INVESTIGATING THE ASSOCIATIONS BETWEEN PHYSICAL ACTIVITY, SLEEP QUALITY, SMOKING AND OTHER LIFESTYLE FACTORS WITH PARKINSON'S DISEASE: A PROSPECTIVE STUDY OF 502,017 UK BIOBANK PARTICIPANTS

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Abstract

Introduction: Parkinson's disease (PD) represents a fast-growing neurodegenerative disease characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta leading to bradykinesia, rigidity and/or rest tremor, and many other non-motor symptoms. In many countries Its global burden of disability and mortality has more than doubled in the last few decades, with age at onset shifting progressively towards more advanced age, strongly suggesting that environmental factors, other than genetic risk variants, are implicated in PD's pathogenesis[1]. Exposure to neurotoxins (e.g., pesticides) and traumatic brain injury are well known risk factors, whereas smoking, coffee intake, physical exercise and healthy sleep quality seem to be protective. Unlike the genetic risk, which is predominantly stable, environmental factors are changing overtime; in the last few decades major changes in lifestyle factors have occurred leading to more diffuse obesity, metabolic syndrome, insulin resistance, and low grade-inflammation, all factors implicated in the development of PD[2].

Objectives: Given this background, we aimed to evaluate associations of physical activity, sleep quality, smoking and other lifestyle factors with the risk of PD diagnosis (ICD-10; 'G20') making use of the large prospective cohort study provided by the UkBiobank project[3]. Moreover, we aimed to investigate the mechanism underlying the protective effect of smoking showed in previous studies to be causally linked to the PD risk[4], more specifically by studying potential mediation and additive interactions between smoking and other lifestyle factors.

Methods: From the UkBiobank database, we obtained a sample of 502,017 participant (228,857 men and 273,160 women, from 40 to 69 years old) recruited between 2006 and 2010. These participants were free from PD diagnosis at baseline and were followed for up to 15.8 years (median = 12.8 years). The cohort documented 3325 incident cases of PD, with a mean age at diagnosis of 71.8 years. Exposures included levels of physical activity, sleep quality, smoking status, dietary habits, alcohol, and coffee. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between each exposure and PD diagnosis were calculated using a Cox proportional-hazard regression model, with age as the underlying timescale, adjusting for several potential confounders measured at baseline, such as sex, BMI, long-standing illness/disability/infirmity, Townsend deprivation index, family history of PD, history of head injury diagnosis, neuroticism score, time spent sitting, and risk-taking personality. We then relied on the approach of VanderWeele (2014)[5], to decompose the total effect of smoking habits on PD risk considering sleep quality, physical activity, and neuroticism as potential mediators/interactors, i.e., the total effect was decomposed into, i) a direct effect, ii) a mediated effect, iii) an additive interaction effect, and iv) both mediation and additive interaction effects.

Results: Our results highlighted a statistically significant protective role for high sleep quality (for "High" vs "Low", HR=0.89 [95%CI: 0.80-0.99]), and high physical activity (for "High" vs "Low" physical activity, HR=0.84 [95%CI: 0.75-0.94]). Both former and current smokers resulted in having a lower risk compared with never smokers (for "Current smokers", HR=0.65 [95%CI: 0.56-0.75]; for "Previous smokers", HR=0.86 [95%CI: 0.80-0.93]). Moderate coffee consumption (≤ 3 cups/day) resulted as a significantly protective factor compared to abstainers (HR = 0.88 [95% CI: 0.82-0.95]), while, compared to a light alcohol consumption (≤ 8 weekly/units), both previous drinking and lifetime abstention resulted in higher PD risk (HR= 1.29 [95%CI: 1.06-1.58] and HR=1.21 [95%CI: 1.02-1.42], respectively). Investigating the four-way decomposition of the total effect for current smokers vs never smokers, we found that 99% of this protective effect is attributable to a statistically significant additive interaction with sleep quality. In particular, the results suggest that smoking protective effect seems to present only when sleep quality is high, while it is negligible when sleep quality is low.

Conclusions: Overall, these results show a protective association between vigorous physical exercise, high sleep quality, smoking and low alcohol/coffee consumption with PD risk, after adjustment for several confounders. These results are in line with previous studies[6] and have the strength to rely on a large longitudinal dataset. Higher levels of physical activity could be safe primary interventions for PD prevention in clinical practice[7], but randomized clinical trials are further needed to establish this causal association. The protective role of current smoking resulted entirely driven by its additive interaction with a high sleep quality. Since additive interactions have been acknowledged to be more useful in assessing mechanistic interactions, and therefore most relevant for assessing the public health significance of interactions, this finding may support the theory which suggests that the protective role of smoking would not derive from the chemical compounds contained in cigarettes, but, instead, due to the fact a lower propensity to smoke would lead to a higher propensity to develop PD due to a dysfunction of dopaminergic reward circuitry[8]. Since this dysfunction has also been associated with sleep disturbances[9], the lower PD risk in smokers would be observed only in individuals with a well-functioning dopaminergic reward circuitry, such as when sleep quality is high, rather than from the mere consumption of cigarettes. Further studies are needed to validate these results.

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