Evaluation of Causality Between ADHD and Parkinson's Disease: Mendelian Randomization study

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Abstract

In a retrospective cohort study, patients with attention-deficit hyperactivity disorder (ADHD) and psychostimulant prescription were associated with increased risk of Parkinson's disease (PD). It is unclear whether ADHD *per se* or psychostimulant prescription is associated with PD. We aim to determine if genetic correlation or/and causal association exists between ADHD and PD using summary statistics obtained from the largest meta-analysis of genome-wide association studies of ADHD (20,183 cases; 35,191 controls) and PD (26,421 cases; 442,271 controls). Genetic correlation was tested between ADHD and PD by linkage disequilibrium score regression. Causal estimate was assessed by inverse-variance weighted (IVW) method as the main mendelian randomization analysis, with sensitivity analyses to detect horizontal pleiotropy. Weak and inverse genetic correlation existed between ADHD and PD (r=-0.100;SE=0.045;P=0.026). Univariable IVW analysis with 10 and 77 genetic instruments respectively revealed null association for ADHD with PD (OR=0.930 per doubling in odds of ADHD; 95% CI:0.792-1.092) and PD with ADHD (OR=0.986 per doubling in odds of PD; 95% CI:0.956-1.015). Multivariable IVW analyses adjusted for BMI/smoking also revealed null association of ADHD with PD. Using 58 PD-associated genetic instruments, multivariable IVW analysis with/without adjustment for BMI/smoking suggested a weak and inverse causal association for PD on ADHD, but cautious interpretation is required. This well-powered study did not support causality between ADHD and PD. The observed positive association between ADHD and PD is more likely to be caused by unmeasured confounders. As psychostimulant use is associated with high risk of early-onset PD, future research should focus on this area.

Introduction

Being one of the most prevalent neurodevelopmental disorders across the lifespan, attention-deficit hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity, and increased impulsivity, leading to impairment on an individual's daily functioning across various settings(Bonvicini et al., 2016). The prevalence of ADHD is estimated to be approximately 5% in school-aged children and 2.5% in adults(Lopez et al., 2018; Polanczyk et al., 2014; Thomas et al., 2015). Functional neuroimaging finds that ADHD patients have dysfunction of brain regions including the frontal cortex, limbic system, basal ganglia, and reticular activating system, and suggests that ADHD is caused by deficits in dopaminergic and noradrenergic neurotransmission(Curtin et al., 2018; Levy and Psychiatry, 1991; Tripp and Wickens, 2009). Current pharmacological treatment of ADHD includes the psychostimulants, methylphenidate (MPH) and amphetamine derivatives (AMP), both of which regulate dopamine and norepinephrine in the brain by reversibly blocking the dopamine reuptake transporter (DAT)(Attention-Deficit and DISORDER, 2011; Volkow et al., 2005).

Parkinson's disease (PD) is the second most common progressive neurological disorder that affects at least six million people globally(De Lau and Breteler, 2006; Dorsey et al., 2018). The neuropathological feature of PD is the presence of α-synuclein-containing Lewy bodies and a pronounced reduction in striatal dopamine, manifesting as severe motor symptoms, including uncontrollable tremor, postural imbalance, slower movement and rigidity(De Lau and Breteler, 2006; Lotharius and Brundin, 2002). It has been observed in a case-control study that ADHD symptoms may precede PD, with no evidence of involvement of psychostimulants(Walitza et al., 2007). However in a recent large retrospective cohort study using medical records between 1996 and 2016 from Utah Population Database (with 31,769 patients with ADHD and 158,790 non-ADHD persons), where patients with ADHD were associated with more than 2-fold

increased risk of early-onset PD or basal ganglia and cerebellum (Parkinson's like) diseases, there was also 8.6-fold increased risk of developing early-onset PD or Parkinson's like diseases for those ADHD patients who were prescribed psychostimulants(Curtin et al., 2018). Curtin *et al* considered the excessive risk in patients treated with psychostimulants is attributed to the severity of the disease rather than psychostimulants(Curtin et al., 2018). It is therefore important to evaluate the association between ADHD and PD. Moreover, our previous study has shown significant increase in the use of ADHD medication in children and 4.5% of children in the North America have been prescribed ADHD medication(Raman et al., 2018), implying a potential public health issue if psychostimulants would increase the risk of developing PD. Currently, it remains unclear whether ADHD has a positive causal effect on PD, or whether the association between the two diseases is due to shared mechanisms. Moreover, PD is influenced by both genetic and environmental factors. It is also possible that the genetic factors of PD also play a causal role in ADHD development, with people susceptible to PD having increased risk of developing ADHD, which is usually manifested at a younger age. With exposure to environmental factors, such as pesticides, disease symptoms of PD may subsequently appear in individuals at a later stage of life.

Mendelian randomization (MR) is considered a powerful approach which makes use of genetic variation as natural and random experiment to evaluate the causal association between two traits or diseases, when such relationships cannot be directly evaluated using clinical trial(Emdin et al., 2017). Its principles were described clinically elsewhere(Emdin et al., 2017). In brief, genetic variants that influence the susceptibility to a disease (like ADHD as exposure) identified from genome-wide association studies (GWAS) could serve as instruments to determine the association of lifelong risk of another disease (like PD as outcome). The naturally assigned genetic variants utilized in MR analyses were fixed at conception, making MR

approach less likely to be influenced by unmeasured confounding and reverse causation when compared to observational studies, relying on several assumptions(Davies et al., 2018). These assumptions for MR and our study design are illustrated in Figure 1.

Based on the findings of the aforementioned large-scale retrospective cohort study, we hypothesized that ADHD might have a positive causal role on PD or vice-versa, which may contribute to the increased risk of PD in ADHD patients, especially for those who were prescribed psychostimulants. Therefore, the aim of this MR study is to examine the causal relationship between ADHD and PD, and study the effect of potential mediators in such relationship.

Experimental Procedures

Data sources

Details of the data sources are listed out in Table 1. Summary statistics of genetic instruments were extracted from the largest publicly available GWAS / GWAS meta-analysis of the exposure, outcome and potential mediators. The risk factor and outcome were ADHD (20,183 cases and 35,191 controls)(Demontis et al., 2019) and PD (around 1.4 million subjects in total; the minimum sample size at which the genetic instruments were tested had 26,421 cases and 442,271 controls)(Nalls et al., 2019). In previous studies, smoking and BMI were found to be genetically correlated with both ADHD(Demontis et al., 2019) and PD(Nalls et al., 2019) although the direction was opposite. Higher BMI was reported to be causally associated with increased risk of ADHD(Martins-Silva et al., 2019) but decreased risk of PD(Noyce et al., 2017). It is possible that ADHD and PD might be linked up by smoking or BMI. Datasets of potential mediators under investigation included a GWAS meta-analysis of body mass index (BMI) (N=681,275)(Yengo et al., 2018), and a meta-analysis of 35 GWAS of smoking status

(N=1,232,091; ever regular versus never regular)(Liu et al., 2019). Ethical approval has been obtained from respective GWAS as stated in the publications.

Estimation of genetic correlation

Linkage disequilibrium (LD) score regression(Bulik-Sullivan et al., 2015a; Bulik-Sullivan et al., 2015b) was employed to estimate the genetic correlation between ADHD and PD based on the summary statistics of GWAS data(Demontis et al., 2019; Nalls et al., 2019) instead of individual-level genotypes. This method has the advantages of not being biased by sample overlap between GWAS datasets and not requiring multiple phenotype measurements to be conducted on the same individual in estimating genetic correlation between complex traits(Bulik-Sullivan et al., 2015a). We used pre-computed LD scores suitable for European-ancestry samples and Python command line tool (http://github.com/bulik/ldsc).

Selection of genetic instruments for MR analyses

Independent genetic variants significantly associated with the exposure (ADHD or PD) were identified by the respective GWAS(Demontis et al., 2019; Nalls et al., 2019). In brief, Demontis *et al* first performed LD clumping, which started with the variant with the strongest association with ADHD (as the index variant). Other variants 500Kb away and uncorrelated (r^2<0.2) from the existing index variant were assigned to a new locus/clump, until all ADHD-associated genome-wide significant ($p<5x10^{-8}$) variants were assigned to one of the risk loci/clumps. Within each locus/clump, independent index variants were subsequently identified (r^2<0.1)(Demontis et al., 2019). Meanwhile, independent PD-associated genetic variants ($p<5x10^{-8}$) were identified by Nalls *et al* in conditional-joint analysis corrected for LD between single nucleotide polymorphisms (SNPs)(Yang et al., 2012), with a window of >1 megabase indicating that SNPs are in complete LD(Nalls et al., 2019). The genome-wide

independent genetic variants uncovered by respective GWAS were initially selected as the genetic instruments in MR analyses. If the summary statistics of a genetic instrument were unavailable in the GWAS of outcome or mediator datasets, the same proxy in high LD ($r^2 \geq 0.8$ with reference to the European samples in the 1000 Genome project) and present in all the exposure, outcome and mediator datasets was selected as the genetic instrument. If no proxies could be identified, or if the proxy was no longer significantly associated with the exposure ($P>0.05$), the genetic instrument/proxy was excluded from MR analysis. This formed the first part of the analysis. In addition, a large portion of the genome is likely pleiotropic. Whether the genetic instruments/proxies were associated with potential confounders of ADHD/PD (such as education attainment(Arnold et al., 2020; Kotagal et al., 2015), schizophrenia(Gudmundsson et al., 2019; Mok et al., 2016), waist circumference(Chen et al., 2004; Fuemmeler et al., 2011), serum lipid levels(Ugur et al., 2018; Xicoy et al., 2019), neuroticism(Knouse et al., 2013; Sieurin et al., 2016), Crohn's disease(Hegvik et al., 2018; Hui et al., 2018), and inflammatory bowel disease(Hegvik et al., 2018; Villumsen et al., 2019)) were checked at PhenoScanner, a database of publicly available genotype-phenotype association results from GWAS(Staley et al., 2016). Notably, genetic instruments associated with BMI and smoking status were kept in the analyses as they were targeted to be examined in the current study by multivariable MR analyses to determine if BMI and smoking status are potential mediators linking up the two diseases. For genetic variants associated with other potential mediators / confounders as identified by large-scale GWAS conducted by relevant representative consortiums, they were considered as pleiotropic genetic instruments and excluded from this second part of analysis. This approach aims to avoid using instruments that might contribute large effects on multiple traits at the same time. As a sensitivity analysis, more stringent selection criterion were adopted to select the genetic instruments for MR analyses, using the clump command in PLINK 1.9(Chang et al., 2015) with a window=10Mb and r^2

cutoff=0.001, which was in line with the MR-Base application(Hemani et al., 2018). In inferring causality of ADHD on PD, 12 independent SNPs significantly associated with ADHD were initially employed as genetic instruments in dissecting the causal effects of ADHD on PD. Similarly, in evaluating the causality of PD on ADHD, 90 independent SNPs significantly associated with PD were initially selected as genetic instruments. Notably, for the PD dataset, the online immediately accessible version of summary statistics does not include the genetic data from 23andMe, Web-Based Study of Parkinson's Disease and the meta-analysis conducted by Nalls *et al* 2014(Nalls et al., 2014), with a sample size of around 470,000 when compared to the full dataset of around 1.4 million individuals. The association between a genetic proxy and PD might be weak in the online diminished dataset due to the insufficient sample size and reduced power. The summary statistics of the selected genetic instruments for each MR analysis are included in Supplemental Tables 1-6. Pleiotropic associations of the excluded genetic instruments were listed in Supplemental Table 7.

Power calculation

Proportion of variance in the exposure explained by the genetic instruments was derived from the Mangrove package in R(Jostins et al., 2013). An online web tool, mRnd (http://cnsgenomics.com/shiny/mRnd/)(Brion et al., 2013), was employed to perform power calculation.

MR analyses

All the genetic instruments were oriented such that the effect alleles were positively associated with the exposure. The effect alleles were matched across the summary data of the exposure, mediator and outcome dataset. Univariable inverse-variance weighted (IVW)(Burgess et al., 2013) method with random-effects model was used for main MR analysis to assess the total

effect of the exposure on the outcome(Burgess et al., 2017), with heterogeneity between the causal estimates of the genetic instruments tested. Although IVW is the conventional method of MR analysis, the major drawback is that it assumes all instrumental variables are valid. If IVW analysis revealed a significant causal association, weighted median method, MR-Egger and MR-PRESSO's main analysis were used as sensitivity analyses. Weighted median method provides consistent estimates even when up to 50% of the information comes from invalid instrumental variables(Bowden et al., 2016). Under the assumption that the magnitude of the pleiotropic effects are independent of the SNP-risk factor associations across all variants, also known as the INstrument Strength Independent of Direct Effect (InSIDE) assumption, the intercept of MR-Egger regression represents the average pleiotropic effects across all SNPs(Bowden et al., 2015). With this InSIDE assumption, MR-Egger regression detects and corrects for bias arising from unbalanced pleiotropy in MR studies(Bowden et al., 2015). MR-Egger intercept test(Bowden et al., 2015) and MR pleiotropy residual sum and outlier (MR-PRESSO)(Verbanck et al., 2018) were employed to test for the presence of directional pleiotropy. MR-PRESSO comprises of three components: (i) global test has adequate power to evaluate the overall horizontal pleiotropy among all instruments even if pleiotropy just occurs in less than half of the instruments; (ii) outlier test provides the causal estimate upon removal of pleiotropic genetic instruments; and (iii) distortion test determines if there is significant difference in the causal estimate before and after the removal of pleiotropic genetic instruments. Due to the use of a large number of instruments, heterogeneity between their causal estimates was not evitable and it was regarded as a chance to examine if multiple distinct causal mechanisms existed between the exposure and outcome using the contamination mixture method(Burgess et al., 2020). Multivariable IVW analysis was also performed to dissect the mechanisms in the causal pathway from the exposure to the outcome(Burgess et al., 2017; Burgess and Thompson, 2015). The direct causal effect of the exposure on the outcome was

evaluated by multivariable IVW by adjusting for the beta estimates of potential mediators, including BMI and smoking status. If multivariable IVW analyses revealed causality, multivariable MR-Egger method was also applied as a sensitivity analysis. Multivariable MR-Egger intercept test was employed to detect for pleiotropies(Rees et al., 2017). MR-PRESSO analysis was performed using "MRPRESSO" package in R(Verbanck et al., 2018) while univariable IVW, weighted median, MR-Egger and contamination mixture analyses were conducted with 'MendelianRandomization' package in R(Yavorska and Burgess, 2017). Multivariable IVW and MR-Egger analyses were also conducted using the 'MendelianRandomization' package(Yavorska and Burgess, 2017).

As the exposures in all the MR analyses are binary variables, the causal estimates were initially equivalent to the change in the outcome per unit change in the exposure in log odds scale [=exponential 1, i.e. 2.72-fold change in the odds of the exposure]. For the sake of interpretation, the causal estimates were converted by multiplying 0.693 (=ln 2) and then exponentiating to represent change in outcome per 2-fold change in the prevalence of the exposure(Burgess and Labrecque, 2018).

Results

Genetic correlation between ADHD and PD

Genetic correlation between ADHD and PD was evaluated by LD score regression. Weak and inverse genetic correlation was observed between ADHD and PD (r=-0.100; SE=0.045; z=-2.220; P=0.026).

Two-sample MR of ADHD with PD

Out of the 12 independent ADHD-associated SNPs, eight SNPs were available in the PD dataset and proxies in high LD with the unmatched SNPs were identified for the remaining four SNPs (For r^2 of the four proxies, median: 0.881; range: 0.812-0.975; Supplemental Table 1). Null causal association was observed in univariable (OR=0.900 per doubling in odds of ADHD; 95% CI: 0.785-1.032; P=0.131; Table 2), with a significant MR-PRESSO global test (P=0.048). For multivariable IVW analysis, the 12 ADHD-associated independent SNPs were matched across the datasets of mediators (including smoking and BMI) and outcome (PD). Five of the SNPs could be matched while proxies were identified for the remaining seven unmatched SNPs (For r^2 of the seven proxies, median: 0.975; range: 0.812-1; Supplemental Table 2). IVW analysis before and after adjustment for potential mediators resulted in a null causal association, with some evidence of pleiotropy (Before adjustment for mediators: MR-Egger intercept test P=0.023; MR-PRESSO global test P=0.028; Upon adjustment for BMI: multivariable Egger intercept test P=0.006; Table 2).

The MR analyses were repeated with exclusion of pleiotropic genetic instruments, as the pleiotropy may violate the MR assumption and affect the validity of the analyses. Two pleiotropic genetic instruments were excluded from MR analyses and a total of 10 genetic instruments were utilized in univariable MR analysis (Supplemental Table 1). Univariable IVW analysis revealed null causal association of ADHD with PD (OR=0.930 per doubling in odds of ADHD; 95% CI: 0.792-1.092; P=0.374; Table 3; Supplemental Figure 1a). Both MR-Egger intercept test (P=0.488) and MR-PRESSO global test (P=0.071) suggested the absence of horizontal pleiotropy (Table 3). For multivariable analysis with instruments matching across the mediator and outcome datasets, three of the proxies were pleiotropic so they were excluded from this part of analyses, and a total of nine genetic instruments were used (Supplemental Table 2). Null causal association between ADHD and PD was observed in univariable (Table

3; Supplemental Figure 1b) and multivariable IVW analysis before and after adjustment for BMI or smoking status. Consistently, the multivariable Egger intercept tests were insignificant (Adjusted for BMI: P=0.451; Adjusted for smoking status: P=0.624), implying no pleiotropy was present (Table 43).

Using contamination mixture method, unimodal distribution of causal estimates was observed in all the above univariable analyses, implying the absence of multiple mechanisms involved. In examining the causal effects of ADHD on PD, majority of the genetic instruments were located on different chromosomes. The only two instruments located on the same chromosome were separated by more than 50Mb with $r^2<0.001$. Even with more stringent criterion of selecting genetic instruments adopted by MR-Base, the same set of genetic instruments was derived. No supplementary sensitivity analysis was performed.

Two-sample MR of PD with ADHD

Out of the 90 PD-associated SNPs, 85 SNPs could be matched with the ADHD dataset and proxy could be identified for one of the remaining unmatched SNPs ($r^2=0.921$; Supplemental Table 3). In univariable IVW analysis, null causal association was observed (OR=0.980; 95% CI: 0.955-1.005; P=0.114; Table 4). Horizontal pleiotropy was unlikely (MR-Egger intercept: P=0.841; MR-PRESSO global test: P=0.127). For multivariable analysis, we matched the 90 PD-associated SNPs across the datasets of BMI, smoking status and ADHD. 34 of the SNPs were available across the datasets and proxies were identified for 38 of the remaining unmatched SNPs (For r^2 of the 38 proxies, median: 1; range: 0.824-1; Supplemental Table 4). Two proxies were no longer associated with PD and were excluded from analysis, leaving 70 genetic instruments. Before adjustment for potential mediators, doubling in odds of PD was

associated with reduced risk of ADHD (IVW: OR=0.967; 95% CI: 0.937-0.997; P=0.032; Table 4). Similar estimate was obtained using weighted-median and MR-PRESSO analysis. Evidence of horizontal pleiotropy was absent (MR-Egger intercept: P=0.731; MR-PRESSO global test: P=0.155). Multivariable IVW adjusted for the beta estimates of BMI and smoking status respectively demonstrated that doubling in odds of PD was associated with lower risk of ADHD (Adjusted for BMI: OR=0.967; 95% CI: 0.938-0.999; P=0.039; Adjusted for smoking status: OR=0.963; 95% CI: 0.934-0.992; P=0.011; Table 4). Meanwhile, multivariable Egger test suggested null association after adjusting for the potential mediators, with insignificant intercept tests (P>0.05), indicating the absence of pleiotropy.

After excluding nine pleiotropic genetic instruments, a total of 77 genetic instruments were utilized in univariable MR analysis (Supplemental Table 3). Univariable IVW analysis revealed null causal association (OR=0.986 per doubling in odds of PD; 95% CI: 0.956-1.015; P=0.341; Table 5; Supplemental Figure 2a). Both MR-Egger intercept test (P=0.234) and MR-PRESSO global test (P=0.063) did not detect any horizontal pleiotropy (Table 5). For multivariable analysis, 12 genetic instruments were pleiotropic. They were excluded from the second part of analysis, making up a total of 58 genetic instruments (Supplemental Table 4). Before adjustment for potential mediators, IVW analysis demonstrated that doubling in odds of PD reduced the risk of ADHD by 4.3% (OR=0.957; 95% CI: 0.925-0.991; P=0.013) (Table 5; Supplemental Figure 2b). Sensitivity analysis of weighted median method yielded similar estimates (OR=0.930; 95% CI: 0.883-0.979; P=0.006). Null association was observed in MR-Egger test (OR=0.943; 95% CI: 0.866-1.026; P=0.173). MR-Egger intercept test (P=0.696) and MR-PRESSO global test (P=0.145) did not detect any horizontal pleiotropy. Similar causal association for PD on ADHD was observed after adjustment for BMI (OR=0.958; 95% CI: 0.926-0.992; P=0.015) and smoking status (OR=0.948; 95% CI: 0.918-0.979; P=0.001) (Table

5). Whereas, null causal association was revealed by multivariable Egger analyses after adjustment for both potential mediators. The multivariable Egger intercept tests were insignificant (Adjusted for BMI: P=0.545; Adjusted for smoking status: P=0.718).

As a sensitivity analysis, stricter criterion with clumping window of 10Mb and r^2 of 0.001 were adopted in selecting genetic instruments. Twenty-four independent SNPs were identified to be associated with PD by clumping. In univariable analysis, twenty-two of the SNPs were matched with the dataset of ADHD while proxy could be identified for one of the unmatched SNPs (r^2=0.902; Supplemental Table 5). Similar null causal association was observed, with some evidence of pleiotropy (MR-PRESSO global test: P=0.012; Supplemental Table 8). For multivariable analysis, eight SNPs were matched across the datasets of mediators and outcome while proxies were identified for the 12 remaining unmatched SNPs (For r^2 of the 12 proxies, median: 1; range: 0.860-1; Supplemental Table 6). IVW analyses demonstrated null association between PD and ADHD before and after adjustment for potential mediators, with multivariable Egger intercept tests suggesting the presence of horizontal pleiotropy (P<0.05; Supplemental Table 8).

This sensitivity analysis was repeated after removing the potential pleiotropic instruments. In univariable analysis, two pleiotropic instruments were excluded from the second part of analysis, leaving 21 genetic instruments (Supplemental Table 5). In univariable analysis, similar null causal association was observed with no evidence of pleiotropy (Supplemental Table 9). Two pleiotropic instruments were also removed from the multivariable analysis. Both before and after adjustment for potential mediators, there was null association between PD and ADHD, and pleiotropy was unlikely (Supplemental Table 9).

In all the univariable MR analyses evaluating the causal effects of PD on ADHD, unimodal distribution of causal estimates was observed using contamination mixture method, implying the absence of multiple causal mechanisms.

Power

Due to the possible violation of MR assumption, MR analyses with exclusion of pleiotropic genetic instruments were considered as the primary analysis. The statistical power and strength of genetic instruments for the primary MR analysis were presented in Table 6. Since the summary statistics of each genetic instrument might be obtained from a subset of GWAS sample, the minimum sample size was adopted to compute the minimum statistical power of our analyses. Assuming the genuine underlying association had an OR of 1.2 of the outcome per doubling in odds of exposure, the primary analyses had >90% power to detect such association. In multivariable MR analysis evaluating the causal effect of ADHD on PD, our study had ≥80% power to detect the causal association if the genuine OR≥1.167 or OR≤0.824. For the causal effect of PD on ADHD, the study also had ≥80% power to detect the causal association if the OR≥1.126 or OR≤0.883.

Discussion

In the two-sample bi-directional MR study, null causal association between ADHD and PD was observed in the univariable analysis, implying the total causal effect between the two disorders was null. Similarly, multivariable MR analyses with adjustment for potential mediators, such as BMI and smoking, did not provide sufficient evidences to demonstrate their roles as mediator between the two disorders. Since the current study is well-powered, the null

association observed is likely to be genuine. The present study also demonstrated that weak and inverse genetic correlation existed between ADHD and PD.

Both ADHD and PD are heritable, with heritabilites estimated to be 0.22 for both diseases in the latest GWAS meta-analysis using LD score regression method(Demontis et al., 2019; Nalls et al., 2019). Large-scale GWAS meta-analyses have identified several susceptibility loci, which can be used to evaluate the relationship between ADHD and PD. Genetic correlation analysis revealed the shared genetic architecture between ADHD and PD. In this study, we observed that ADHD and PD were inversely correlated with each other, indicating that genetic variants leading to increased risk of ADHD are associated with reduced risk of PD; however, the association is weak. To enhance the understanding on the pathogenesis of the two genetically correlated diseases, future studies, such as gene-based and enriched pathway analyses, are warranted to examine the genetic overlap and difference between ADHD and PD. The present finding of weak genetic correlation was inconsistent with the null genetic correlation observed(Demontis et al., 2019; Nalls et al., 2019) with the use of smaller datasets of ADHD and PD derived from 9 population-based pediatric ADHD cohorts comprising 17,666 children(Middeldorp et al., 2016) and a Caucasian PD cohort with 5,691 participants(Simon-Sanchez et al., 2009) respectively. In particular, the previous GWAS meta-analysis of ADHD could not identify any genome-wide significant signals for the disorder(Middeldorp et al., 2016). Their null genetic correlation may be attributed by the limited power of the GWAS.

We performed MR analyses using different sets of genetic instruments based on different selection criterion. In the first part of the analysis using all exposure-associated SNPs as the genetic instruments, some evidence of pleiotropy was shown by MR-Egger intercept and MR-

PRESSO global tests. Potential pleiotropic instruments were therefore identified by PhenoScanner (Supplemental Table 7) and excluded from the second part of the analysis, where horizontal pleiotropy was unlikely. Since the presence of pleiotropy would violate MR assumption and might invalidate the MR findings, we considered the analyses with exclusion of pleiotropic instruments as the primary analyses of our study. Additional sensitivity analyses were also performed utilizing stricter selection criterion adopted by MR-Base. In the primary MR analysis, we found no causal association between ADHD and PD, which is indeed consistent with a previous small-scale genetic association study evaluating the relationship of nine ADHD risk variants with PD(Geissler et al., 2017). However, the null association observed in that European study could be due to small sample size (5,333 PD cases and 12,019 controls) and hence limited power. Moreover, they did not evaluate the causal association using MR approach. In the current study, estimates from 26,421 PD cases and 442,271 controls (minimum sample size at which the genetic instruments were tested) were adopted in the MR analysis. Still, no significant causal association was observed. The current well-powered study provides an evidence that ADHD does not casually increase risk of PD development.

BMI and cigarette smoking were individually associated with ADHD and PD. While the pooled prevalence of obesity (defined by BMI) was greatly increased by 70% and 40% respectively in adults and children with ADHD, a two-sample MR study demonstrated that higher BMI might reduce the risk of PD(Noyce et al., 2017). Not only the prevalence of smoking among individuals with ADHD was significantly higher than that of the general population, but significant association was also observed between the number of ADHD symptoms and lifetime risk of regular smoking(McClernon and Kollins, 2008). Meanwhile, tobacco components, such as nicotine, were speculated to be neuroprotective and contribute to the reduced PD risk among tobacco smokers in dose-dependent manner(Ascherio and

Schwarzschild, 2016). BMI and smoking had a heritable component, with heritabilities of 0.192 and 0.054 respectively derived by LD score regression(Demontis et al., 2019). Previous studies also revealed that BMI and smoking were genetically correlated with ADHD and PD although the direction was opposite in the two disorders. BMI was found to have positive and inverse genetic correlation with ADHD (r=0.258; SE=0.032; z=7.96; P=$1.68x10^{-15}$)(Demontis et al., 2019) and PD (r=-0.062; SE=0.024; z=-2.556; P=0.011) respectively(Nalls et al., 2019). Whereas, number of cigarettes smoked per day had positive and modest genetic correlation with ADHD (r=0.451; SE=0.103; z=4.40; P=$1.07x10^{-5}$)(Demontis et al., 2019), but inverse genetic correlation with PD (r=-0.192; SE=0.071; z=-2.713; P=0.007)(Nalls et al., 2019). Thus, it is possible that the null association observed in univariable IVW is due to the opposite effect of these potential mediators in the two disorders. Notably, there was weak though significant causal association for PD on ADHD when 58 genetic instruments were used in the multivariable IVW analysis (Table 5). However, sensitivity analysis of multivariable MR-Egger method and using strictly selected genetic instruments did not yield significant causal association. Such inconsistent findings would require cautious interpretations and further studies are required to confirm if such negative causality is genuine. Even if such causal association is genuine, the direction of association was opposite to our hypothesis, i.e. ADHD increases risk of PD or vice-versa. This observation further strengthens the possibility that the observed increased risk of PD among ADHD patients is contributed by other factors (such as psychostimulants and other shared risk factors), instead of the causal relationship between these two diseases.

The current study has several important clinical implications. Our findings did not support causal association exists between ADHD and PD. In addition to the findings from the retrospective study using medical records from the Utah Population Database(Curtin et al.,

2018), medications of ADHD instead of the disorder itself, may be the contributing factor for increased risk of developing PD among ADHD patients. Given their robust clinical efficacy(Cortese et al., 2018), psychostimulants including methylphenidate (MPH) and amphetamines (AMP) have been the mainstay of treatment for ADHD for the last two decades and widely used in many countries(Raman et al., 2018). Early studies have shown that high doses of AMP might damage dopaminergic pathways(Advokat, 2007; Arnsten, 2006). MPH might have dopamine neurotoxic potential(Wang et al., 2013; Yuan et al., 1997), and such damage may be irreversible. Yet, only limited number of studies have examined the pharmacological risk of psychostimulants and further investigations will be required. A previous empirical assessment reported the exposure to a high dose of MPH or AMP lead to persistent basal ganglia dopaminergic deficits, which suggested patients who abuse MPH or AMP are more likely to develop PD(Gerlach et al., 2003). This is in line with the Utah cohort study that ADHD patients who had been prescribed stimulant medications had an even greater increased risk of developing PD by six to eight fold(Curtin et al., 2018). While the current study eliminated the possibility that the increased PD risk was caused by ADHD, a safety concern arises: ADHD medications may be associated with increase in risk of PD. Nevertheless, other shared risk factors, including brain injury, environmental factors such as exposure to toxic chemicals and metals, can also put an individual at greater risk for being diagnosed with both ADHD and PD(Banerjee et al., 2007; Gorell et al., 1997; Hubble et al., 1993; Priyadarshi et al., 2001). Given that the causal relationship between ADHD per se and PD is unlikely to be present, as demonstrated in the current study, whether psychostimulants that are commonly used to treat ADHD would lead to increased risk of PD warrants further investigation. The European ADHD Guidelines Group has recommended that continued monitoring of potential neurological adverse effects in older patients is needed(Wong et al., 2019). Further research should focus on this area.

The key strength of our study is the adoption of two-sample MR study to evaluate the causal association between two diseases, which is infeasible to be assessed by clinical trials. We utilized summary statistics derived from the largest GWAS meta-analysis of ADHD and PD to-date. These well-powered GWAS meta-analyses provided strong genetic instruments for the current MR study. The relatively high F-statistics suggested that our study unlikely suffers from weak instrument bias. We have over 90% power to detect association with an OR of 1.2 per doubling in odds of exposure in this study, implying that the null association observed is likely to be genuine. In addition, sample overlap between the exposure and outcome datasets was unlikely, avoiding bias that would arise in the direction of confounded association if overlapping sample increases(Burgess et al., 2016). Nevertheless, there are limitations. First, presence of horizontal pleiotropy may be inevitable that the genetic instruments may have an indirect effect on the outcome via a pathway that does not involve the risk factor of interest. However, we have used two different methods to test for the presence of horizontal pleiotropy (MR-Egger intercept and MR-PRESSO global tests) and found no evidence of pleiotropy upon exclusion of potentially pleiotropic instruments, though horizontal pleiotropy cannot be ruled out unequivocally. Second, the original instruments significantly associated with the exposure may not be available across the datasets of mediators and outcome in multivariable MR analyses. Proxies in high LD with the original instruments present in all the datasets were adopted in the multivariable analysis. However, these proxies were identified based on the LD pattern of Europeans in 1000 Genome Project, instead of the LD pattern in the respective GWAS cohorts. Although most of the genetic proxies had effect size and standard error comparable to that of original instruments regarding their association with the exposure, a few proxies had relatively different summary statistics. Studies with individual-level genotyping data may be warranted to identify reliable proxies of high LD in the GWAS cohort. Third, like

many other epidemiological studies, there are possible unmeasured and residual confounding factors. Fourth, while the GWAS of PD, BMI and smoking status were conducted in European participants, approximately 95% of the individuals in the ADHD dataset were of European ancestry. This may lead to violation of MR assumption as association between a genetic variant and the disease outcome may be confounded by population substructure(Davies et al., 2018). Nonetheless, the results of GWAS meta-analysis of ADHD in Europeans were similar to that in ethnically mixed population(Demontis et al., 2019), suggesting that the 5% population admixture may not confound the genetic association. Fifth, the GWAS were conducted in participants of mainly European ancestry, generalization of the findings to other ethnic groups need to be cautious.

Conclusions

Our study findings suggest no causal association exists between ADHD and PD. Although previous studies showed BMI and smoking status had significant yet opposite genetic correlation with ADHD and PD respectively, they are unlikely the mediators of the two diseases. The positive association between ADHD and increased PD risk observed in a recent retrospective study is more likely to be caused by other unmeasured confounders that warrant further investigation. As previous study showed psychostimulant use is associated with remarkably high risk of subsequent early-onset PD and Parkinson's like diseases, future research should focus on this area.

Author Disclosures

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CLC, ICW, PI and DC contributed to the conception of the work. CLC and ICW designed the study. CLC and GHL performed the data analysis. GHL, GMG, CLC and ICW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. GHL, GMG and CLC wrote the first draft of the manuscript. GHL, GMG, CLC, PI, DC and ICW interpreted, critically evaluated, and improved the study design and manuscript, and shared the responsibility for the final manuscript and the decision to submit.

Table 1. Data sources of the diseases / traits included in genetic correlation and/or MR analyses

	Disease or trait	Exposure / outcome / mediating factor in MR analyses?	Description of data source	Ancestry	Sample size
1	Attention-Deficit/Hyperactivity Disorder (ADHD)	Exposure / Outcome	A GWAS meta-analysis from 12 cohorts that identified the first genome-wide significant ADHD loci(Demontis et al., 2019).	Majority European (approximately 95%)	Cases: 20,183; Controls: 35,191
2	Parkinson's Disease (PD)	Exposure / Outcome	The largest GWAS meta-analysis of PD to-date, including three published studies and 13 new case-control sample series(Nalls et al., 2019).	European	@ Cases: 26,421 Controls: 442,271
3	Body mass index (BMI)	Mediating factor	A meta-analysis of UK Biobank data with a previous GWAS of the Genetic Investigation of ANthropometric Traits (GIANT) consortium(Yengo et al., 2018).	European	681,275
4	Smoking status (ever regular vs never regular)	Mediating factor	A meta-analysis of 35 GWAS of multiple stages of tobacco use and alcohol use(Liu et al., 2019).	European	1,232,091

@Minimum sample size at which the genetic instruments were tested

Table 2. Result of Mendelian Randomization analysis in evaluating the causal association between ADHD and PD without excluding pleiotropic genetic instruments.

Method	Odds Ratio (95% Confidence Interval)	P-value
Univariable MR analyses with the use of 12 genetic instruments		
(8 independent SNPs identified from the GWAS of ADHD + 4 proxies)		
IVW	0.900 (0.785 - 1.032)	0.131
Heterogeneity test statistics	N/A	**0.047**
MR-Egger (intercept)	N/A	0.524
MR-PRESSO Global Test	N/A	**0.048**
Multivariable MR analyses with the use of 12 genetic instruments		
(5 independent SNPs identified from the GWAS of ADHD + 7 proxies)		
Before adjustment for potential mediators		
IVW	0.994 (0.862 – 1.147)	0.935
Heterogeneity test statistics	N/A	**0.027**
MR-Egger (intercept)	N/A	**0.023**
MR-PRESSO Global Test	N/A	**0.028**
Multivariable MR analyses adjusted for BMI		
Multivariable IVW	1.010 (0.868 – 1.174)	0.903
Heterogeneity test statistics	N/A	**0.024**
Multivariable Egger (intercept)	N/A	**0.006**
Multivariable MR analyses adjusted for smoking status		
Multivariable IVW	0.999 (0.888 – 1.126)	0.993
Heterogeneity test statistics	N/A	0.191
Multivariable Egger (intercept)	N/A	0.143

Table 3. Result of Mendelian Randomization analysis in evaluating the causal association between ADHD and PD after excluding pleiotropic genetic instruments.

Method	**Odds Ratio (95% Confidence Interval)**	**P-value**
Univariable MR analyses with the use of 10 genetic instruments		
(7 independent SNPs identified from the GWAS of ADHD + 3 proxies)		
IVW	0.930 (0.792 – 1.092)	0.374
Heterogeneity test statistics	N/A	**0.049**
MR-Egger (intercept)	N/A	0.488
MR-PRESSO Global Test	N/A	0.071
Multivariable MR analyses with the use of 9 genetic instruments		
(5 independent SNPs identified from the GWAS of ADHD + 4 proxies)		
Before adjustment for potential confounders		
IVW	1.123 (0.996 – 1.267)	0.059
Heterogeneity test statistics	N/A	0.952
MR-Egger (intercept)	N/A	0.587
MR-PRESSO Global Test	N/A	0.954
Multivariable MR analyses adjusted for BMI		
Multivariable IVW	1.132 (0.999 – 1.282)	0.052
Heterogeneity test statistics	N/A	0.928
Multivariable Egger (intercept)	N/A	0.451
Multivariable MR analyses adjusted for smoking status		
Multivariable IVW	1.107 (0.973 – 1.261)	0.122
Heterogeneity test statistics	N/A	0.937
Multivariable Egger (intercept)	N/A	0.624

Table 4. Result of Mendelian Randomization analysis in evaluating the causal association between PD and ADHD without excluding pleiotropic genetic instruments.

Method	Odds Ratio (95% Confidence Interval)	P-value
Univariable MR analyses with the use of 86 genetic instruments		
(85 independent SNPs identified from the GWAS of PD + 1 proxy)		
IVW	0.980 (0.955 – 1.005)	0.114
Heterogeneity test statistics	N/A	0.112
MR-Egger (intercept)	0.999 (0.994 – 1.005)	0.841
MR-PRESSO Global Test	N/A	0.127
Multivariable MR analyses with the use of 70 genetic instruments		
(34 independent SNPs identified from the GWAS of PD + 36 proxies)		
Before adjustment of potential mediators		
IVW	0.967 (0.937 – 0.997)	**0.032**
Heterogeneity test statistics	N/A	0.168
Weighted-median	0.941 (0.899 – 0.985)	**0.009**
MR-Egger	0.956 (0.882 – 1.037)	0.277
MR-Egger (intercept)	N/A	0.775
MR-PRESSO Global Test	N/A	0.175
MR-PRESSO main analysis	0.967 (0.937 – 0.997)	**0.036**
Multivariable MR analyses adjusted for BMI		
Multivariable IVW	0.967 (0.938 – 0.999)	**0.039**
Heterogeneity test statistics	N/A	0.151
Multivariable Egger	0.955 (0.880 – 1.025)	0.263
Multivariable Egger (intercept)	N/A	0.725
Multivariable MR analyses adjusted for smoking status		
Multivariable IVW	0.963 (0.934 – 0.992)	**0.011**
Heterogeneity test statistics	N/A	0.379
Multivariable Egger	0.952 (0.883 – 1.028)	0.213
Multivariable Egger (intercept)	N/A	0.773

Table 5. Result of Mendelian Randomization analysis in evaluating the causal association between PD and ADHD after excluding pleiotropic genetic instruments.

Method	Odds Ratio (95% Confidence Interval)	P-value
Univariable MR analyses with the use of 77 genetic instruments		
(76 independent SNPs identified from the GWAS of PD + 1 proxy)		
IVW	0.986 (0.956 – 1.015)	0.341
Heterogeneity test statistics	N/A	**0.049**
MR-Egger (intercept)	N/A	0.234
MR-PRESSO Global Test	N/A	0.063
Multivariable MR analyses with the use of 58 genetic instruments		
(31 independent SNPs identified from the GWAS of PD + 27 proxies)		
Before adjustment of potential confounders		
IVW	0.957 (0.925 – 0.991)	**0.013**
Heterogeneity test statistics	N/A	0.171
Weighted median method	0.930 (0.883 – 0.979)	**0.006**
MR-Egger	0.943 (0.866 – 1.026)	0.173
MR-Egger (intercept)	N/A	0.696
MR-PRESSO main analysis	0.957 (0.925 – 0.991)	**0.016**
MR-PRESSO Global Test	N/A	0.145
Multivariable MR analyses adjusted for BMI		
Multivariable IVW	0.958 (0.926 – 0.992)	**0.015**
Heterogeneity test statistics	N/A	0.170
Multivariable Egger	0.935 (0.858 – 1.019)	0.127
Multivariable Egger (intercept)	N/A	0.545
Multivariable MR analyses adjusted for smoking status		
Multivariable IVW	0.948 (0.918 – 0.979)	**0.001**
Heterogeneity test statistics	N/A	0.498
Multivariable Egger	0.936 (0.866 – 1.012)	0.095
Multivariable Egger (intercept)	N/A	0.718

Table 6. Power calculation of MR analyses

	Exposure		Outcome		Number of genetic instruments (Number of independent SNPs - SNPs without exposure-associated proxies – pleiotropic SNPs)	Proportion of variance explained by the genetic instruments on exposure (%)	F-statistics	Power# (%)	Odds Ratio at 80% power#	
	Disease	Sample size	Disease	Sample size					Negative	Positive
1	ADHD	Cases: 20,183; Controls: 35,191	PD	@Cases: 26,421; Controls: 442,271	10^ (12 - 0 - 2)	0.58	2714.62	94	0.834	1.159
2	ADHD	Cases: 20,183; Controls: 35,191	PD	@Cases: 26,421; Controls: 442,271	9~ (12 - 0 - 3)	0.52	2442.93	92	0.824	1.167
3	PD	Cases: 26,421; Controls: 442,271	ADHD	Cases: 20,183; Controls: 35,191	77^ (90 - 4 - 9)	2.96	1690.07	100	0.903	1.103
4	PD	Cases: 26,421; Controls: 442,271	ADHD	Cases: 20,183; Controls: 35,191	58~ (90 - 20 - 12)	1.99	1125.32	99	0.883	1.126

^ Genetic instruments were selected by matching across the datasets of ADHD and PD.
~ Genetic instruments were selected by matching across the datasets of ADHD, PD, BMI and smoking status.
@ Minimum sample size was used to calculate the power
# Statistical power to detect an odds ratio of 1.2 per doubling of odds of exposure

Figure Legends

Figure 1. Key assumptions in MR analyses
(a) Key assumptions of univariable MR analyses and traits included in the current study.
(b) Key assumptions of multivariable MR analyses and traits included in the current study.

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