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Parkinson's Disease

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June 2024

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

Authors: Ahern, J.;Boyle, M. E. T.;Thompson, W. K.;Fan, C. C. and Loughnan, R.

Publication Date: 2024

Journal: medRxiv (pagination), pp. Date of Publication: 15 Mar 2024

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. Method(s): 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. Result(s): We found multiple highly significant associations with measures of brain iron accumulation and preferences for alcohol (factor 7: t=4.02, pFDR=0.0003), exercise (factor 11: t=-4.31, pFDR=0.0001), and high-sugar foods (factor 2: t=-3.73, pFDR=0.0007). Preference for alcohol (factor 7: t=-5.83, pFDR-8), exercise (factor 11: t=-7.66, pFDR-13), and high sugar foods (factor 2: t=6.03, pFDR-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(s): 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.

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2. **MRI-derived brain iron, grey matter volume, and risk of dementia and Parkinson's disease: Observational and genetic analysis in the UK Biobank cohort.**

Authors: Casanova, Francesco;Tian, Qu;Williamson, Daniel S.;Qian, Yong;Zweibaum, David;Ding, Jun;Atkins, Janice L.;Melzer, David;Ferrucci, Luigi and Pilling, Luke C.

Publication Date: Jul ,2024

Journal: Neurobiology of Disease 197, pp. 106539

Abstract: BACKGROUND: Iron overload is observed in neurodegenerative diseases, especially Alzheimer's disease (AD) and Parkinson's disease (PD). Homozygotes for the iron-overload (haemochromatosis) causing HFE p.C282Y variant have increased risk of dementia and PD. Whether brain iron deposition is causal or secondary to the neurodegenerative processes in the general population is unclear. METHODS: We analysed 39,533 UK Biobank participants of European genetic ancestry with brain MRI data. We studied brain iron estimated by R2* and quantitative susceptibility mapping (QSM) in 8 subcortical regions: accumbens, amygdala, caudate, hippocampus, pallidum, putamen, substantia nigra, and thalamus. We performed genome-wide associations studies (GWAS) and used Mendelian Randomization (MR) methods to estimate the causal effect of brain iron on grey matter volume, and risk of AD, non-AD and PD. We also used MR to test whether genetic liability to AD or PD causally increased brain iron (R2* and QSM). FINDINGS: In GWAS of R2* and QSM we replicated 83% of previously reported genetic loci and identified 174 further loci across all eight brain regions. Higher genetically predicted brain iron, using both R2* and QSM, was associated with lower grey matter volumes in the caudate, putamen and thalamus (e.g., Beta-putamenQSM: -0.37, p = 2*10-46). Higher genetically predicted thalamus R2* was associated with increased risk of non-AD dementia (OR 1.36(1.16;1.60), p = 2*10-4) but not AD (p > 0.05). In males, genetically predicted putamen R2* increased non-AD dementia risk, but not in females. Higher genetically predicted iron in the caudate, putamen, and substantia nigra was associated with an increased risk of PD (Odds Ratio QSM ~ substantia-nigra 1.21(1.07;1.37), p = 0.003). Genetic liability to AD or PD was not associated with R2* or QSM in the dementia or PD-associated regions. INTERPRETATION: Our genetic analysis supports a causal effect of higher iron deposition in specific subcortical brain regions for Parkinson's disease, grey matter volume, and non-Alzheimer's dementia.

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3. **Branched-chain amino acids and the risks of dementia, Alzheimer's disease, and Parkinson's disease.**

Authors: Fu, Yidong;Wang, Yue;Ren, Huiming;Guo, Xu and Han, Liyuan

Publication Date: 2024

Journal: Frontiers in Aging Neuroscience 16, pp. 1369493

Abstract: Background: We aimed to examine the association between blood levels of Branched-chain amino acids (BCAAs) - specifically isoleucine, leucine, and valine - and the susceptibility to three neurodegenerative disorders: dementia, Alzheimer's disease (AD), and Parkinson's disease (PD). Methods: Based on data from the UK Biobank, a Cox proportional hazard regression model and a dose-response relationship were used to analyze the association between BCAAs and the risks of dementia, AD, and PD. We also generated a healthy lifestyle score and a polygenic risk score. Besides, we conducted a sensitivity analysis to ensure the robustness of our findings. Results: After adjusting for multiple covariates, blood concentrations of isoleucine, leucine, and valine were significantly associated with a reduced

risk of dementia and AD. This association remained robust even in sensitivity analyses. Similarly, higher levels of isoleucine and leucine in the blood were found to be associated with an increased risk of PD, but this positive correlation could potentially be explained by the presence of covariates. Further analysis using a dose-response approach revealed that a blood leucine concentration of 2.14 mmol/L was associated with the lowest risk of dementia. Conclusion: BCAAs have the potential to serve as a biomarker for dementia and AD. However, the specific mechanism through which BCAAs are linked to the development of dementia, AD, and PD remains unclear and necessitates additional investigation.

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4. **Social isolation and the risk of Parkinson disease in the UK biobank study.**

Authors: Geng, Tingting;Li, Yaqi;Peng, Yinshun;Chen, Xiao;Xu, Xinming;Wang, Jian;Sun, Liang and Gao, Xiang

Publication Date: Apr 08 ,2024

Journal: Npj Parkinsons Disease 10(1), pp. 79

Abstract: Parkinson disease (PD) has become one of the most rapidly growing causes of disability among the older population and social isolation is a major concern in the PD community. However, the relationship between social isolation and future risk of PD remains unclear. This study included 192,340 participants aged 60 or older who were free of dementia and PD at baseline from the UK Biobank study. Social isolation was measured using a composite score derived from three questions on number in household, frequency of friend/family visits, and leisure/social activities. Incident PD cases were identified through electronic health records. Multivariable-adjusted Cox regression models were used to compute the hazard ratio (HR) and 95% confidence interval (CI). Among the 192,340 participants (mean [standard deviation] age, 64.2 [2.9] years; 103,253 [53.7%] women), 89,075 (46.3%) participants were in the least isolated group and 26,161 (13.6%) were in the most isolated group. Over a median follow-up of 12.5 years, 2048 incident PD cases were documented. Compared to the least isolated group, the multivariable-adjusted HRs (95% CIs) for PD were 1.00 (0.91-1.10) for the moderately isolated group and 1.19 (1.05-1.36) for the most isolated group (P-trend = 0.04). The observed association was independent of the genetic susceptibility to PD and consistent in subgroup analyses. Social isolation was associated with a higher risk of PD regardless of genetic risk. Our findings highlighted the importance of developing screening and intervention strategies for social isolation among older adults to reduce the risk of PD. Copyright © 2024. The Author(s).

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5. **RAB32 Ser71Arg in autosomal dominant Parkinson's disease: linkage, association, and functional analyses.**

Authors: Gustavsson, Emil K.;Follett, Jordan;Trinh, Joanne;Barodia, Sandeep K.;Real, Raquel;Liu, Zhiyong;Grant-Peters, Melissa;Fox, Jesse D.;Appel-Cresswell, Silke;Stoessl, A. Jon;Rajput, Alex;Rajput, Ali H.;Auer, Roland;Tilney, Russel;Sturm, Marc;Haack, Tobias B.;Lesage, Suzanne;Tesson, Christelle;Brice, Alexis;Vilarino-Guell, Carles, et al

Publication Date: Jun ,2024

Journal: Lancet Neurology 23(6), pp. 603-614

Abstract: BACKGROUND: Parkinson's disease is a progressive neurodegenerative disorder with multifactorial causes, among which genetic risk factors play a part. The RAB GTPases are regulators and substrates of LRRK2, and variants in the LRRK2 gene are important risk factors for Parkinson's disease. We aimed to explore genetic variability in RAB GTPases within cases of familial Parkinson's disease. METHODS: We did whole-exome sequencing in probands from families in Canada and Tunisia with Parkinson's disease without a genetic cause, who were recruited from the Centre for Applied Neurogenetics (Vancouver, BC, Canada), an international consortium that includes people with Parkinson's disease from 36 sites in 24 countries. 61 RAB GTPases were genetically screened, and candidate variants were genotyped in relatives of the probands to assess disease segregation by linkage analysis. Genotyping was also done to assess variant frequencies in individuals with idiopathic Parkinson's disease and controls, matched for age and sex, who were also from the Centre for Applied Neurogenetics but unrelated to the probands or each other. All participants were aged 18 years or older. The sequencing and genotyping findings were validated by case-control association analyses using bioinformatic data obtained from publicly available clinicogenomic databases (AMP-PD, GP2, and 100 000 Genomes Project) and a private German clinical diagnostic database (University of Tubingen). Clinical and pathological findings were summarised and haplotypes were determined. In-vitro studies were done to investigate protein interactions and enzyme activities. FINDINGS: Between June 1, 2010, and May 31, 2017, 130 probands from Canada and Tunisia (47 [36%] female and 83 [64%] male; mean age 72.7 years [SD 11.7; range 38-96]; 109 White European ancestry, 18 north African, two east Asian, and one Hispanic] underwent whole-exome sequencing. 15 variants in RAB GTPase genes were identified, of which the RAB32 variant c.213C>G (Ser71Arg) cosegregated with autosomal dominant Parkinson's disease in three families (nine affected individuals; non-parametric linkage Z score=1.95; p=0.03). 2604 unrelated individuals with Parkinson's disease and 344 matched controls were additionally genotyped, and five more people originating from five countries (Canada, Italy, Poland, Turkey, and Tunisia) were identified with the RAB32 variant. From the database searches, in which 6043 individuals with Parkinson's disease and 62 549 controls were included, another eight individuals were identified with the RAB32 variant from four countries (Canada, Germany, UK, and USA). Overall, the association of RAB32 c.213C>G (Ser71Arg) with Parkinson's disease was significant (odds ratio [OR] 13.17, 95% CI 2.15-87.23; p=0.0055; I2=99.96%). In the people who had the variant, Parkinson's disease presented at age 54.6 years (SD 12.75, range 31-81, n=16), and two-thirds had a family history of parkinsonism. RAB32 Ser71Arg heterozygotes shared a common haplotype, although penetrance was incomplete. Findings in one individual at autopsy showed sparse neurofibrillary tangle pathology in the midbrain and thalamus, without Lewy body pathology. In functional studies, RAB32 Arg71 activated LRRK2 kinase to a level greater than RAB32 Ser71. INTERPRETATION: RAB32 Ser71Arg is a novel genetic risk factor for Parkinson's disease, with reduced penetrance. The variant was found in individuals with Parkinson's disease from multiple ethnic groups, with the same haplotype. In-vitro assays show that RAB32 Arg71 activates LRRK2 kinase, which indicates that genetically distinct causes of familial parkinsonism share the same mechanism. The discovery of RAB32 Ser71Arg also suggests several genetically inherited causes of Parkinson's disease originated to control intracellular immunity. This shared aetiology should be considered in future translational research, while the global epidemiology of RAB32 Ser71Arg needs to be assessed to inform genetic counselling. FUNDING: National Institutes of Health, the Canada Excellence Research Chairs program, Aligning Science Across Parkinson's, the Michael J Fox Foundation for

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6. **Associations between multimorbidity and neuropathology in dementia: consideration of functional cognitive disorders, psychiatric illness and dementia mimics.**

Authors: Hamilton, Calum A.;Matthews, Fiona E.;Attems, Johannes;Donaghy, Paul C.;Erskine, Daniel;Taylor, John-Paul and Thomas, Alan J.

Publication Date: Jun ,2024

Journal: British Journal of Psychiatry 224(6), pp. 237-244

Abstract: BACKGROUND: Multimorbidity, the presence of two or more health conditions, has been identified as a possible risk factor for clinical dementia. It is unclear whether this is due to worsening brain health and underlying neuropathology, or other factors. In some cases, conditions may reflect the same disease process as dementia (e.g. Parkinson's disease, vascular disease), in others, conditions may reflect a prodromal stage of dementia (e.g. depression, anxiety and psychosis). AIMS: To assess whether multimorbidity in later life was associated with more severe dementia-related neuropathology at autopsy. METHOD: We examined ante-mortem and autopsy data from 767 brain tissue donors from the UK, identifying physical multimorbidity in later life and specific brain-related conditions. We assessed associations between these purported risk factors and dementia-related neuropathological changes at autopsy (Alzheimer's-disease related neuropathology, Lewy body pathology, cerebrovascular disease and limbic-predominant age-related TDP-43 encephalopathy) with logistic models. RESULTS: Physical multimorbidity was not associated with greater dementia-related neuropathological changes. In the presence of physical multimorbidity, clinical dementia was less likely to be associated with Alzheimer's disease pathology. Conversely, conditions which may be clinical or prodromal manifestations of dementia-related neuropathology (Parkinson's disease, cerebrovascular disease, depression and other psychiatric conditions) were associated with dementia and neuropathological changes. CONCLUSIONS: Physical multimorbidity alone is not associated with greater dementia-related neuropathological change; inappropriate inclusion of brain-related conditions in multimorbidity measures and misdiagnosis of neurodegenerative dementia may better explain increased rates of clinical dementia in multimorbidity.

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7. **Adherence to Parkinson's disease medication: A case study to illustrate reasons for non-adherence, implications for practice and engaging under-represented participants in research**

Authors: James, D., Smith, J., Lane, E., Thomas, R., Brown, S. and Seage, H.

Publication Date: 2024

Publication Details: United States:

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disease which

primarily presents with the core symptoms of rigidity, postural instability, tremor, and bradykinesia. Non-adherence to prescribed PD treatments can have significant ramifications, such as poor symptom control and greater disease burden. Reasons for poor adherence are multifaceted, particularly when medication regimens are complex and often based on perceptual and practical barriers. Additionally, engaging fully non-adherent patients in research is challenging since they may have dropped out of service provision, yet their contribution is vital to fully understand the rationale for non-adherence. This paper aims to present a case study on the perspectives of one person with PD, a participant in a previously published qualitative study investigating the barriers and facilitators to medication adherence in PD. In this paper, the participant's diagnostic journey is described, and experiences of medical consultations are summarised to explain their reasons for not adhering to any of the standard UK PD treatments prescribed. The participant's preferences for using Vitamin B1 (thiamine) injections to manage the symptoms are reported and the rationale for doing so is discussed. We consider the case through the lens of a behavioural science approach, drawing on health psychology theory, the Theoretical Domains Framework (TDF), to inform the review and the practical challenges faced when analysing the data for this participant. Implications for pharmacy practice, in particular, are also put forward with view to ensuring that patients such as Mr. Wilkinson are provided with the opportunity to discuss treatment choices and self-management of long-term conditions such as PD. We also discuss the importance of reaching under-represented members of the population in medication adherence research, which embraces the principles of equality, diversity, and inclusion in research.

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8. **Combined systematic screening for malnutrition and dysphagia in hospitalized older adults: a scoping review.**

Authors: Javorszky, S. M.;Palli, C.;Domkar, S. and Iglseder, B.

Publication Date: 2024

Journal: BMC Geriatrics 24(1), pp. 445

Abstract: BACKGROUND: Dysphagia affects about 40% of patients admitted to acute geriatric wards, as it is closely associated with diseases that rise in prevalence with advancing age, such as stroke, Parkinson's disease, and dementia. Malnutrition is a highly associated predictive factor of dysphagia as well as one of the most common symptoms caused by dysphagia. Thus, the two conditions may exist simultaneously but also influence each other negatively and quickly cause functional decline especially in older adults. The purpose of this review was to determine whether institutions have established a protocol combining screenings for dysphagia and malnutrition on a global scale. If combined screening protocols have been implemented, the respective derived measures will be reported. METHOD(S): A scoping review was conducted. A systematic database search was carried out in January and February 2024. Studies were included that examined adult hospitalized patients who were systematically screened for dysphagia and malnutrition. The results were managed through the review software tool Covidence. The screening of titles and abstracts was handled independently by two reviewers; conflicts were discussed and resolved by consensus between three authors. This procedure was retained for full-text analysis and extraction. The extraction template was piloted and revised following feedback prior to extraction, which was carried out

in February 2024. RESULT(S): A total of 2014 studies were found, 1075 of which were included for abstract screening, 80 for full text screening. In the end, 27 studies were extracted and reported following the reporting guideline PRISMA with the extension for Scoping Reviews. CONCLUSION(S): Most of the studies considered the prevalence and association of dysphagia and malnutrition with varying outcomes such as nutritional status, pneumonia, oral nutrition, and swallowing function. Only two studies had implemented multi-professional nutrition teams.

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9. **The landscape of rare genetic variation associated with inflammatory bowel disease and Parkinson's disease comorbidity.**

Authors: Kars, Meltem Ece;Wu, Yiming;Stenson, Peter D.;Cooper, David N.;Burisch, Johan;Peter, Inga and Itan, Yuval

Publication Date: May 14 ,2024

Journal: Genome Medicine 16(1), pp. 66

Abstract: BACKGROUND: Inflammatory bowel disease (IBD) and Parkinson's disease (PD) are chronic disorders that have been suggested to share common pathophysiological processes. LRRK2 has been implicated as playing a role in both diseases. Exploring the genetic basis of the IBD-PD comorbidity through studying high-impact rare genetic variants can facilitate the identification of the novel shared genetic factors underlying this comorbidity. METHODS: We analyzed whole exomes from the BioMe BioBank and UK Biobank, and whole genomes from a cohort of 67 European patients diagnosed with both IBD and PD to examine the effects of LRRK2 missense variants on IBD, PD and their co-occurrence (IBD-PD). We performed optimized sequence kernel association test (SKAT-O) and network-based heterogeneity clustering (NHC) analyses using high-impact rare variants in the IBD-PD cohort to identify novel candidate genes, which we further prioritized by biological relatedness approaches. We conducted phenome-wide association studies (PheWAS) employing BioMe BioBank and UK Biobank whole exomes to estimate the genetic relevance of the 14 prioritized genes to IBD-PD. RESULTS: The analysis of LRRK2 missense variants revealed significant associations of the G2019S and N2081D variants with IBD-PD in addition to several other variants as potential contributors to increased or decreased IBD-PD risk. SKAT-O identified two significant genes, LRRK2 and IL10RA, and NHC identified 6 significant gene clusters that are biologically relevant to IBD-PD. We observed prominent overlaps between the enriched pathways in the known IBD, PD, and candidate IBD-PD gene sets. Additionally, we detected significantly enriched pathways unique to the IBD-PD, including MAPK signaling, LPS/IL-1 mediated inhibition of RXR function, and NAD signaling. Fourteen final candidate IBD-PD genes were prioritized by biological relatedness methods. The biological importance scores estimated by protein-protein interaction networks and pathway and ontology enrichment analyses indicated the involvement of genes related to immunity, inflammation, and autophagy in IBD-PD. Additionally, PheWAS provided support for the associations of candidate genes with IBD and PD. CONCLUSIONS: Our study confirms and uncovers new LRRK2 associations in IBD-PD. The identification of novel inflammation and autophagy-related genes supports and expands previous findings related to IBD-PD pathogenesis, and underscores the significance of therapeutic interventions for reducing systemic inflammation. Copyright © 2024. The Author(s).

10. **Resting state changes in aging and Parkinson's disease are shaped by underlying neurotransmission - a normative modeling study.**

Authors: Kasper, J.;Caspers, S.;Lotter, L. D.;Hoffstaedter, F.;Eickhoff, S. B. and Dukart, J.

Publication Date: 2024

Journal: Biological Psychiatry.Cognitive Neuroscience and Neuroimaging (pagination), pp. Date of Publication: 26 Ar 2024

Abstract: BACKGROUND: Human healthy and pathological aging is linked to a steady decline in brain resting state activity and connectivity measures. The neurophysiological mechanisms underlying these changes remain poorly understood. METHOD(S): Making use of recent developments in normative modeling and availability of in vivo maps for various neurochemical systems, we test in the UK Biobank cohort (N=25917) if and how age- and Parkinson's disease related resting state changes in commonly applied local and global activity and connectivity measures co-localize with underlying neurotransmitter systems. RESULT(S): We find the distributions of several major neurotransmitter systems including serotonergic, dopaminergic, noradrenergic, and glutamatergic neurotransmission to correlate with age-related changes as observed across functional activity and connectivity measures. Co-localization patterns in Parkinson's disease deviate from normative aging trajectories for these, as well as for cholinergic and GABAergic, neurotransmission. The deviation from normal co-localization of brain function and GABAa correlates with disease duration. CONCLUSION(S): These findings provide new insights into molecular mechanisms underlying age- and Parkinson's related brain functional changes by extending the existing evidence elucidating the vulnerability of specific neurochemical attributes to normal aging and Parkinson's disease. The results particularly indicate that alongside dopamine and serotonin, increased vulnerability of glutamatergic, cholinergic, and GABAergic systems may also contribute to Parkinson's disease-related functional alterations. Combining normative modeling and neurotransmitter mapping may aid future research and drug development through deeper understanding of neurophysiological mechanisms underlying specific clinical conditions.

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11. **Making a difference: neurological support in the community.**

Authors: Kinnear, Eleanor Ellie;Beales, David;Paton, Alan and Challice, Sara

Publication Date: Apr 02 ,2024

Journal: British Journal of Community Nursing 29(4), pp. 190-194

Abstract: Nearly 3 million people in the UK have a neurological condition; stroke, traumatic brain injury, Parkinson's disease, multiple sclerosis, brain tumour, motor neurone disease, among others - all affecting the person for the rest of their life. The NHS provides treatment at the onset of a condition but after that, there is a huge need for ongoing support. Research shows that those who are supported and know more about their condition are less likely to have to call on further in-hospital and GP care. There is enormous scope for improving the quality of life for those with neurological conditions. The right support-therapeutic and social-

makes all the difference. The book, which this article is based on, shows how those with neurological conditions benefit from integrated ongoing support provided in the local community and self-help, and how lives can be improved. It explains good practice and encouraging methods in the support and treatment of those with life changing conditions.

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12. **Rifaximin Modulates Severity of Symptoms of Parkinson's Disease with Concomitant Small Intestinal Bacterial Overgrowth**

Authors: Korbecka, J., Mulak, A. and Budrewicz, S.

Publication Date: 2024

Publication Details: Gastroenterology. Conference: DDW 2024. Washington, DC United States. 166(5 Supplement) (pp S-871); W.B. Saunders,

Abstract: Background/objectives: Mounting evidence suggests that the gut dysbiosis through dysregulation of the microbiome-gut-brain axis plays an important role in the pathogenesis and symptomatology of Parkinson's disease (PD). Rifaximin, a non-absorbable antibiotic used for the treatment of small intestinal bacterial overgrowth (SIBO), has been recently shown to exert a neuroprotective effect on the transgenic PD mice by modulating gut microbiota (Hong et al. Cells 2022). The aim of the study was to assess the impact of gut microbiota modification with rifaximin on severity of symptoms and activation of the immune system in PD patients with concomitant SIBO. Method(s): This double-blind, placebo-controlled study was conducted in 32 PD patients (20 M, 12 F, mean age 65 years) with SIBO diagnosed based on the results of lactulose hydrogen breath test. The patients were randomly assigned to rifaximin treatment (400 mg t.i.d. for 7 days) or placebo. Basal evaluation of the severity of PD symptoms was performed using the Movement Disorder Society-Unified PD Rating Scale (MDS-UPDRS), Hoehn-Yahr, and Schwab-England scales. Additionally, all PD patients completed the modified Hospital Anxiety and Depression Scale (HADS-M) and the Gastrointestinal Symptom Rating Scale (GSRS). Prior to initiation of the treatment, fecal calprotectin level and serum cytokine profile were assessed. A follow-up clinical evaluation according to the aforementioned scales as well as control stool and blood tests were conducted 4-5 weeks after the completion of rifaximin or placebo treatment. Result(s): In PD patients receiving rifaximin, a significant reduction in the severity of PD motor symptoms, as indicated by the scores in part III of the MDS-UPDRS (pResult(s): In PD patients receiving rifaximin, a significant reduction in the severity of PD motor symptoms, as indicated by the scores in part III of the MDS-UPDRS (pResult(s): In PD patients receiving rifaximin, a significant reduction in the severity of PD motor symptoms, as indicated by the scores in part III of the MDS-UPDRS (pResult(s): In PD patients receiving rifaximin, a significant reduction in the severity of PD motor symptoms, as indicated by the scores in part III of the MDS-UPDRS (pResult(s): In PD patients receiving rifaximin, a significant reduction in the severity of PD motor symptoms, as indicated by the scores in part III of the MDS-UPDRS (pConclusion(s): Rifaximininduced gut microbiota modification in PD patients with concomitant SIBO results in a significant reduction in the severity of PD motor symptoms, anxiety and depression levels, and gastrointestinal symptoms including constipation. The drug seems to exert also modulatory effects on both the local immune response in the gut and systemic immunity. Therefore, rifaximin may be considered as a potential adjunctive therapy in the treatment of PD.

13. **Association of physical activity pattern and risk of Parkinson's disease.**

Authors: Lin, Fabin;Lin, Yixiang;Chen, Lina;Huang, Tingting;Lin, Tianxin;He, Jiarui;Lu, Xiaoyang;Chen, Xiaochun;Wang, Yingqing;Ye, Qinyong and Cai, Guoen

Publication Date: May 23 ,2024

Journal: Npj Digital Medicine 7(1), pp. 137

Abstract: Increasing evidence suggests an association between exercise duration and Parkinson's disease. However, no high-quality prospective evidence exists confirming whether differences exist between the two modes of exercise, weekend warrior and equal distribution of exercise duration, and Parkinson's risk. Hence, this study aimed to explore the association between different exercise patterns and Parkinson's risk using exercise data from the UK Biobank. The study analyzed data from 89,400 UK Biobank participants without Parkinson's disease. Exercise data were collected using the Axivity AX3 wrist-worn triaxial accelerometer. Participants were categorized into three groups: inactive, regularly active, and engaged in the weekend warrior (WW) pattern. The relationship between these exercise patterns and Parkinson's risk was assessed using a multifactorial Cox model. During a mean follow-up of 12.32 years, 329 individuals developed Parkinson's disease. In a multifactorial Cox model, using the World Health Organization-recommended threshold of 150 min of moderate-to-vigorous physical activity per week, both the active WW group [hazard ratio (HR) = 0.58; 95% confidence interval (CI) = 0.43-0.78; P

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14. **Assessment of Pulmonary Functions in Parkinson's Disease and Unveiling the Role of Levodopa Therapy: A Cross-Sectional Study.**

Authors: Mishra, Om;Mallik, Ashok K.;Dash, Santosh Kumar;Das, Pragateshnu and Dash, Manoranjan

Publication Date: Apr ,2024

Journal: Cureus 16(4), pp. e58662

Abstract: INTRODUCTION: This investigation aimed to thoroughly characterize the range of pulmonary function abnormalities present in individuals with Parkinson's disease (PD) and to evaluate the effects of levodopa therapy on these respiratory dysfunctions. METHODS: Ninety-five PD patients diagnosed via the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria were recruited, excluding those with a smoking history or unable to perform pulmonary function tests (PFTs). Severity was assessed using the Hoehn and Yahr Scale. Spirometry-measured PFT parameters (forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and peak expiratory flow rate (PEFR)) were compared against matched predicted values. The changes in PFT parameters post-levodopa challenge were assessed. RESULTS: Most of the PD patients were aged between 51-60 years, with a mean age of 55.89 +/- 8.37 years. Of these, 65.3% were male. A significant proportion of the cohort exhibited restrictive pulmonary patterns (73.7%), while a smaller fraction displayed obstructive (7.4%) or normal (18.9%) pulmonary function patterns. Notably, levodopa treatment correlated with marked improvements in all measured PFT parameters, especially evident in the

enhancements from the "off" medication stage to the "on" stage for FVC and FEV1 (P=0.0001). A weak positive correlation between the severity of respiratory restriction and the duration of PD (r = 0.139, P = 0.021) was found, suggesting that PD's progression exerts an increasingly adverse effect on respiratory function over time. CONCLUSION: The findings of this study illustrate that restrictive pulmonary abnormalities are more prevalent than obstructive patterns in PD patients and that these patients respond favorably to levodopa therapy.

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15. **Anxiety-related attentional changes and their relation to freezing of gait in people with Parkinson's: a cross validation of the Adapted Gait Specific Attentional Profile (G-SAPa).**

Authors: Rosenblum, U.;Cocks, A. J.;Norris, M.;Kal, E. and Young, W. R.

Publication Date: 2024

Journal: bioRxiv (pagination), pp. Date of Publication: 18 Mar 2024

Abstract: Background: Anxiety often exacerbates freezing of gait (FOG) in people with Parkinson's (PwP). Research shows that anxiety-related cognitive processes and associated processing inefficiencies, such as conscious movement processing and ruminations, can substantially impact movement control. However, the impact of these attentional changes on FOG remains largely unexplored. We therefore aimed to (i) validate a questionnaire designed to measure relevant subscales (adapted Gait-Specific Attentional Profile (G-SAPa)) in PwP, and (ii) assess if G-SAPa-subscales (Physiological Arousal, Conscious Movement Processing (CMP), Rumination, and Processing Inefficiencies) are associated with self-reported FOG frequency. Method(s): We recruited 440 PwP (Mage = 65.5+/-8.7; 5.8+/-5.0 years since diagnosis) across the UK. Participants completed an adapted 10-item G-SAP (1-5 Likert scale), and questions on demographics, years since diagnosis, self-reported balance problems, other Parkinson's symptoms, and FOG frequency (scale of 0: "never freeze" to 4: "every day"). We assessed G-SAPa's internal consistency (alpha), and structural validity (confirmatory factor analysis). Ordinal regression was used to explore associations between G-SAPa subscale scores and FOG frequency. Result(s): The G-SAPa's internal consistency was high (alpha>0.61). Confirmatory factor analysis showed acceptable to good model fit (chi2(29)=82.833, p(29)=82.833, p2/df=2.856; CFI=0.976; GFI=0.963; RMSEA=0.066; SRMR=0.035). Measurement invariance testing revealed that the Physiological Arousal and CMP subscale scores were less strongly correlated for PwP with FOG (PwP+FOG, r= .52) compared to PwP without FOG (PwP-FOG, r= .79; p=0.001). Higher Rumination (OR: 1.323, 95% CI: [1.214-1.440]) and Physiological Arousal (OR: 1.195, 95% CI: [1.037-1.377]) were significantly associated with higher FOG frequency, when controlling for age, time since diagnosis and balance/gait problems. Conclusion(s): The G-SAPa is a reliable self-report tool to measure attentional factors implicated in influencing FOG. Rumination scores were most strongly associated with freezing frequency. Such ruminations likely disrupt conscious goal-directed behaviour - an important compensatory process in maintaining motor performance in PwP - and have been associated with perceptions of increased physiological arousal. Indeed, PwP+FOG demonstrated weaker correlation between CMP and Physiological Arousal compared to PwP-FOG, suggesting a relative inability to engage in compensatory goal-directed attentional focus. The G-SAPa represents a short and convenient method for

identifying potentially maladaptive anxiety-related attentional processes impacting FOG in research and clinical contexts.

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16. **Deep brain stimulation in Parkinson's disease: A scientometric and bibliometric analysis, trends, and research hotspots.**

Authors: Suresh, Vinay;Dave, Tirth;Ghosh, Shankhaneel;Jena, Rahul and Sanker, Vivek

Publication Date: May 17 ,2024

Journal: Medicine 103(20), pp. e38152

Abstract: Parkinson disease (PD), a prevalent neurodegenerative ailment in the elderly, relies mainly on pharmacotherapy, yet deep brain stimulation (DBS) emerges as a vital remedy for refractory cases. This study performs a bibliometric analysis on DBS in PD, delving into research trends and study impact to offer comprehensive insights for researchers, clinicians, and policymakers, illuminating the current state and evolutionary trajectory of research in this domain. A systematic search on March 13, 2023, in the Scopus database utilized keywords like "Parkinson disease," "PD," "Parkinsonism," "Deep brain stimulation," and "DBS." The top 1000 highly cited publications on DBS in PD underwent scientometric analysis via VOS Viewer and R Studio's Bibliometrix package, covering publication characteristics, co-authorship, keyword co-occurrence, thematic clustering, and trend topics. The bibliometric analysis spanned 1984 to 2021, involving 1000 cited articles from 202 sources. The average number of citations per document were 140.9, with 31,854 references. "Movement Disorders" led in publications (n = 98), followed by "Brain" (n = 78) and "Neurology" (n = 65). The University of Oxford featured prominently. Thematic keyword clustering identified 9 core research areas, such as neuropsychological function and motor circuit electrophysiology. The shift from historical neurosurgical procedures to contemporary focuses like "beta oscillations" and "neuroethics" was evident. The bibliometric analysis emphasizes UK and US dominance, outlining 9 key research areas pivotal for reshaping Parkinson treatment. A discernible shift from invasive neurosurgery to DBS is observed. The call for personalized DBS, integration with NIBS, and exploration of innovative avenues marks the trajectory for future research. Copyright © 2024 the Author(s). Published by Wolters Kluwer Health, Inc.

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17. **Enhancing recruitment of individuals living with frailty, multimorbidity and cognitive impairment to Parkinson's research: experiences from the PRIME-UK cross-sectional study.**

Authors: Tenison, Emma;Smith, Matthew D.;Pendry-Brazier, Danielle;Cullen, Anisha;Lithander, Fiona E.;Ben-Shlomo, Yoav and Henderson, Emily J.

Publication Date: May 01 ,2024

Journal: Age & Ageing 53(5)

Abstract: BACKGROUND AND OBJECTIVES: People with parkinsonism who are older, living

in a care home, with frailty, multimorbidity or impaired capacity to consent are under-represented in research, limiting its generalisability. We aimed to evaluate more inclusive recruitment strategies. METHODS: From one UK centre, we invited people with parkinsonism to participate in a cross-sectional study. Postal invitations were followed by telephone reminders and additional support to facilitate participation. Personal consultees provided information on the views regarding research participation of adults with impaired capacity. These approaches were evaluated: (i) using external data from the Parkinson's Real World Impact assesSMent (PRISM) study and Clinical Practice Research Datalink (CPRD), a sample of all cases in UK primary care, and (ii) comparing those recruited with or without intensive engagement. RESULTS: We approached 1,032 eligible patients, of whom 542 (53%) consented and 477 (46%) returned questionnaires. The gender ratio in PRIME-UK (65% male) closely matched CPRD (61% male), unlike in the PRISM sample (46%). Mean age of PRIME participants was 75.9 (SD 8.5) years, compared to 75.3 (9.5) and 65.4 (8.9) years for CPRD and PRISM, respectively. More intensive engagement enhanced recruitment of women (13.3%; 95% CI 3.8, 22.9%; P = 0.005), care home residents (6.2%; 1.1, 11.2%; P = 0.004), patients diagnosed with atypical parkinsonism (13.7%; 5.4, 19.9%; P : We approached 1,032 eligible patients, of whom 542 (53%) consented and 477 (46%) returned questionnaires. The gender ratio in PRIME-UK (65% male) closely matched CPRD (61% male), unlike in the PRISM sample (46%). Mean age of PRIME participants was 75.9 (SD 8.5) years, compared to 75.3 (9.5) and 65.4 (8.9) years for CPRD and PRISM, respectively. More intensive engagement enhanced recruitment of women (13.3%; 95% CI 3.8, 22.9%; P = 0.005), care home residents (6.2%; 1.1, 11.2%; P = 0.004), patients diagnosed with atypical parkinsonism (13.7%; 5.4, 19.9%; P : We approached 1,032 eligible patients, of whom 542 (53%) consented and 477 (46%) returned questionnaires. The gender ratio in PRIME-UK (65% male) closely matched CPRD (61% male), unlike in the PRISM sample (46%). Mean age of PRIME participants was 75.9 (SD 8.5) years, compared to 75.3 (9.5) and 65.4 (8.9) years for CPRD and PRISM, respectively. More intensive engagement enhanced recruitment of women (13.3%; 95% CI 3.8, 22.9%; P = 0.005), care home residents (6.2%; 1.1, 11.2%; P = 0.004), patients diagnosed with atypical parkinsonism (13.7%; 5.4, 19.9%; P CONCLUSIONS: These recruitment strategies resulted in a less biased and more representative sample, with greater inclusion of older people with more complex parkinsonism.

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18. **GenoTools: An Open-Source Python Package for Efficient Genotype Data Quality Control and Analysis.**

Authors: Vitale, D.;Koretsky, M.;Kuznetsov, N.;Hong, S.;Martin, J.;James, M.;Makarious, M. B.;Leonard, H.;Iwaki, H.;Faghri, F.;Blauwendraat, C.;Singleton, A. B.;Song, Y.;Levine, K.;Sreelatha, A. A. K.;Fang, Z. H. and Nalls, M.

Publication Date: 2024

Journal: bioRxiv (pagination), pp. Date of Publication: 29 Mar 2024

Abstract: GenoTools, a Python package, streamlines population genetics research by integrating ancestry estimation, quality control (QC), and genome-wide association studies (GWAS) capabilities into efficient pipelines. By tracking samples, variants, and quality-specific measures throughout fully customizable pipelines, users can easily manage genetics data for

large and small studies. GenoTools' "Ancestry" module renders highly accurate predictions, allowing for high-quality ancestry-specific studies, and enables custom ancestry model training and serialization, specified to the user's genotyping or sequencing platform. As the genotype processing engine that powers several large initiatives including the NIH's Center for Alzheimer's and Related Dementias (CARD) and the Global Parkinson's Genetics Program (GP2). GenoTools was used to process and analyze the UK Biobank and major Alzheimer's Disease (AD) and Parkinson's Disease (PD) datasets with over 400,000 genotypes from arrays and 5000 sequences and has led to novel discoveries in diverse populations. It has provided replicable ancestry predictions, implemented rigorous QC, and conducted genetic ancestry-specific GWAS to identify systematic errors or biases through a single command. GenoTools is a customizable tool that enables users to efficiently analyze and scale genotype data with reproducible and scalable ancestry, QC, and GWAS pipelines.

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19. **Twelve Years of Drug Prioritization to Help Accelerate Disease Modification Trials in Parkinson's Disease: The International Linked Clinical Trials Initiative**

Authors: Wyse, Richard K.;Isaacs, Tom;Barker, Roger A.;Cookson, Mark R.;Dawson, Ted M.;Devos, David;Dexter, David T.;Duffen, Joy;Federoff, Howard;Fiske, Brian;Foltynie, Thomas;Fox, Susan;Greenamyre, J. Timothy;Kieburtz, Karl;Kordower, Jeffrey H.;Krainc, Dimitri;Matthews, Helen;Moore, Darren J.;Mursaleen, Leah;Schwarzschild, Michael A., et al

Publication Date: 2024

Journal: Journal of Parkinsons Disease Print 14(4), pp. 657-666

Abstract: In 2011, the UK medical research charity Cure Parkinson's set up the international Linked Clinical Trials (iLCT) committee to help expedite the clinical testing of potentially disease modifying therapies for Parkinson's disease (PD). The first committee meeting was held at the Van Andel Institute in Grand Rapids, Michigan in 2012. This group of PD experts has subsequently met annually to assess and prioritize agents that may slow the progression of this neurodegenerative condition, using a systematic approach based on preclinical, epidemiological and, where possible, clinical data. Over the last 12 years, 171 unique agents have been evaluated by the iLCT committee, and there have been 21 completed clinical studies and 20 ongoing trials associated with the initiative. In this review, we briefly outline the iLCT process as well as the clinical development and outcomes of some of the top prioritized agents. We also discuss a few of the lessons that have been learnt, and we conclude with a perspective on what the next decade may bring, including the introduction of multi-arm, multi-stage clinical trial platforms and the possibility of combination therapies for PD.

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20. **Patient and Public Involvement and Engagement in the Development of a Platform Clinical Trial for Parkinson's Disease: An Evaluation Protocol.**

Authors: Zeissler, Marie-Louise;Bakshi, Nikul;Bartlett, Michele;Batla, Amit;Byrom, David;Chapman, Rebecca;Collins, Sally;Cowd, Elaine;Deeson, Eric;Ellis-Doyle, Romy;Forbes, Jodie;Gonzalez-Robles, Cristina;Jewell, Anna;Lane, Emma L.;LaPelle, Nancy R.;Martin,

Keith;Matthews, Helen;Miller, Laurel;Mills, Georgia;Morgan, Antony, et al

Publication Date: 2024

Journal: Journal of Parkinsons Disease Print 14(4), pp. 809-821

Abstract: Background: Patient and public involvement and engagement (PPIE) in the design of trials is important, as participant experience critically impacts delivery. The Edmond J Safra Accelerating Clinical Trials in PD (EJS ACT-PD) initiative is a UK consortium designing a platform trial for disease modifying therapies in PD. Objective: The integration of PPIE in all aspects of trial design and its evaluation throughout the project. Methods: PwP and care partners were recruited to a PPIE working group (WG) via UK Parkinson's charities, investigator patient groups and participants of a Delphi study on trial design. They are supported by charity representatives, trial delivery experts, researchers and core project team members. PPIE is fully embedded within the consortium's five other WGs and steering group. The group's terms of reference, processes for effective working and PPIE evaluation were co-developed with PPIE contributors. Results: 11 PwP and 4 care partners have supported the PPIE WG and contributed to the development of processes for effective working. A mixed methods research-in-action study is ongoing to evaluate PPIE within the consortium. This includes the Patient Engagement in Research Scale -a quantitative PPIE quality measure; semi-structured interviews -identifying areas for improvement and overall impressions of involvement; process fidelity- recording adherence; project documentation review - identifying impact of PPIE on project outputs. Conclusions: We provide a practical example of PPIE in complex projects. Evaluating feasibility, experiences and impact of PPIE involvement in EJS ACT-PD will inform similar programs on effective strategies. This will help enable future patient-centered research.

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21. **Cost-effectiveness of Levodopa-Carbidopa Intestinal Gel in treating people with Advanced Parkinson's disease.**

Authors: Raj, Sonia;Sarvankar, Rekha;Filipe, Luis;Benedetto, Valerio;Mason, Nicola;Dawber, Jennifer;Hill, James and Clegg, Andrew

Publication Date: Aug 02 ,2023

Journal: British Journal of Neuroscience Nursing 19(4), pp. 140-144

Abstract: Advanced Parkinson's disease affects patients with existing Parkinson's disease by further deteriorating their physical and cognitive functions. In this commentary we critically assess an economic evaluation which compared the cost-effectiveness of levodopa/carbidopa intestinal gel against standard of care in treating patients with Advanced Parkinson's disease. While the economic evaluation indicated that levodopa/carbidopa intestinal gel could be cost-effective within the UK parameters, we highlight important limitations related to its design, modelling and analysis. Future research should consider the incorporation of a separate arm dedicated to the re-infusion of apomorphine on eligible Advanced Parkinson's disease patients, a wider set of levodopa/carbidopa intestinal gel adverse events and related costs, and a sub-group analysis on different socio-economic strata.

Sources Used:

The following databases are used in the creation of this bulletin: EMBASE and Medline.

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