumental variable regression revealed a significant negative relationship, highlighting that nutrients increasing brain iron levels were related to decreased PD risk. Error bars are included for results that are significant on a given axis.

Preference Analyses

Preference Level Analysis

To understand how food and lifestyle preferences may be related to brain iron accumulation and PD risk we fit a series of linear and logistic regression models associating each diet/lifestyle preference with the hemochromatosis brain PVS and PD risk. Notably we found significant positive associations between the hemochromatosis brain PVS and preferences for alcoholic beverages, especially wine (red: p_{FDR}<1e-8; white: p_{FDR}<1e-5), and red meat (p_{FDR}<0.001). There were also significant negative associations between the hemochromatosis brain PVS and preferences for sweet foods (biscuits: p_{FDR}=0.004; cake: p_{FDR}=0.004), exercise (bicycling p_{FDR}=0.010; exercising alone: p_{FDR}=0.015), and cereal grains (corn flakes: p_{FDR}<0.001; porridge: p_{FDR}=0.004). There were significant associations between increased PD risk preferences for sweet foods as category (p_{FDR}<1e-4) as well as individual sweet food preferences (sweet coffee house drinks: p_{FDR}<1e-5; cake icing: p_{FDR}<1e-4) and between reduced PD risk and preferences for alcoholic beverages (spirits: p_{FDR}<10e-7; red wine: p_{FDR}<10e-6), exercise (taking the stairs: p_{FDR}<1e-24; working up a sweat: p_{FDR}<1e-12), and vegetable as a category and other produce items (vegetables: p_{FDR}<1e-7; salad leaves: p_{FDR}<1e-13).

A preference level exploration of the results can be found in the Supplementary Note, and are displayed graphically in Supplementary Figures 2 and 3. A full numeric outline of all of the results of these regressions can be found in Supplementary Table 3 and 4.

Dietary/Lifestyle Preferences, Brain Iron and Parkinson's Disease Instrumental Variable Regression

To understand the joint effect of dietary/lifestyle preferences on brain iron accumulation and PD risk we performed an instrumental variable regression from the results from the previous two sections. In Figure 2A, we see, when restricting to dietary preferences, we find that PVS and PD results display a significant negative association (r=-0.247, p=0.004) - indicating that preference for food and drinks linked with higher levels of brain iron appear to also be associated with lower PD risk. Across dietary and non-dietary preferences we do not find a significant relationship (r=-0.129, p=0.125). The difference between these two results is due to the inclusion/exclusion of exercise preference measures (see red points in Figure 3 C) - which have a significant negative association with the PVS and PD risk. As described above we believe that in the association between PD risk a lack of preference for exercise is likely driven by reverse causation hence our choice to distinguish between dietary and non-dietary preferences for this analysis. In Figure 2A, we see a broad pattern emerging within dietary measures where a preference toward sweet and high-carbohydrate foods are related to lower PVS (lower iron levels in motor circuits) and higher PD risk, while a preference for alcohol is associated both with higher PVS (higher iron levels in motor circuits) and higher PD risk.

Factor Analysis of Preferences

Due to the high correlation structure in food preferences (Supplementary Figure 4) and the multiple measures (144 in total), we performed factor analysis to identify interpretable latent factors. We found 20 factors accounted for approximately half (49.77%) of the total variance in the preference space - Supplementary Figure 5. A summary of each Factor's top loadings as well as an interpretive description of each factor can be found in Table 2. A dendrogram showing the correlation between the pre-reduced preferences can be found in Supplementary Figure 4 and their full loadings in the reduced preference space can be found visually in Supplementary Figure 6 and numerically in Supplementary Table 5. Based on the factor analysis a large amount of variance in preference space (28.51%) is encapsulated through an individual's preference for red meat (factor 1: 11.77% variance explained), sweets (factor 2: 8.20%), fruits (factor 3: 4.43%), and fish (factor 4: 4.11%).

Table 2: Factor Loadings

Factor	Top Preferences (Loading)	Interpretation	Variance Explained (%)	Cumulative Variance Explained (%)
Factor 1	red meat (0.844), beef steak (0.790), barbequed or grilled meat (0.765)	Red Meat	11.77	11.77
Factor 2	cake (0.794), sweet foods (0.756), biscuits (0.709)	Sweets	8.20	19.97
Factor 3	fruit (0.717), plums (0.672), oranges (0.577)	Fruit	4.43	24.40
Factor 4	haddock (0.743), baked steamed fish (0.735), mackerel (0.721)	Fish	4.11	28.51
Factor 5	spicy foods (0.886), chili pepper (0.790), burn of spicy foods (0.746)	Spicy Foods	2.30	30.81
Factor 6	cabbage (0.711), cauliflower (0.685), brussel sprouts (0.641)	Brassica Vegetables	2.00	32.81
Factor 7	spirits (0.648), whisky (0.604), red wine (0.578)	Alcohol	1.88	34.68
Factor 8	avocados (0.509), aubergine (0.465), asparagus (0.443)	Savory Fruits & Vegetables	1.74	36.42
Factor 9	hard cheese (0.596), soft cheese (0.589), blue cheese (0.468)	Cheese	1.54	37.96
Factor 10	tea with sugar (-0.732), coffee with sugar (-0.731), coffee without sugar (0.541)	Unsweetened Tea and Coffee	1.42	39.38
Factor 11	working up a sweat (0.753), exercising alone (0.529), bicycling (0.497)	Exercise	1.30	40.68
Factor 12	salty foods (0.701), adding salt to foods (0.526), salty pretzels (0.463)	Salty Foods	1.24	41.93
Factor 13	green olives (0.767), black olives (0.753), gherkins (0.340)	Olives	1.23	43.15
Factor 14	whole grain breakfast cereal (0.481), brown rice (0.351), porridge (0.350)	Cereal Grains	1.14	44.30
Factor 15	potatoes (0.377), chips french fries (0.370), pasta (0.366)	Potatoes and Carbs	1.04	45.34
Factor 16	salad dressing (0.504), mayonnaise (0.419), vinegar (0.370)	Condiments	0.99	46.33
Factor 17	whole milk (0.496), cream (0.416), dairy products (0.384)	Dairy	0.93	47.27
Factor 18	chicken (-0.337), roast chicken (-0.319), herring (0.294)	Fish and Not Chicken	0.87	48.14
Factor 19	orange juice (0.501), apple juice (0.399), grapefruit (0.253)	Juices	0.85	48.99
Factor 20	diet fizzy drinks (0.356), corn flakes (0.222), regular nondiet fizzy drinks (0.204)	Fizzy Drinks and Unknown	0.78	49.77

Table 2: Summary Table of the lower-dimensional factor space. Visual Factor loadings can be found in Supplementary Figure 6. A full numeric summary of all factor loadings can be found in Supplementary Table 5.

Dietary/Lifestyle Preference Factors and Brain Iron

To formalize and confirm the results identified in the preference level analysis we performed linear regressions in our imaging sample (N=28,388) predicting the PVS from the first 20 preference factors. All of the results from the individual-level analysis were recapitulated namely the positive association between alcohol (factor 7: t=4.02, p_{FDR}<0.001), and red meat (factor 1: t=4.73, p_{FDR}<1e-4) and the negative associations for cereal grains (factor 14: t=-2.54, p_{FDR}=0.012), sweets (factor 2: t=-3.73, p_{FDR}<0.001), and exercise (factor 11: t=-4.31, p_{FDR}<0.001).

We found additional positive associations between the hemochromatosis brain PVS and savory fruit and vegetables (factor 8: t=4.86, p_{FDR}<1e-4) and salty foods (factor 12: t=3.36, p_{FDR}=0.001). We found additional negative associations between the hemochromatosis brain PVS and fizzy drinks and unknown (factor 20: t=-4.00, p_{FDR}<0.001); brassica vegetables (factor 6: t=-2.74, p_{FDR}=0.008); and preference for fish and a dislike for chicken (factor 18: t=-2.36, p_{FDR}=0.018).

A graphical representation of these results can be found in Figure 2B and a full numeric summary of all the relationships between preferences and the hemochromatosis brain PVS can be found in Supplementary Table 6.

Dietary/Lifestyle Preference Factors and Parkinson's Disease Risk

Using the same top 20 preference factors we fit models to predict PD risk in our non-imaging sample (N_{Case}=456, $N_{Control}$=131,567). Again we were able to recapitulate the results from the individual item level analysis namely increased PD risk was associated with a lower preference of exercising (factor 11: t=-7.66, p_{FDR}<1e-12) (likely driven by reverse causation), lower alcohol preference (factor 7: t=-5.82, p_{FDR}<1e-7), lower vegetable preference (factor 6: t=-6.11, p_{FDR}<1e-8), fruits (factor 3: t=-2.98, p_{FDR}=0.018), and higher sweet preference (factor 2: t=6.03, p_{FDR}<1e-8). In addition, we found that increased PD risk was associated with a lower preference for: potato products and carbohydrates (factor 15: t=-4.03, p_{FDR}<0.001); a higher preference for: juices (factor 19: t=3.89, p_{FDR}<0.001), fizzy drinks and unknown (factor 20: t=3.23, p_{FDR}=0.002), and olives (factor 13: t=2.35, p_{FDR}=0.018).

A forest plot of these results can be found in Figure 2C and a full numeric summary of all the relationships between preferences and the hemochromatosis brain PVS can be found in Supplementary Table 7.

Figure 2: Preference Analysis

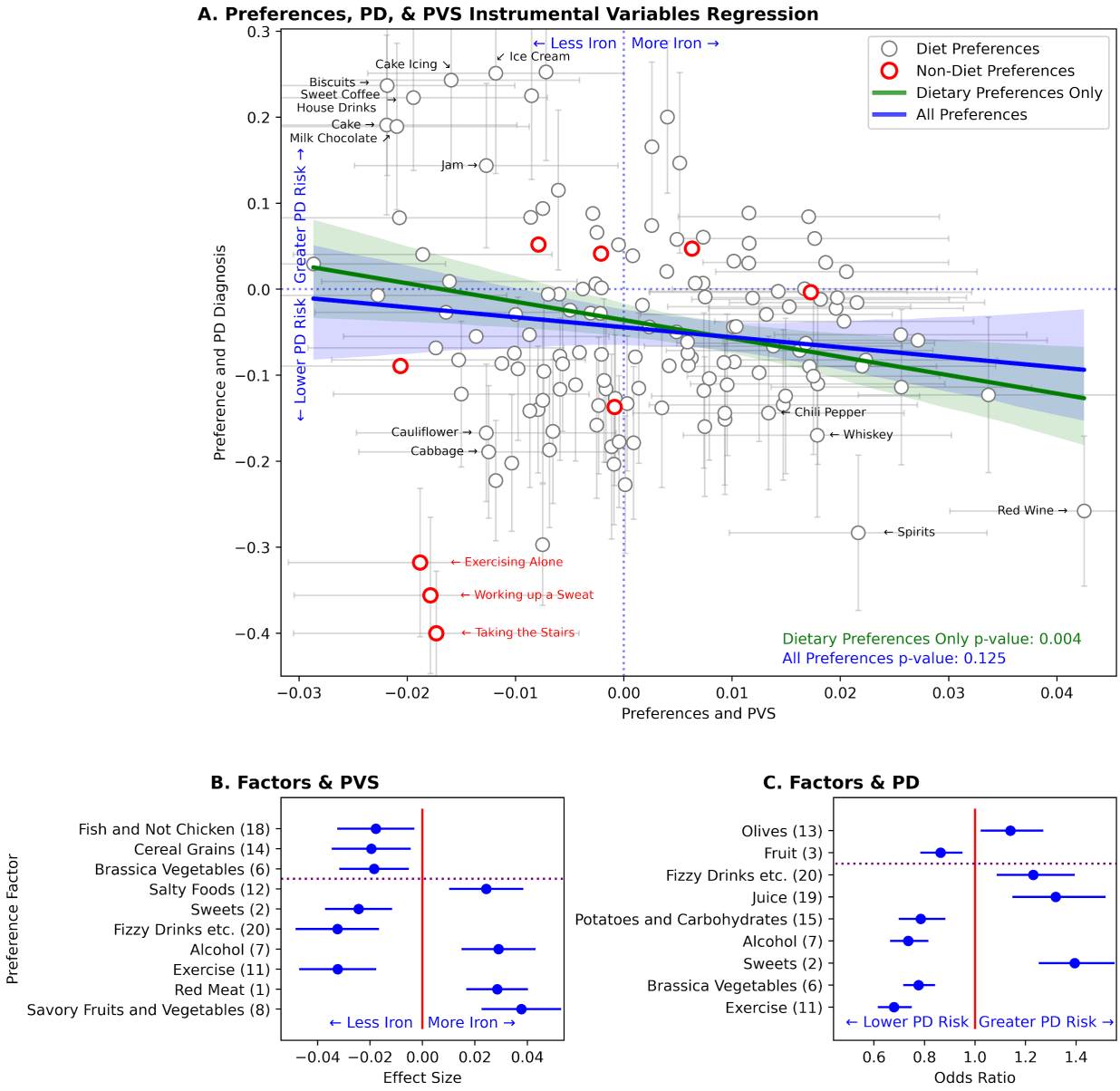


Figure 2: (A) Scatter plot of the instrumental variable regression between preferences and the hemochromatosis brain PVS and preferences and the odds ratio of developing PD. Error bars are shown for factors that are significantly associated with both PD and the hemochromatosis brain PVS. Of those factors, the top sixteen preference factors furthest from the origin are annotated. Regression lines show the relationship of data. (B) Forest plot showing the FDR associations between preference factors and the hemochromatosis brain PVS. Results below the dotted line are additionally Bonferoni Significant. A full numeric summary of all the results analyzed can be found in Supplementary Table 6. (C) Forest plot showing the FDR associations between preference factors and odds ratio of developing PD. Results below the dotted line are additionally Bonferoni Significant. A full numeric summary of all the results analyzed can be found in Supplementary Table 7.

Brain Association Maps of Sweet and Alcohol Factors

Brain association maps, derived from T2-weighted imaging, were created to visualize dietary factors 2 (sweets) and 7 (alcohol). These factors were selected because they were significantly and individually associated with both PD risk and the hemochromatosis brain PVS.

Factor 2 (sweets) was found to be associated with increased risk of PD and decreased hemochromatosis brain PVS. These findings are consistent with our brain association maps of factor 2 that show T2-weighted MRI imaging hyperintensities in movement related regions including basal ganglia and cerebellar regions indicating decreased iron accumulation (Figure 3).

On the other end of the spectrum Factor 7 (alcohol) was found to be associated with decreased PD risk and increased hemochromatosis brain PVS. The brain association map of factor 7 showed T2-weighted MRI hypointensities in movement related regions including the cerebellum and basal ganglia (Figure 3).

Figure 3: Sweets and Alcohol Association Maps Brain Images

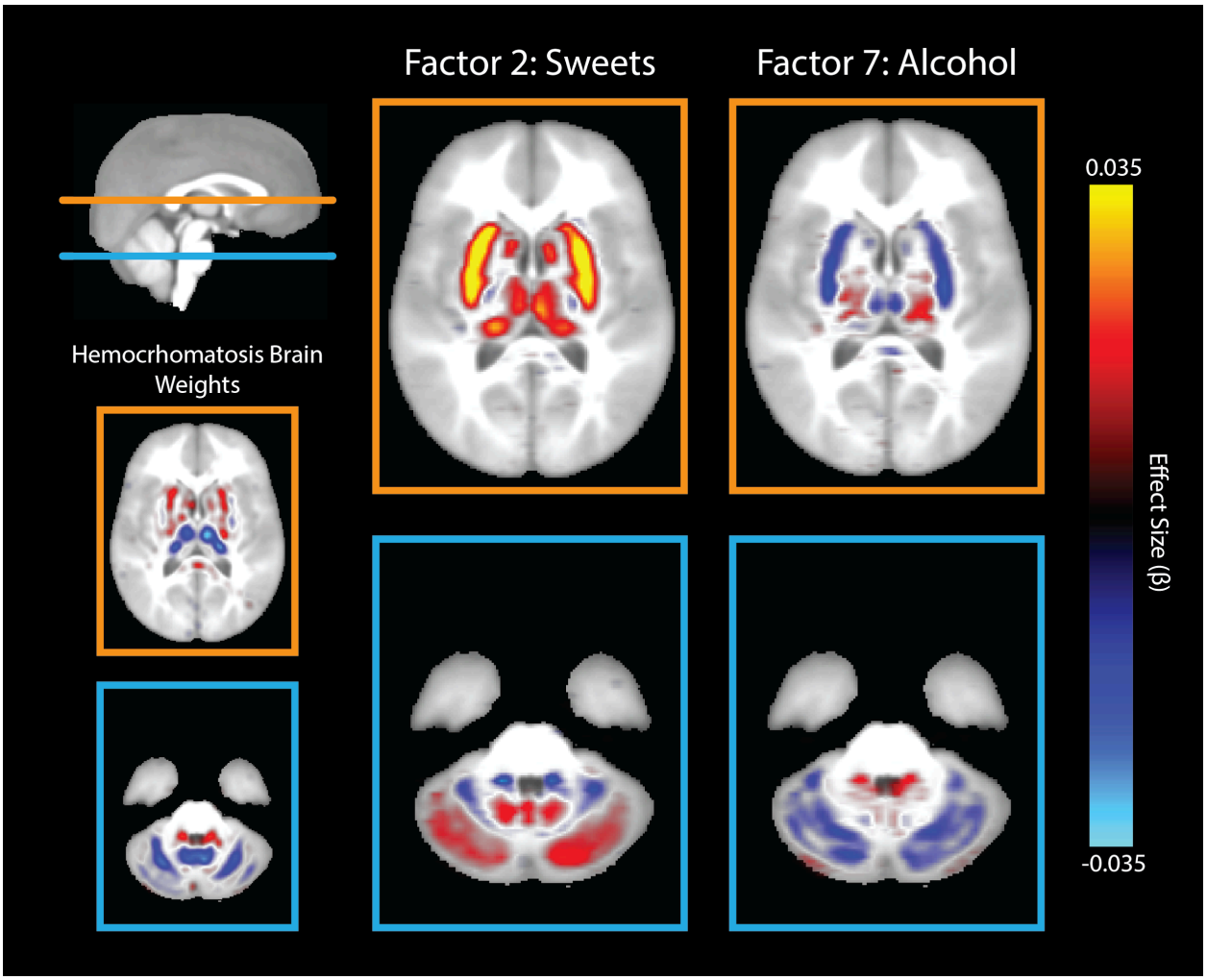


Figure 3: Voxel-wise association map of T2-w signal intensity with preference for i) factor 2 (sweets) and ii) factor 7 (alcohol). Voxels are restricted to those which have non-zero weights for

Hemochromatosis PVS (Supplementary Figure 1). The hemochromatosis brain weights indicate the relative weighting that intensities in different regions of the brain contribute to the calculation of the hemochromatosis brain PVS with red regions representing positive weightings and blue regions representing negative weightings – expressed in arbitrary units (Supplementary Figure 1). In our brain association maps, beta effects are displayed, orange regions represent increased T2-weighted intensities, consistent with lower iron concentrations, for individuals with a higher scoring in on the spectrum of a given dietary factor and blue regions represent decreased T2-weighted intensities, consistent with higher iron concentrations.

Discussion

These findings demonstrate that dietary preferences toward alcohol, and fresh produce consumption are associated with reduced risk of PD, and dietary intake and preferences toward sweet foods are associated with increased risk of PD. Furthermore, our instrumental variable regression analysis revealed a significant relationship in which nutrients and dietary preferences linked with lower brain iron levels were associated with increased PD risk. This is consistent with previous findings that higher brain iron levels in motor regions are associated with lower PD risk in typical individuals[2].

These results may seem counter to existing attempts to use chelation therapy. As previously mentioned iron dysregulation is a common feature of PD[39], and therapeutic research has turned its attention toward chelation, a method of pharmacologically sequestering metals, as a potential treatment avenue for PD[59,60] and other neurodegenerative conditions[61]. When examined as a treatment for Pantothenate kinase-associated neurodegeneration, a genetic disorder related to increased brain iron accumulation and movement related symptoms, deferiprone was shown to reduce brain iron concentration and lead to an insignificant reduction in disease progression[62]. Trials of deferiprone, an iron chelator, for PD have had mixed results. Trials have shown reduced iron accumulation in areas of the brain[63,64], but results related to reduction to symptoms severity have either shown insignificant reduction in symptom severity compared to controls[63] or worsening symptoms compared to controls[64].

As iron is required for the rate limiting enzyme, tyrosine hydroxylase, in dopamine production it was suggested that the negative results from this trial could have been a result of inhibited dopamine synthesis due to iron reduction[64]. These results are consistent that iron concentrations that are both too high and too low can lead to worse outcomes for individuals with PD and means that our results may explain recent failed iron chelation clinical trials in the treatment of this disorder. More work will need to be done to find treatments that can both limit the negative impacts of excessive iron accumulation in the brain while maintaining a large enough labile iron pool for proper cellular functioning.

Sugars and Carbohydrates

Across all our analysis we found carbohydrate related factors in both preferences and estimated nutrient intake were associated with decreases in the hemochromatosis brain PVS, a measure of brain iron, and an increase in PD risk. Decreases in brain iron in regions associated with the hemochromatosis brain were also confirmed by our association maps of Factor 2 (sweets) and T2-weighted imaging, where we found hyperintensities in movement related regions of the brain indicating reduced iron accumulation in those areas.

There is a well-established relationship between carbohydrates and iron though the direction and mechanism of the relationship is unclear. Literature suggests a bidirectional effect with: a) high iron influencing glycemic regulation and increasing the risk of type 2 diabetes mellitus (T2DM), a disease primarily caused by acutely impaired glycemic regulation, and b) oral glucose ingestion causing changes in iron metabolism factors resulting in peripheral iron

falling[65,66]. The effects we see in our analysis about association between iron and measures of carbohydrates may be mediated by the effect of iron on glycemic control via its impact on insulin sensitivity. Iron may play a role in the development of insulin resistance, as measures of iron have been shown to be associated with insulin sensitivity[65]. Existing literature also shows that glycemic dysregulation and related diseases are related to increased PD risk and worse PD outcomes[67–69]. This may be partially caused by a shared dysregulation of both glycemic control and iron metabolism. Imaging studies have found that individuals with T2DM, a condition of dysregulated glycemic regulation, show imaging features that indicate increased brain iron accumulation compared to controls[70–72]. The findings related to T2DM may generalize to a normative sample of individuals with dysregulated carbohydrate intake or subacutely dysregulated glucose metabolism. These findings support the bidirectional influence that glucose and iron metabolism have on one another[65,73], and future research should work to disentangle the relationship between glucose and iron and work to see how their influences on one another may impact disease pathology.

The sharded dysregulation of iron and glucose metabolism may also incidentally explain why an occasional manifestation of iron deficiency is pika which includes a desire to eat carbohydrate-rich foods like starch, uncooked rice, and uncooked pasta among other things[74]. Dysregulated iron metabolism could lead to maladaptive cravings for carbohydrates which may jointly dysregulate glucose and iron metabolism leading to a feedback loop. The presence of both metabolic glucose dysregulation[75] and iron dysregulation[39] in and their known interrealtionship[65,73] may provide new avenues for treatment.

Sugars and carbohydrates may also impact PD risk and iron accumulation at the level of the microbiome. A strong dietary preference for sweets and carbohydrates can elevate levels of pro-inflammatory, opportunistic pathogenic bacteria in the gut, which is strongly linked to an increased risk of PD[76]. This dietary pattern also correlates with α-synuclein pathology, which can emerge from a pro-inflammatory, dysbiotic gut state[77]. There is evidence that aggregated α-synuclein, originating in the enteric nervous system, can travel to the brainstem[78,79] and contribute to ferroptosis, cell toxicity related to iron-dependent lipid peroxide accumulation, in the brain[80].

Alcohol

We also found that nutritional estimates of alcohol intake and preferences related to alcohol (preferences for red wine, spirits, etc.) were associated with greater brain iron, as evidenced by the hemochromatosis brain PVS, and decreased PD risk. Increases in brain iron in regions associated with the hemochromatosis brain were confirmed by our association maps of Factor 7 (alcohol) and T2-weighted imaging, where we found hypointensities in movement related regions of the brain indicating iron accumulation in those areas.

As mentioned in the introduction there is an extensive and consistent literature suggesting that moderate alcohol consumption is associated with decreased risk of PD[9,10], with one meta-analysis suggesting a U-shaped risk profile with the most beneficial associations seen with consumption of 26-35 g/day of alcohol[9]. Other studies have also found that both abstinence from alcohol and excessive consumption were associated with increased risk for dementia[81],

indicating that a hormetic risk profile for alcohol consumption may be an aspect of multiple neurodegenerative disorders.

There also exists significant literature that alcohol consumption impacts iron absorption and accumulation. Alcohol can lead to increased iron accumulation in the brain[82]. Alcohol is known to down-regulate the synthesis of hepcidin, an iron regulating hormone, and, with excessive consumption, is able to cause iron overload in otherwise hemodynamically typical individuals[83–86]. Specifically in individuals with hereditary hemochromatosis alcohol consumption is broadly associated with worse health outcomes[87,88]. Similar effects are observed in other iron overload disorders like beta-thalasemia[89]. On the other end of the spectrum, in genetically typical individuals the moderate consumption of alcohol (fewer than 2 drinks a day) is associated with decreased risk of iron deficiency and its associated anemia[86] and anemia has been suggested to be associated with increased PD risk in some[41–44] but not all[45] previous studies. Measures of iron in the brain has also been suggested to have a hormetic, U-shaped association with PD risk[2]. Taken together with the literature of a U-shaped relationship between alcohol consumption and PD risk, our results suggest that this surprising relationship could potentially be explained by the effect alcohol has on iron metabolism.

Exercise

We found that preferences related to exercise are significantly associated with reduced PD risk and reduced brain iron as measured with the hemochromatosis brain PVS. This result is discordant with the trends observed for estimated nutrient intake and dietary preferences where items that were linked to increases in brain iron were related to decreases in PD. We suspect that this discordant result may be spurious due to the negative exercise and PD association being likely driven by reverse causation - e.g. the core motor deficits of the disease make physical activity less desirable - hence the distinction between dietary and non-dietary measures in our instrumental variable regression. Nevertheless, the association between exercise and brain iron levels in motor regions appears to be consistent with other research indicating exercise can modulate iron stores in the body by both changing internal rates of hemolysis[90] as well as modulating hepcidin[91]. Although we believe reverse causation explains the discordant result of exercise between brain iron and PD risk, it is possible that our findings are not a result of reverse causation. Indeed, moderate to high levels of activity were found to be associated with a lower risk for developing PD later in life and individuals with PD who report higher physical activity were found to have slower symptom progression and better quality of life[92,93]. Population analyses in UKBiobank have also found that sedentary behavior is associated with an increased incidence of dementia[94]. Though in these studies it is difficult to account for survivorship bias. Animal models of Alzheimer's disease have found that treadmill exercise helps to alleviate disease-related iron dysregulation as well as disease-induced cognitive decline and neuronal death[95]. More research is needed to understand the direction of causation of effects and the mechanisms behind the apparent benefit of physical exercise for PD patients.

Additional Factors that Influence PD Risk

Analysis showed that preferences for vegetables and fruits were associated with decreased risk of PD, and no significant association with the PVS. These results are consistent with the findings from previous studies that found high fruit and vegetable intake is related to lower PD risk[96,97]. High consumption of fruits and vegetables could explain a portion of the PD-protective effects seen in the mediterranean diet[26–28]. We believe that our results are consistent with a beneficial effect of vegetable and fruit intake on PD risk that does not converge on altered central iron levels and may instead result from bioactive compounds in vegetables that may reduce PD risk in an iron-agnostic way. Furthermore, a diet rich in fruits and vegetables fosters the growth of short-chain fatty acid-producing bacteria in the gut microbiota, which can reduce gut permeability, lower inflammation, and decrease PD risk[98].

Additional Factors that Influence the Hemochromatosis Brain PVS

We also identified some factors that affected the hemochromatosis brain PVS but not risk of PD. We found that preferences related to meat (preferences for red meat, lamb, beef steak, grilled meat, etc. and Factor 1), especially red meat, were associated with increased measures of the hemochromatosis brain PVS - i.e. greater iron levels in motor regions. This is consistent with previous findings that vegetarians have markers indicative of depleted iron stores and higher proportion of iron deficiency anemia compared to non-vegitarians[99]. Red meat, especially beef, contains high concentrations of highly bioavailable heme iron and animal proteins and as such red meat and is not recommended for those at risk of iron overload[87,88]. The relationship between red meat consumption and neurodegeneration and PD is still unclear. Our research identified a significant association between a preference for beef steak and an increased brain iron in motor regions as well as a decreased risk of PD; however, recent systematic reviews have found no association between red meat consumption and cognitive impairment, Alzheimer's disease, dementia, or PD[100,101]. Results may be so variegated because the actual iron absorbed from a meat will vary based on the cut and cooking method[102] as well as the presence or absence of iron absorption inhibitors or promoters in the meal[103]. Future research should overcome this by carefully specifying their measure of beef or working to understand the effects of diet at a nutrient level.

Our analyses found that preferences related to cereal grains were associated with reduced brain iron as captured by the PVS. This result is surprising given that cereal is a common vehicle for iron fortification. Cereal grains can be 50-80% carbohydrates by weight[104] so it is possible that those factors we have previously identified as being related to sugars and carbohydrates could be driving this interaction. Additionally cereals and dairy products, usually consumed alongside cereals, are high in iron-absorption inhibitors like phytic acid and calcium which reduce iron bioavailability by chelating and cloistering iron in the digestive tract[105]. There are ways to overcome these inhibitory factors by removing the inhibitory phytic acid, adding enhancers, or using more bioavailable forms of iron[106], but the use of these methods is discretionary. Our current interpretation is that lower brain iron levels observed in individuals preferring cereal grains are due to iron-absorption inhibitors in these meals and that the association we observe occurs in spite of cereal iron fortification not because of it.

Limitations

The results of our nutritional analysis are based on estimates of nutrient intake based on self-report assessments of dietary recall from data from a maximum of two days. While efforts were made to remove data that represented deviations from an individual's typical diet, a maximum of two days of data likely represents an incomplete picture of an individual's diet. To attempt a more complete understanding of an individual's diet we also examined lifestyle and dietary preferences. While preferences are known to be predictors of diet[107], it is possible that indicators of preference are not complete representations of an individual's diet.

The PVS is a univariate measure that only looks at potential iron levels in specific - regions, albeit regions that are related to movement and/or predictive of PD[108] risk including the substantia nigra, thalamus, putamen, and cerebellum[58]. Additionally, the transition from images to a PVS necessarily reduces the distinction between brain regions and represents larger regions like the cerebellum with greater weight than smaller regions like the substantia nigra[2]. While the hemochromatosis brain PVS has been shown to be representative of iron accumulation in motor regions it will not pick up changes in other regions of the brain. T2-w signal, while being an iron-sensitive measure, is also correlated with other non-iron processes[58] that could be adding noise to our measure, but given the classifier training and the strong iron genetic signature[2] - we believe the PVS is largely capturing variability in iron levels in critical motor brain regions.

This is an observational study, so it is difficult to infer causation. It is possible that the pattern of iron accumulation could be the result of some additional factor like altered transferrin-Fe uptake related to changes in α-synuclein ferrireductase activity[109]. Additionally, due to the demographics of the UK, the majority of individuals within this study are of European descent, so it is important to validate these findings in non-European ancestry individuals.

Conclusion

We have shown that dietary factors and preferences, mainly those related to carbohydrates and alcohol, have a measurable effect on iron in motor regions of the brain and with risk for PD. Together these results add to the existing body of knowledge showing that changes in diet and differences in preferences can lead to measurable differences in brain iron, and those differences in brain iron are associated with differences in PD risk. Our results suggest that a lower measure of brain iron is associated with increased risk of PD. This apparently falls contrary to other indicators that suggest that higher iron in regions PD-related like the substancia nigra[108] is associated with increased PD risk. However, our results are in fact consistent with these previous findings as the hemochromatosis brain PVS is a multivariate instrument in which some brain regions have opposite signed weights (Supplementary Table 1). One region with an opposing weight, which has a modest contribution to the overall PVS, is the substantia nigra. In aggregate low brain iron is associated with greater PD risk for the majority of signal and regions making up the PVS, however for the substantia nigra higher iron concentration is linked to greater PD risk. Nevertheless, the substantia nigra makes up a very small proportion of the PVS signal which is much more driven by the T2-w signal in the

cerebellum and thalamus. Additionally, we have shown that in a population that is not homozygous for hemochromatosis, patterns of central iron accumulation are related to lifestyle factors like diet and exercise. These findings provide clear directions for future research on the relationships between diet and lifestyle factors and PD and can strengthen our understanding of the factors that influence iron accumulation in the brain. Future research should focus on clarifying the direction of causality and mechanisms related to the associations found in this analysis with an emphasis on identifying mechanistic targets for pharmacological and lifestyle interventions. This work could improve outcomes for patients with PD and ways to manage dysregulation of iron in the brain in both healthy individuals and those with clinical disorders of iron metabolism such as hemochromatosis.

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URLs

UK Biobank: https://www.ukbiobank.ac.uk/
Statsmodels: https://www.statsmodels.org/stable/index.html
FactorAnalyser: https://factor-analyzer.readthedocs.io/en/latest/index.html

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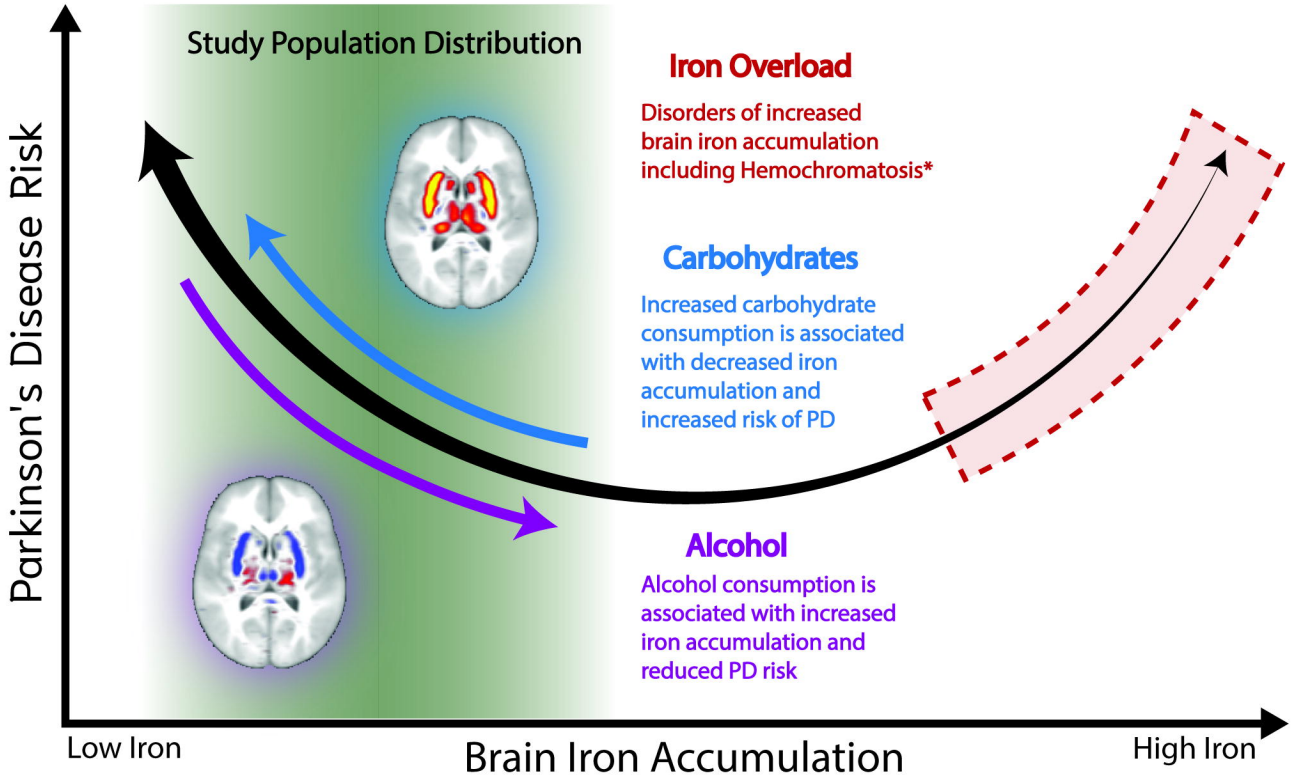
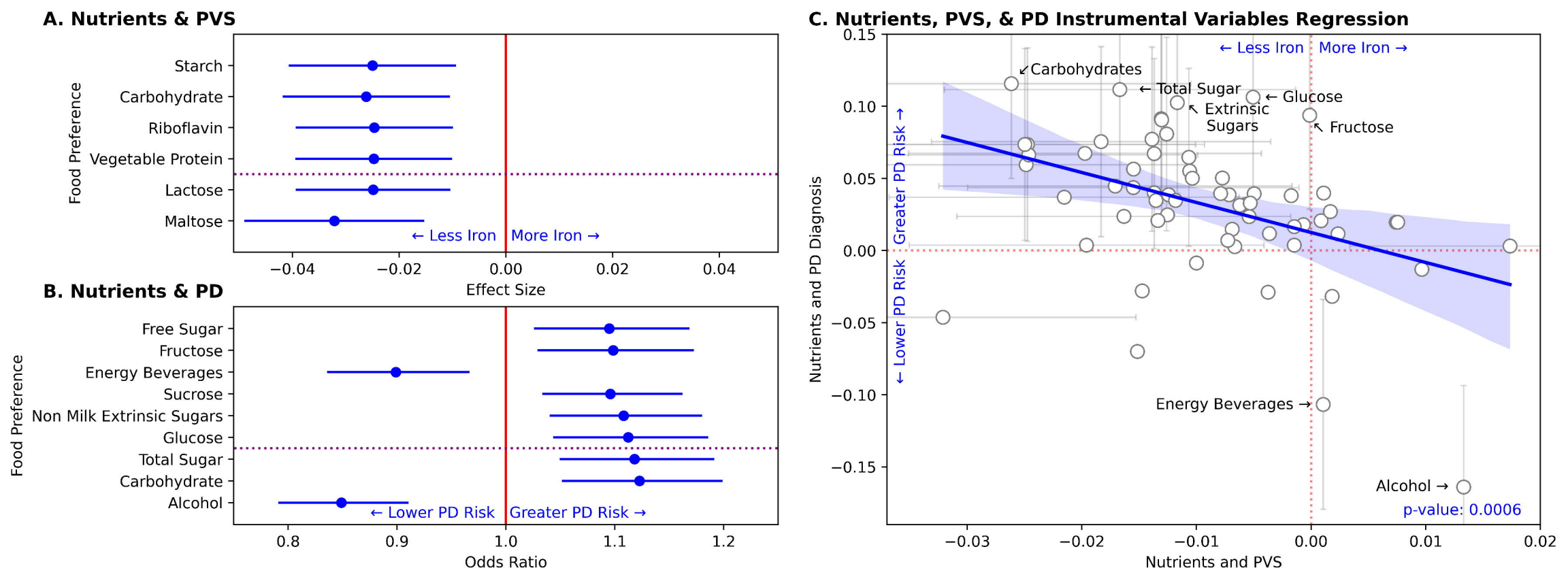
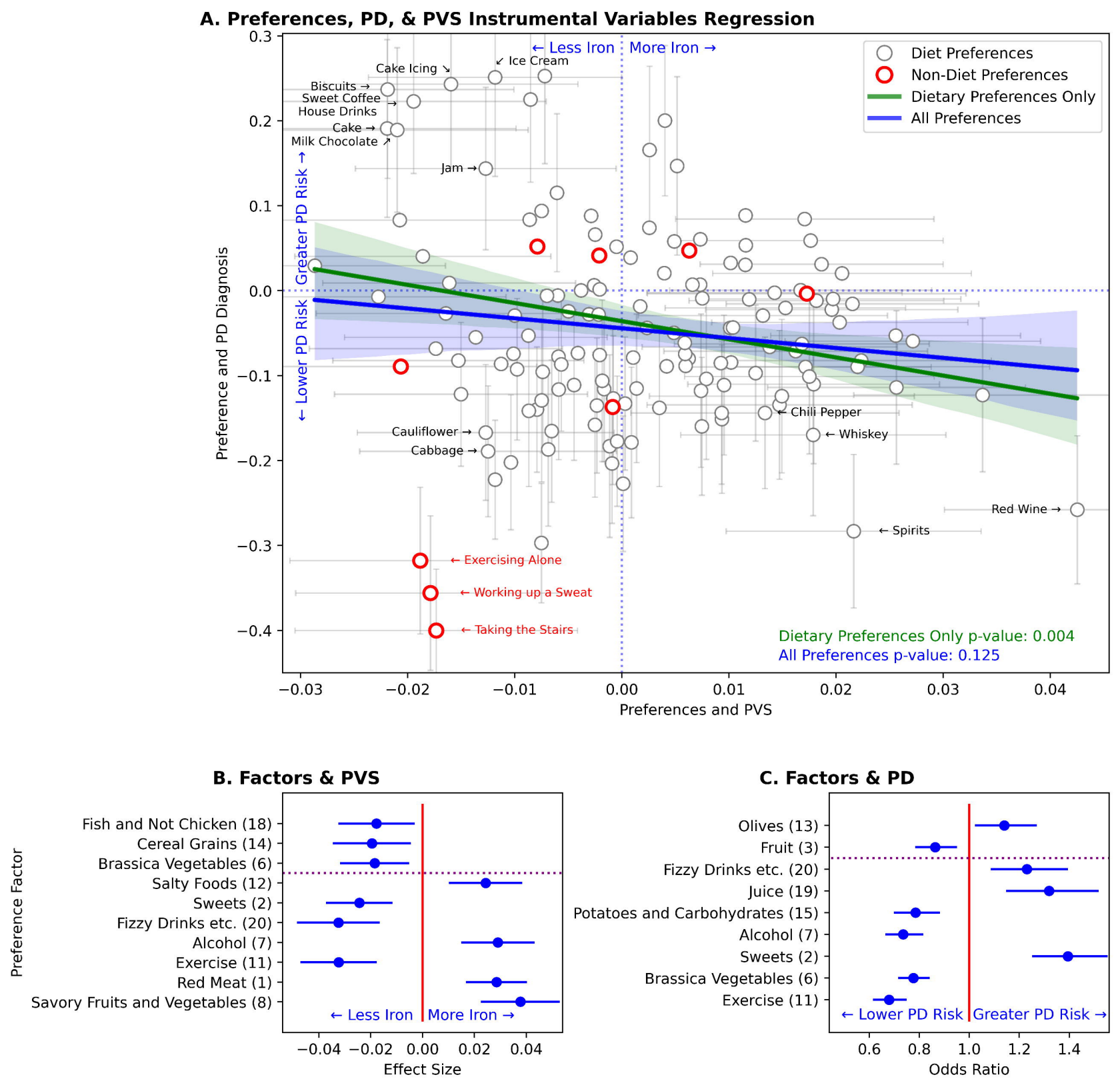
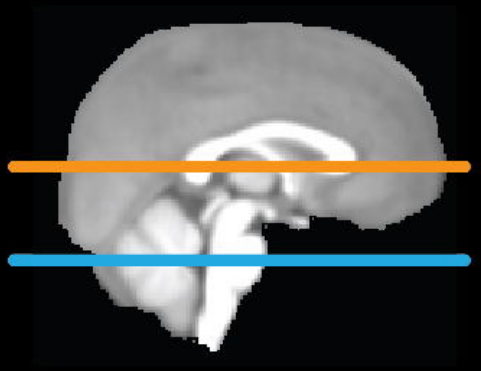
Dietary and Lifestyle Factors of Brain Iron Accumulation and Parkinson's Disease Risk



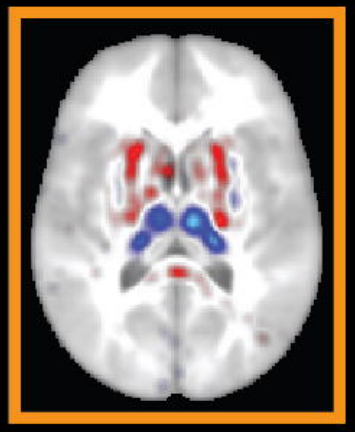
			Imaging				Non Imaging	
Preferences	Sample Size:		28,388		Sample Size:		132,023	
	Mean Age (SD)		64.13 (7.45)		Mean Age (SD)		66.65 (7.70)	
	# Female (%)		14,871 (52.38)		# Female (%)		74,360 (56.32)	
	# PD Cases (%)		45 (0.16)		# PD Cases (%)		456 (0.35)	
	Max Income	Category	%		Max Income	Category	%	
		<£18,000	6.47			<£18,000	13.29	
		£18,000-£30,999	18.86			£18,000-£30,999	23.29	
		£31,000-£51,999	30.22			£31,000-£51,999	28.97	
		£52,000-£100,000	33.40			£52,000-£100,000	26.23	
		>£100,000	11.05			>£100,000	8.22	
Nutrients	Sample Size:		20,477		Sample Size:		150,603	
	Mean Age (SD)		64.06 (7.56)		Mean Age (SD)		58.63 (8.05)	
	# Female (%)		10,545 (51.50)		# Female (%)		80,595 (53.51)	
	# PD Cases (%)		37 (0.18)		# PD Cases (%)		979 (0.65)	
	Max Income	Category	%		Max Income	Category	%	
		<£18,000	5.97			<£18,000	15.88	
		£18,000-£30,999	18.83			£18,000-£30,999	24.79	
		£31,000-£51,999	30.52			£31,000-£51,999	28.37	
		£52,000-£100,000	33.31			£52,000-£100,000	23.81	
		>£100,000	11.38			>£100,000	7.15	

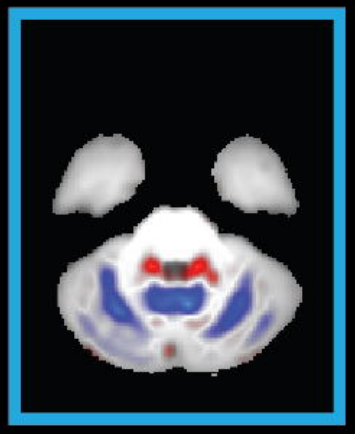

A. Nutrients & PVS
Food Preference
Starch
Carbohydrate
Riboflavin
Vegetable Protein
Lactose
Maltose
← Less Iron
More Iron →
−0.04
−0.02
0.00
0.02
0.04
Effect Size
B. Nutrients & PD
Food Preference
Free Sugar
Fructose
Energy Beverages
Sucrose
Non Milk Extrinsic Sugars
Glucose
Total Sugar
Carbohydrate
Alcohol
← Lower PD Risk
Greater PD Risk →
0.8
0.9
1.0
1.1
1.2
Odds Ratio
C. Nutrients, PVS, & PD Instrumental Variables Regression
Nutrients and PD Diagnosis
← Less Iron
More Iron →
← Lower PD Risk
Greater PD Risk →
↙Carbohydrates
← Total Sugar
← Glucose
↖ Extrinsic Sugars
↖ Fructose
Energy Beverages →
Alcohol →
p-value: 0.0006
0.15
0.10
0.05
0.00
−0.05
−0.10
−0.15
−0.03
−0.02
−0.01
0.00
0.01
0.02
Nutrients and PVS


A. Preferences, PD, & PVS Instrumental Variables Regression
Diet Preferences
Non-Diet Preferences
Dietary Preferences Only
All Preferences
← Less Iron
More Iron →
← Lower PD Risk
Greater PD Risk →
Preference and PD Diagnosis
Preferences and PVS
Cake Icing ↘
↙ Ice Cream
Biscuits →
Sweet Coffee →
House Drinks
Cake →
Milk Chocolate ↗
Jam →
Cauliflower →
Cabbage →
← Chili Pepper
← Whiskey
Red Wine →
← Spirits
← Exercising Alone
← Working up a Sweat
← Taking the Stairs
Dietary Preferences Only p-value: 0.004
All Preferences p-value: 0.125
B. Factors & PVS
Preference Factor
Fish and Not Chicken (18)
Cereal Grains (14)
Brassica Vegetables (6)
Salty Foods (12)
Sweets (2)
Fizzy Drinks etc. (20)
Alcohol (7)
Exercise (11)
Red Meat (1)
Savory Fruits and Vegetables (8)
← Less Iron
More Iron →
Effect Size
C. Factors & PD
Olives (13)
Fruit (3)
Fizzy Drinks etc. (20)
Juice (19)
Potatoes and Carbohydrates (15)
Alcohol (7)
Sweets (2)
Brassica Vegetables (6)
Exercise (11)
← Lower PD Risk
Greater PD Risk →
Odds Ratio

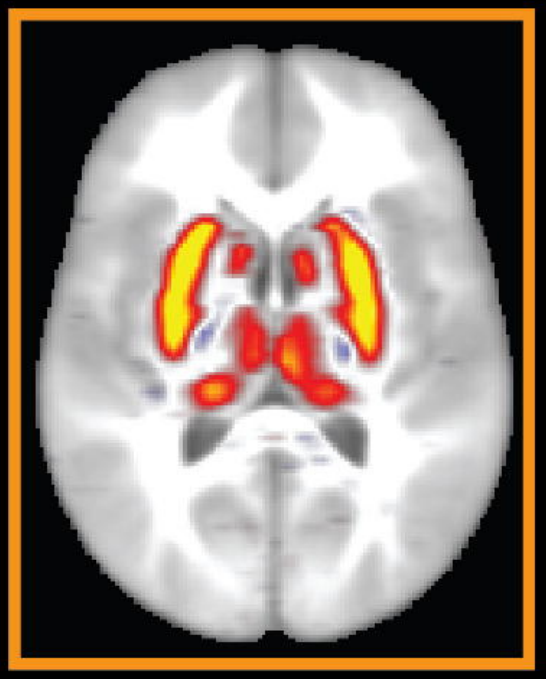


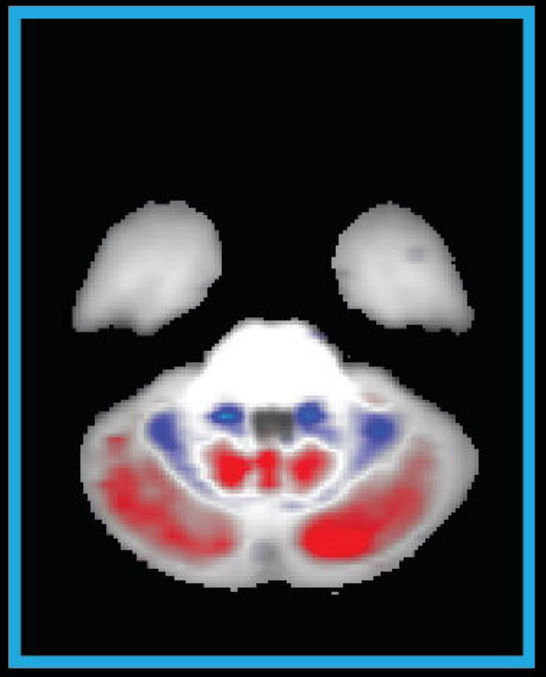
Hemocrhomatosis Brain Weights





Factor 2: Sweets





Factor 7: Alcohol