Probing the Pre-diagnostic Phase of Parkinson's Disease in Population-Based Studies

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Parkinson's disease covers a wide spectrum of symptoms, ranging from early non-motor symptoms to the characteristic bradykinesia, tremor and rigidity. Although differences in the symptomatology of Parkinson's disease are increasingly recognized, there is still a lack of insight into the heterogeneity of the pre-diagnostic phase of Parkinson's disease. In this perspective, we highlight three aspects regarding the role of population-based studies in providing new insights into the heterogeneity of pre-diagnostic Parkinson's disease. First we describe several specific advantages of population-based cohort studies, including the design which overcomes some common biases, the broad data collection and the high external validity. Second, we draw a parallel with the field of Alzheimer's disease to provide future directions to uncover the heterogeneity of pre-diagnostic Parkinson's disease. Finally, we anticipate on the emergence of prevention and disease-modification trials and the potential role of population-based studies herein. In the coming years, bridging gaps between study designs will be essential to make vital advances in elucidating the heterogeneity of pre-diagnostic Parkinson's disease.

Keywords: heterogeneity, pre-diagnostic Parkinson's disease, prodromal Parkinson's disease, population-based, epidemiology, prevention trials, prediction, target trial emulation

INTRODUCTION

Parkinson's disease (PD) covers a wide spectrum of symptoms, ranging from early non-motor symptoms, such as constipation, REM-sleep behavior disorder (RBD) and hyposmia (1, 2), to the characteristic motor symptoms bradykinesia, tremor and rigidity (3). A similar appearing Parkinson syndrome can result from many different causes and even one specific cause can bring about heterogeneous symptomatology (4). Although the diversity of clinical PD is increasingly being recognized (5), there is still a lack of insight into the heterogeneity of the pre-diagnostic phase of PD (6, 7).

Studying the heterogeneous nature of pre-diagnostic PD is challenging but essential to unravel etiology and to recognize symptoms and modify disease progression in an early phase. Population-based cohort studies are particularly suitable to gain insight into pre-diagnostic PD (8). In this perspective, we will discuss some unique design advantages of population-based cohort studies for elucidating preclinical PD. In addition, we will elaborate on lessons learned from population-based studies in the field of Alzheimer's disease (AD) to provide future directions for understanding the diversity of risk factors and prodromal symptoms of PD. Finally, we will describe how population-based studies can be used optimally on the way toward prevention and disease-modification trials.

PHASES OF PRE-DIAGNOSTIC PARKINSON'S DISEASE

The Movement Disorders Society (MDS) task force on the definition of PD has suggested to divide early PD into three phases: preclinical, prodromal and clinical PD (9, 10). Besides these three phases, even an earlier risk phase can be distinguished (2). The risk phase, the preclinical phase and the prodromal phase together are considered pre-diagnostic PD (2, 11). Clinical and case-control studies have thus far provided important insights into clinical PD and have uncovered initial clues regarding pre-diagnostic PD (2, 12). However, population-based studies are necessary to better understand the different phases of the pre-diagnostic period of PD (8).

The first phase of pre-diagnostic PD is also known as the *risk phase* (2, 13, 14). In this phase, people can be exposed to several risk factors and pathophysiological processes may initiate, but no PD-related pathology is present yet. Case-control studies have increased our understanding of the genetic risk of PD, including the identification of novel risk loci (15). The case-control design is especially valuable for studying genetic risk factors because these per definition precede the PD diagnosis. However, PD risk is also importantly influenced by a combination of environmental and lifestyle factors which usually have a long latency period and accumulate during life course (16, 17). Studying these type of risk factors in case-control studies yields several methodological challenges and potential sources of bias (18). Additional research by population-based studies is thus indispensable to obtain further insight into the risk phase of PD.

The second phase of pre-diagnostic PD is the *preclinical phase*, during which the pathology has initiated and biomarkers can be found that are suggestive of PD. During the preclinical phase, however, no symptoms of disease have yet arisen (2). Currently, the predictive ability of preclinical biomarkers for future PD diagnosis is limited, but research is ongoing (4, 11, 19, 20). Promising biomarkers for early detection and diagnosis of PD include α-synuclein measurements in the cerebrospinal fluid, blood and peripheral tissue (11, 19, 20). Furthermore, as dopamine loss occurs steadily throughout pre-diagnostic PD (2, 21, 22), dopamine transporter scanning might be used as an imaging marker of the early phases of PD (11, 20). Interestingly, one study found a reduced striatal uptake in 44% of asymptomatic mutation carriers of the LRRK2 mutation G2019S1 (23), a mutation with incomplete penetrance for PD (24, 25). Only two carriers (14%) in this study had hyposmia and the motor score was comparable to non-carriers (23). This might reflect that dopamine transporter abnormalities could already be found in the preclinical phase of PD. However, a more recent study found only 11% of non-manifest LRRK2 carriers to have a dopamine transporter deficit, even though their clinical characteristics already differed significantly from healthy controls (26). The value of this marker in preclinical PD thus requires further consideration. Although studies in clinical populations, such as people with RBD, can provide some initial insights into possible biomarkers for early PD (27–30), only large population-based studies can determine the ability of these markers to identify preclinical PD.

The final phase of pre-diagnostic PD is the *prodromal phase*. This phase can last over a decade and is mainly characterized by non-motor symptoms (1, 2), although recent studies have also shown subtle motor deficits years before the diagnosis (1, 2, 31). Symptoms in the prodromal phase of PD are often not yet recognized as belonging to PD because of their low specificity (2). RBD, however, is a highly specific symptom of prodromal α-synucleinopathies (PD, dementia with Lewy bodies and multiple system atrophy) (2, 32). The relation between RBD and α-synucleinopathies was first described in clinical case studies (33) and has since been confirmed by many other clinical studies with long-term follow-up (32, 34). However, studies recruiting patients in sleep clinics will not be generalizable to all people with RBD since RBD is generally underdiagnosed (32, 35, 36). Therefore, confirmation of the association between RBD and α-synucleinopathies in population-based studies is needed (37).

IMPORTANCE OF POPULATION-BASED STUDIES IN PRE-DIAGNOSTIC PARKINSON'S DISEASE

Studying risk factors, preclinical biomarkers and prodromal symptoms in case-control studies is methodologically challenging. For these type of study questions regarding pre-diagnostic PD, the design of population-based cohort studies offers several important advantages.

First, prospective cohort studies surmount some common biases in case-control studies (13, 18, 38). Recall bias, a type of differential misclassification bias, is an important issue in case-control studies, which prospective cohort studies overcome (18). This bias is especially relevant to PD because of the very long prodromal period in which symptoms, such as constipation (2), can appear that could be more often recognized by cases than controls (13). In addition, case-control studies often suffer from selection bias at study entry (13, 18, 39). Selection bias could, for instance, occur in case-controls studies investigating the association of diet with PD (40). If controls are selected on the basis of an advertisement about research on nutrition, usually this will attract people who have an interest in this topic and who already have a healthy diet (18, 41). As such, the exposure of interest, diet, will be associated with study participation and with having the outcome PD, which results in selection bias. Selection bias in case-control studies can also occur in the selection of cases, when the exposure is related to survival and only cases who survive are included (42). This bias is often referred to as survivor bias (42). Survivor bias could importantly distort the findings of case-control studies, if this is not taken into account appropriately. In population-based cohort studies, selection bias can also be an issue, especially due to selective loss to follow-up or competing risks (18, 43). Fortunately, frameworks are now being developed for the appropriate adjustment for this possible source of bias in cohort studies (44).

Second, population-based studies often routinely collect data on many population characteristics. These variables can be used to extensively adjust for confounding bias. If we again take the example of the association between diet and PD, appropriate

adjustment for smoking is necessary because smoking behavior is associated with both diet and PD risk and thus could be a confounder in this association (39, 45). In addition, broad data collection provides the opportunity to study the interdependence of markers of pre-diagnostic PD (46, 47) and to combine multiple markers in a prediction algorithm for PD (48–54), such as the PREDICT-PD algorithm (55, 56) and the naïve Bayesian classifier approach of the MDS research criteria for prodromal PD (54). Finally, the large datasets of population-based studies offer possibilities to study the combined effect of multiple risk factors on PD, as well as on clusters of chronic diseases (57), which is essential given that many risk factors and chronic diseases co-occur.

Third, contrary to clinical studies, the generalizability of population-based studies is usually high because of limited selection criteria at baseline (58). This difference in external validity might explain some common discrepancies in findings between clinical studies and population-based studies. As an illustration, while specialized clinics found a substantial increased likelihood for PD in people with neurogenic orthostatic hypotension (54, 59, 60), in the population-based Rotterdam study we previously found no significant association between neurogenic orthostatic hypotension and PD (61). The high external validity of population-based studies also offers several possibilities, for example to study the prevalence and trajectories of symptoms in pre-diagnostic PD, which is necessary to determine the predictive ability of these symptoms (8, 31). For example, hyposmia is a common symptom of prodromal PD (2), but is also highly prevalent in the general older population (62). Estimating the prevalence of hyposmia in the general population thus provides imperative information on the usefulness of this symptom to predict PD. Lastly, trends over time in PD incidence and mortality can easily be studied in population-based studies because of the often standardized criteria for determining PD (63).

Currently, several population-based studies are ongoing with a focus on PD (2, 8, 13, 14). Some of these studies are specifically designed for the outcome PD, such as the PREDICT-PD (55) and the PRIPS study (64), which have the advantage of choosing specific measures of importance to PD. Other studies, such as the Rotterdam Study (65) and the Honolulu-Asia Aging Study (HAAS) (66), take PD into account as one of the outcomes. The advantage of this approach is the often larger available sample, but this comes at the price of less PD-specific measurements.

LEARNING FROM POPULATION-BASED STUDIES IN ALZHEIMER'S DISEASE

Over the last decades, the AD field has made significant progress in the discovery of risk factors and preclinical biomarkers (67). Population-based studies have played an important role in these advances. For example, population-based studies have provided crucial insights into the role of vascular factors in the etiology of AD (68, 69). Taking a broader perspective and recognizing similarities between PD and AD will help to make further progress in PD research (70–72).

PD and AD are both complex diseases in which modifiable risk factors play an important role (67). The AD field has shown the value of studying the interplay between different risk factors. A recent meta-analysis, for instance, has illustrated a dose-response relationship between the number of modifiable risk factors and the risk of dementia (73). Additionally, several studies have calculated the population-attributable fraction for each modifiable risk factor separately as well as for all risk factors combined, which shows the prevention potential of improving lifestyle (67, 74). In the AD field, moreover, a greater emphasis is placed on life course determinants and differences in risk factors in early-, mid, and late-life (67, 68, 70). Such a holistic approach to modifiable risk factors in population-based studies could help PD research in moving toward prevention and disease-modification trials.

Furthermore, both PD and AD require easy-to-measure preclinical biomarkers for earlier disease recognition and recruitment of participants in trials (4, 11, 19, 75–78). AD research has shown the benefit of considering distinct biomarkers at different disease phases (78, 79) and of creating panels of multiple biomarkers (78, 79). This is especially relevant to PD, given the heterogeneity of the disease (11, 19, 20, 72, 75, 80) and the diverse pathophysiological mechanisms at play at different disease stages (4, 20, 75). Population-based cohort studies provide opportunities to study biomarkers for PD at very early stages (75, 78, 81).

Finally, both the PD and AD field have recognized the importance of harmonization of measurements and data sharing (47, 70, 80, 82). Data sharing enables population-based studies to study small effects, to perform subgroup analyses and to replicate findings (47, 70, 80, 82). Harmonization of measurements and subsequent data pooling is of particular importance in PD research given the low disease incidence, which requires a large study population and long follow-up period for sufficient study power (14, 18, 83). Good examples of harmonization of measurements and data sharing include the Parkinson's Progression Markers Initiative (PPMI) (20, 84), including more than 30 centers across different countries, the Global Parkinson's Genetics Program (GP2), including 150,000 volunteers around the world (85), and the Alzheimers Cohorts Consortium, including nine population-based cohort studies in the United States and Europe (86). In addition to data sharing, several initiatives have been launched in the AD field to promote knowledge and expertise sharing (47, 87), including Methods for Longitudinal Studies in Dementia (MELODEM) (88) and Alzheimer's Association Professional Interest Areas (PIAs) (70). Both initiatives promote knowledge sharing, either through recommendations for dealing with common methodological difficulties, or through networking, mentoring and collaborations. In the PD field, very recently the Dutch Parkinson Alliance was founded (89), which includes an association aiming to connect PD researchers (90). Such initiatives help to adopt novel and more advanced methodologies and to avoid common pitfalls in research (70).

STUDYING THE HETEROGENEITY OF PRE-DIAGNOSTIC PARKINSON'S DISEASE IN POPULATION-BASED STUDIES

The pre-diagnostic phase of PD is heterogeneous with regards to risk factors, biomarkers and prodromal symptoms (2, 4, 12). Taking into account this heterogeneity in population-based studies is essential because a lack of insight into interactions between risk factors and subgroup differences in prodromal symptoms precludes our understanding of the different pathophysiological processes involved in PD and hinders early disease recognition.

Important developments regarding the complex interaction between risk factors of PD stem from studies on gene-environment interactions (12, 91–94). Studying the interplay between genetics and the environment provides insights into why only certain individuals exposed to environmental risk factors develop PD. The interaction between genetic mutations and pesticides is a major field of study herein (91, 92). A 2012 study, for example, showed that the association between paraquat exposure and PD was seven times greater in men with homozygous deletions of GSTT1, a gene involved in the metabolism of chemical substances, than in men with functional GSTT1 (95). Further application of these methods in population-based studies on environmental and lifestyle risk factors is warranted.

Heterogeneity in the prodromal phase of PD is currently understudied (12, 96). A recent review article has highlighted the importance of acknowledging heterogeneity in prodromal PD for early disease recognition and targeted neuroprotective interventions (96). Several subtypes in the prodromal phase were mentioned in this review, including RBD subtypes, brain-first and body-first subtypes, genetic subtypes and biological subtypes. With regards to differences in RBD subtypes, RBD in the prodromal phase seems to predispose to a more malignant PD subtype, especially regarding non-motor symptoms (97–99). The brain-first vs. body-first subtypes, suggesting that α-synuclein pathology originates either in the brain itself or in the autonomic nervous system, might explain the difference in the sequence of the occurrence of symptoms in the prodromal phase (96, 100, 101). These subtypes of prodromal PD require further investigation in longitudinal studies (96). Recognition of these different subtypes in the prodromal phase is important, but acknowledging heterogeneity in basic patient characteristics, for instance by sex and ethnicity, is also essential (6, 47). However, the current MDS criteria for prodromal PD do not distinguish prodromal symptoms between men and women or people of different ethnicities (54). Nevertheless, some initial studies have shown important differences in prodromal symptoms between men and women (6, 102–105). One of these studies reported more sexual dysfunction, memory complaints and dream re-enactment in men and more unexplained weight change and anxiety in women (102). In addition, symptoms in the prodromal as well as the clinical phase of PD have been suggested to differ between people of different ethnicities (103–105), but evidence regarding the prodromal phase is very limited. Some initiatives have been launched to increase our understanding of PD in underrepresented areas (106–109). However, for instance in Africa the conducted studies are still mainly door-to-door surveys or case-control studies (106, 110, 111) and population-based cohort studies are missing (63, 106–109). Studies in underrepresented areas are needed to understand variations in occurrence and phenotype of PD in different populations and to elucidate complex interactions between risk factors (4, 63, 104, 105, 107, 108). More diverse study populations, as well as more elaborate stratification by population characteristics, symptoms and biomarkers are desired (20).

THE ROLE OF POPULATION-BASED STUDIES IN MOVING TOWARD TRIALS

From Population-Based Studies to Trials

Input from observational studies is necessary to guide future prevention and disease-modification trials in recruiting at-risk populations, choosing preventive interventions and selecting outcome measures (8, 20, 112). Population-based studies provide especially important insights into the first two categories.

First, selecting an appropriate study population is pivotal for the success of future prevention and disease-modification trials (8). Currently, multiple enriched risk cohort studies are ongoing, including the Tübinger evaluation of Risk factors for Early detection of NeuroDegeneration (TREND) study, the Parkinson Associated Risk Study (PARS), the Parkinson's Progression Markers Initiative prodromal cohort (PPMI) and the Oxford Parkinson's Disease Centre (OPDC), which provide insight into early phases of PD and create platforms to recruit subjects for trials (8, 11, 53). These studies include various populations with a high risk of PD, such as asymptomatic mutation carriers, people with RBD or people with composite prodromal features. Each of these study populations have specific advantages and disadvantages for future trial recruitment. For instance, the advantage of recruiting individuals with prodromal symptoms is the short lead time to PD, whereas this is simultaneously a disadvantage since the disease might be too advanced for trials to be successful (11). Because trial recruitment of people in an earlier stage of PD will be necessary (11, 112), population-based studies are essential to provide prediction algorithms based on environmental risk factors, biomarkers and polygenic risks (53, 55, 56).

Second, prevention or disease-modification trials need sufficient information on the strength of the causal relationship between a risk factor and PD in order to choose appropriate interventions. Insights from population-based studies, especially regarding environmental and lifestyle interventions, are highly important herein. Advanced statistical methods can be used to increase confidence in the causal association between risk factors and PD. A promising example includes Mendelian randomization, in which a genetic variation is used as a natural randomization to study the causal relation between a risk factor, for instance serum urate, and the risk of PD (113, 114). Mendelian randomization, however, still relies on several important assumptions, including the assumption that the genetic variant influences the outcome only through the

exposure of interest (113). Furthermore, most current Mendelian randomization studies are performed in case-control settings (115), with the possibility of the previously reported survivor bias (116). Therefore, in order to draw causal conclusions from observational data, it remains crucial to combine the results of several types of studies with different potential sources of bias (117, 118).

From Trials to Population-Based Studies

Theoretically, observational study designs are a direct extension of the underlying principles of a randomized controlled trial (RCT) (18, 119). Nevertheless, in practice, many important design principles of RCTs are not made explicit in the analyses of observational studies (119–121). Explicitly specifying the protocol of an intended (hypothetical) trial, including eligibility criteria and treatment strategies, and resembling this protocol as closely as possible in observational studies is called emulating a target trial (120, 122).

In other fields, emulating target trials in observational studies has already shown promising results, which more closely resemble real trial results than usual methods deployed in observational research (121, 123, 124). For example, large observational studies suggested that postmenopausal hormone users had a reduced risk of coronary heart disease, whereas the Women's Health Initiative randomized trial found a greater risk in women assigned to hormone replacement therapy than in those assigned to placebo (121). Hernán et al. mimicked the design of the randomized trial in a large observational study and showed that the discrepancies in results could largely be explained by differences in distribution of time since menopause and length of follow-up (121). This example illustrates that common differences in the results of observational and randomized studies could be accounted for when applying the design principles of RCTs in observational studies.

The approach of emulating target trials is novel in PD research, but it provides promising perspectives. Emulating a target trial helps observational studies to ask the most meaningful questions (125), to clarify assumptions underlying the analyses and to overcome common biases, such as immortal time bias and confounding bias (119, 120, 125, 126). In addition, emulating a target trial could be useful when trials cannot be performed because they are too costly, unethical or not timely (120). Results from observational studies and trials could also be combined, for instance to translate the results to a population with less restrictive eligibility criteria or to more long-term outcome measures instead of surrogate endpoints (119, 121). In the coming years, collaboration between trial initiatives and observational population-based studies is essential to make the first steps toward PD prevention.

CONCLUSION

In this perspective we have explicated the role of population-based studies in unraveling the heterogeneous nature of pre-diagnostic PD. Population-based studies provide unique design advantages for studying pre-diagnostic PD, but they remain relatively sparse (2, 8, 13, 14). It is therefore pivotal that population-based studies join forces. Data sharing is essential to study interactions between genetic and environmental risk factors and to determine subgroup differences in the preclinical and prodromal phase of PD. Moreover, knowledge sharing and collaboration initiatives are required to bridge gaps between different study designs and to facilitate the transition toward prevention and disease-modification trials (20, 47).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

LD drafted the manuscript. AB and MI critically revised the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Kalia LV, Lang AE. Parkinson's disease. *Lancet.* (2015) 386:896–912. doi: 10.1016/S0140-6736(14)61393-3

2. Postuma RB, Berg D. Advances in markers of prodromal Parkinson disease. *Nat Rev Neurol.* (2016) 12:622–34. doi: 10.1038/nrneurol.2016.152

3. Armstrong MJ, Okun MS. Diagnosis and treatment of parkinson disease: a review. *JAMA.* (2020) 323:548–60. doi: 10.1001/jama.2019.22360

4. Bloem BR, Okun MS, Klein C. Parkinson's disease. *Lancet.* 397:2284–303. doi: 10.1016/S0140-6736(21)00218-X

5. Greenland JC, Williams-Gray CH, Barker RA. The clinical heterogeneity of Parkinson's disease and its therapeutic implications. *Eur J Neurosci.* (2019) 49:328–38. doi: 10.1111/ejn.14094

6. Heinzel S, Kasten M, Behnke S, Vollstedt EJ, Klein C, Hagenah J, et al. Age- and sex-related heterogeneity in prodromal Parkinson's disease. *Mov Disord.* (2018) 33:1025–7. doi: 10.1002/mds.27349

7. Schrag A, Zhelev SS, Hotham S, Merritt RD, Khan K, Graham L. Heterogeneity in progression of prodromal features in Parkinson's disease. *Parkinsonism Relat Disord.* (2019) 64:275–9. doi: 10.1016/j.parkreldis.2019.05.013

8. Berg D, Marek K, Ross GW, Poewe W. Defining at-risk populations for Parkinson's disease: lessons from ongoing studies. *Mov Disord.* (2012) 27:656–65. doi: 10.1002/mds.24985

9. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's disease. *Mov Disord.* (2015) 30:1600–11. doi: 10.1002/mds.26431

10. Berg D, Postuma RB, Bloem B, Chan P, Dubois B, Gasser T, et al. Time to redefine PD? Introductory statement of the MDS task force on the definition of Parkinson's disease. *Mov Disord.* (2014) 29:454–62. doi: 10.1002/mds.25844

11. Noyce AJ, Lees AJ, Schrag A. The prediagnostic phase of Parkinson's disease. *J Neurol Neurosurg Psychiatry.* (2016) 87:871–8. doi: 10.1136/jnnp-2015-311890

12. Obeso JA, Stamelou M, Goetz CG, Poewe W, Lang AE, Weintraub D, et al. Past, present, and future of Parkinson's disease: a special essay on the 200th Anniversary of the Shaking Palsy. *Mov Disord.* (2017) 32:1264–310. doi: 10.1002/mds.27115

13. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol.* (2016) 15:1257–72. doi: 10.1016/S1474-4422(16)30230-7

14. Elbaz A, Carcaillon L, Kab S, Moisan F. Epidemiology of Parkinson's disease. *Rev Neurol.* (2016) 172:14–26. doi: 10.1016/j.neurol.2015.09.012

15. Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet Neurol.* (2019) 18:1091–102. doi: 10.1016/S1474-4422(19)30320-5

16. Logroscino G. The role of early life environmental risk factors in Parkinson disease: what is the evidence? *Environ Health Perspect.* (2005) 113:1234–8. doi: 10.1289/ehp.7573

17. Kumar A, Calne SM, Schulzer M, Mak E, Wszolek Z, Van Netten C, et al. Clustering of Parkinson disease: shared cause or coincidence? *Arch Neurol.* (2004) 61:1057–60. doi: 10.1001/archneur.61.7.1057

18. Rothman KJ. *Epidemiology: An Introduction.* New York, NY: Oxford University Press (2012).

19. Du T, Wang L, Liu W, Zhu G, Chen Y, Zhang J. Biomarkers and the role of α-synuclein in Parkinson's disease. *Front Aging Neurosci.* (2021) 13:645996. doi: 10.3389/fnagi.2021.645996

20. Yilmaz R, Hopfner F, van Eimeren T, Berg D. Biomarkers of Parkinson's disease: 20 years later. *J Neural Transm.* (2019) 126:803–13. doi: 10.1007/s00702-019-02001-3

21. Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain.* (1991) 114 (Pt 5):2283–301. doi: 10.1093/brain/114.5.2283

22. de la Fuente-Fernández R, Schulzer M, Kuramoto L, Cragg J, Ramachandiran N, Au WL, et al. Age-specific progression of nigrostriatal dysfunction in Parkinson's disease. *Ann Neurol.* (2011) 69:803–10. doi: 10.1002/ana.22284

23. Sierra M, Sánchez-Juan P, Martínez-Rodríguez MI, González-Aramburu I, García-Gorostiaga I, Quirce MR, et al. Olfaction and imaging biomarkers in premotor LRRK2 G2019S-associated Parkinson disease. *Neurology.* (2013) 80:621–6. doi: 10.1212/WNL.0b013e31828250d6

24. Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, Bressman S, et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. *Lancet Neurol.* (2008) 7:583–90. doi: 10.1016/S1474-4422(08)70117-0

25. Goldwurm S, Zini M, Mariani L, Tesei S, Miceli R, Sironi F, et al. Evaluation of LRRK2 G2019S penetrance: relevance for genetic counseling in Parkinson disease. *Neurology.* (2007) 68:1141–3. doi: 10.1212/01.wnl.0000254483.19854.ef

26. Simuni T, Uribe L, Cho HR, Caspell-Garcia C, Coffey CS, Siderowf A, et al. Clinical and dopamine transporter imaging characteristics of non-manifest LRRK2 and GBA mutation carriers in the Parkinson's progression markers initiative (PPMI): a cross-sectional study. *Lancet Neurol.* (2020) 19:71–80. doi: 10.1016/S1474-4422(19)30319-9

27. Iranzo A, Lomeña F, Stockner H, Valldeoriola F, Vilaseca I, Salamero M, et al. Decreased striatal dopamine transporter uptake and substantia nigra hyperechogenicity as risk markers of synucleinopathy in patients with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective study. *Lancet Neurol.* (2010) 9:1070–7. doi: 10.1016/S1474-4422(10)70216-7

28. Eisensehr I, Linke R, Noachtar S, Schwarz J, Gildehaus FJ, Tatsch K. Reduced striatal dopamine transporters in idiopathic rapid eye movement sleep behaviour disorder: comparison with Parkinson's disease and controls. *Brain.* (2000) 123:1155–60. doi: 10.1093/brain/123.6.1155

29. Siderowf A, Jennings D, Stern M, Seibyl J, Eberly S, Oakes D, et al. Clinical and imaging progression in the PARS cohort: long-term follow-up. *Mov Disord.* (2020) 35:1550–7. doi: 10.1002/mds.28139

30. Ponsen MM, Stoffers D, Booij J, van Eck-Smit BLF, Wolters EC, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. *Ann Neurol.* (2004) 56:173–81. doi: 10.1002/ana.20160

31. Darweesh SKL, Verlinden VJA, Stricker BH, Hofman A, Koudstaal PJ, Ikram MA. Trajectories of prediagnostic functioning in Parkinson's disease. *Brain.* (2016) 139:429–41. doi: 10.1093/brain/aww291

32. Dauvilliers Y, Schenck CH, Postuma RB, Iranzo A, Luppi PH, Plazzi G, et al. REM sleep behaviour disorder. *Nat Rev Dis Prim.* (2018) 4:19. doi: 10.1038/s41572-018-0016-5

33. Schenck CH, Hurwitz TD, Mahowald MW. REM sleep behaviour disorder: an update on a series of 96 patients and a review of the world literature. *J Sleep Res.* (1993) 2:224–31. doi: 10.1111/j.1365-2869.1993.tb00093.x

34. Högl B, Stefani A, Videnovic A. Idiopathic REM sleep behaviour disorder and neurodegeneration — an update. *Nat Rev Neurol.* (2018) 14:40–55. doi: 10.1038/nrneurol.2017.157

35. White C, Hill EA, Morrison I, Riha RL. Diagnostic delay in REM sleep behavior disorder (RBD). *J Clin Sleep Med.* (2012) 8:133–6. doi: 10.5664/jcsm.1762

36. Boeve BF. REM sleep behavior disorder: updated review of the core features, the REM sleep behavior disorder-neurodegenerative disease association, evolving concepts, controversies, and future directions. *Ann N Y Acad Sci.* (2010) 1184:15–54. doi: 10.1111/j.1749-6632.2009.05115.x

37. Dommershuijsen LJ, Darweesh SKL, Luik AI, Kieboom BCT, Koudstaal PJ, Boon AJW, et al. Ethical considerations in screening for rapid eye movement sleep behavior disorder in the general population. *Mov Disord.* (2020) 35:1939–44. doi: 10.1002/mds.28262

38. Belvisi D, Pellicciari R, Fabbrini G, Tinazzi M, Berardelli A, Defazio G. Modifiable risk and protective factors in disease development, progression and clinical subtypes of Parkinson's disease: what do prospective studies suggest? *Neurobiol Dis.* (2020) 134:104671. doi: 10.1016/j.nbd.2019.104671

39. Brendel PC. *Applications of Multi-Bias Analysis in Studies of the Associations between Parkinson's Disease and Cancer.* Los Angeles: UCLA (2019).

40. Chen Y, Sun X, Lin Y, Zhang Z, Gao Y, Wu IXY. Non-genetic risk factors for Parkinson's disease: an overview of 46 systematic reviews. *J Parkinsons Dis.* (2021). doi: 10.3233/JPD-202521. [Epub ahead of print].

41. Young LM, Gauci S, Scholey A, White DJ, Pipingas A. Self-selection bias: an essential design consideration for nutrition trials in healthy populations. *Front Nutr.* (2020) 7:587983. doi: 10.3389/fnut.2020.587983

42. van Rein N, Cannegieter SC, Rosendaal FR, Reitsma PH, Lijfering WM. Suspected survivor bias in case–control studies: stratify on survival time and use a negative control. *J Clin Epidemiol.* (2014) 67:232–5. doi: 10.1016/j.jclinepi.2013.05.011

43. Biele G, Gustavson K, Czajkowski NO, Nilsen RM, Reichborn-Kjennerud T, Magnus PM, et al. Bias from self selection and loss to follow-up in prospective cohort studies. *Eur J Epidemiol.* (2019) 34:927–38. doi: 10.1007/s10654-019-00550-1

44. Young JG, Stensrud MJ, Tchetgen Tchetgen EJ, Hernán MA. A causal framework for classical statistical estimands in failure-time settings with competing events. *Stat Med.* (2020) 39:1199–236. doi: 10.1002/sim.8471

45. Mappin-Kasirer B, Pan H, Lewington S, Kizza J, Gray R, Clarke R, et al. Tobacco smoking and the risk of Parkinson disease. A 65-year follow-up of 30,000 male British doctors. *Neurology.* (2020) 94:e2132–8. doi: 10.1212/WNL.0000000000009437

46. Fereshtehnejad S, Montplaisir JY, Pelletier A, Gagnon J-F, Berg D, Postuma RB. Validation of the MDS research criteria for prodromal Parkinson's disease: longitudinal assessment in a REM sleep behavior disorder (RBD) cohort. *Mov Disord.* (2017) 32:865–73. doi: 10.1002/mds.26989

47. Berg D, Postuma RB. From prodromal to overt Parkinson's disease: towards a new definition in the year 2040. *J Parkinsons Dis.* (2018) 8:S19–23. doi: 10.3233/JPD-181457

48. Mahlknecht P, Gasperi A, Djamshidian A, Kiechl S, Stockner H, Willeit P, et al. Performance of the movement disorders society criteria for prodromal Parkinson's disease: a population-based 10-year study. *Mov Disord.* (2018) 33:405–13. doi: 10.1002/mds.27281

49. Mahlknecht P, Gasperi A, Willeit P, Kiechl S, Stockner H, Willeit J, et al. Prodromal Parkinson's disease as defined per MDS research criteria in the general elderly community. *Mov Disord.* (2016) 31:1405–8. doi: 10.1002/mds.26674

50. Marini K, Mahlknecht P, Tutzer F, Stockner H, Gasperi A, Djamshidian A, et al. Application of a simple Parkinson's disease risk score in

a longitudinal population-based cohort. *Mov Disord.* (2020) 35:1658–62. doi: 10.1002/mds.28127

51. Pilotto A, Heinzel S, Suenkel U, Lerche S, Brockmann K, Roeben B, et al. Application of the movement disorder society prodromal Parkinson's disease research criteria in 2 independent prospective cohorts. *Mov Disord.* (2017) 32:1025–34. doi: 10.1002/mds.27035

52. Plouvier AOA, Hameleers RJMG, Van Den Heuvel EAJ, Bor HH, Olde Hartman TC, Bloem BR, et al. Prodromal symptoms and early detection of Parkinson's disease in general practice: a nested case-control study. *Fam Pract.* (2014) 31:373–8. doi: 10.1093/fampra/cmu025

53. Mantri S, Morley JF, Siderowf AD. The importance of preclinical diagnostics in Parkinson disease. *Parkinsonism Relat Disord.* (2019) 64:20–8. doi: 10.1016/j.parkreldis.2018.09.011

54. Heinzel S, Berg D, Gasser T, Chen H, Yao C, Postuma RB, et al. Update of MDS research criteria for prodromal Parkinson's disease. *Mov Disord.* (2019) 34:1464–70. doi: 10.1002/mds.27802

55. Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Knowles CH, Hardy J, et al. PREDICT-PD: Identifying risk of Parkinson's disease in the community: methods and baseline results. *J Neurol Neurosurg Psychiatry.* (2014) 85:31–7. doi: 10.1136/jnnp-2013-305420

56. Bestwick JP, Auger SD, Simonet C, Rees RN, Rack D, Jitlal M, et al. Improving estimation of Parkinson's disease risk—the enhanced PREDICT-PD algorithm. *NPJ Parkinsons Dis.* (2021) 7:33. doi: 10.1038/s41531-021-00176-9

57. Licher S, Heshmatollah A, van der Willik K, Stricker B, Ruiter R, de Roos E, et al. Lifetime risk and multimorbidity of non-communicable diseases and disease-free life expectancy in the general population: a population-based cohort study. *PLoS Med.* (2019) 16:e1002741. doi: 10.1371/journal.pmed.1002741

58. Kukull WA, Ganguli M. Generalizability: the trees, the forest, and the low-hanging fruit. *Neurology.* (2012) 78:1886–91. doi: 10.1212/WNL.0b013e318258f812

59. Gibbons CH, Freeman R. Clinical implications of delayed orthostatic hypotension: a 10-year follow-up study. *Neurology.* (2015) 85:1362–7. doi: 10.1212/WNL.0000000000002030

60. Kaufmann H, Norcliffe-Kaufmann L, Palma JA, Biaggioni I, Low PA, Singer W, et al. Natural history of pure autonomic failure: a United States prospective cohort. *Ann Neurol.* (2017) 81:287–97. doi: 10.1002/ana.24877

61. Dommershuijsen LJ, Heshmatollah A, Mattace Raso FUS, Koudstaal PJ, Ikram MA, Ikram MK. Orthostatic hypotension: a prodromal marker of Parkinson's disease? *Mov Disord.* (2021) 36:164–70. doi: 10.1002/mds.28303

62. Attems J, Walker L, Jellinger KA. Olfaction and aging: a mini-review. *Gerontology.* (2015) 61:485–90. doi: 10.1159/000381619

63. Dorsey ER, Elbaz A, Nichols E, Abd-Allah F, Abdelalim A, Adsuar JC, et al. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the global burden of disease study 2016. *Lancet Neurol.* (2018) 17:939–53. doi: 10.1016/S1474-4422(18)30295-3

64. Berg D, Godau J, Seppi K, Behnke S, Liepelt-Scarfone I, Lerche S, et al. The PRIPS study: screening battery for subjects at risk for Parkinson's disease. *Eur J Neurol.* (2013) 20:102–8. doi: 10.1111/j.1468-1331.2012.03798.x

65. Ikram MA, Brusselle G, Ghanbari M, Goedegebure A, Ikram MK, Kavousi M, et al. Objectives, design and main findings until 2020 from the Rotterdam Study. *Eur J Epidemiol.* (2020) 35:483–517. doi: 10.1007/s10654-020-00640-5

66. Ross GW, Abbott RD, Petrovitch H, Tanner CM, White LR. Pre-motor features of Parkinson's disease: the Honolulu-Asia aging study experience. *Parkinsonism Relat Disord.* (2012) 18:S199–202. doi: 10.1016/S1353-8020(11)70062-1

67. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet.* (2020) 396:413–46. doi: 10.1016/S0140-6736(20)30367-6

68. Knopman DS, Gottesman RF, Sharrett AR, Tapia AL, DavisThomas S, Windham BG, et al. Midlife vascular risk factors and midlife cognitive status in relation to prevalence of mild cognitive impairment and dementia in later life: the atherosclerosis risk in communities study. *Alzheimers Dement.* (2018) 14:1406–15. doi: 10.1016/j.jalz.2018.03.011

69. Ma Y, Wolters FJ, Chibnik LB, Licher S, Ikram MA, Hofman A, et al. Variation in blood pressure and long-term risk of

dementia: a population-based cohort study. *PLOS Med.* (2019) 16:e1002933. doi: 10.1371/journal.pmed.1002933

70. Stephan BCM, Siervo M, Brayne C. How can population-based studies best be utilized to reduce the global impact of dementia? Recommendations for researchers, funders, and policymakers. *Alzheimers Dement.* (2020) 16:1448–56. doi: 10.1002/alz.12127

71. Smedinga M, Darweesh SKL, Bloem BR, Post B, Richard E. Towards early disease modification of Parkinson's disease: a review of lessons learned in the Alzheimer field. *J Neurol.* (2020) 268:724–33. doi: 10.1007/s00415-020-10162-5

72. Berg D. Biomarkers for the early detection of Parkinson's and Alzheimer's disease. *Neurodegen Dis.* (2008) 5:133–6. doi: 10.1159/000113682

73. Peters R, Booth A, Rockwood K, Peters J, D'Este C, Anstey KJ. Combining modifiable risk factors and risk of dementia: a systematic review and meta-analysis. *BMJ Open.* (2019) 9:e022846. doi: 10.1136/bmjopen-2018-022846

74. de Bruijn RFAG, Bos MJ, Portegies MLP, Hofman A, Franco OH, Koudstaal PJ, et al. The potential for prevention of dementia across two decades: the prospective, population-based Rotterdam Study. *BMC Med.* (2015) 13:132. doi: 10.1186/s12916-015-0377-5

75. Parnetti L, Gaetani L, Eusebi P, Paciotti S, Hansson O, El-Agnaf O, et al. CSF and blood biomarkers for Parkinson's disease. *Lancet Neurol.* (2019) 18:573–86. doi: 10.1016/S1474-4422(19)30024-9

76. Molinuevo JL, Minguillon C, Rami L, Gispert JD. The rationale behind the new Alzheimer's disease conceptualization: lessons learned during the last decades. *J Alzheimers Dis.* (2018) 62:1067–77. doi: 10.3233/JAD-170698

77. Zetterberg H, Blennow K. Moving fluid biomarkers for Alzheimer's disease from research tools to routine clinical diagnostics. *Mol Neurodegen.* (2021) 16:10. doi: 10.1186/s13024-021-00430-x

78. Zetterberg H, Bendlin BB. Biomarkers for Alzheimer's disease—preparing for a new era of disease-modifying therapies. *Mol Psychiatry.* (2021) 26:296–308. doi: 10.1038/s41380-020-0721-9

79. Beltrán JF, Wahba BM, Hose N, Shasha D, Kline RP, For the Alzheimer's Disease Neuroimaging I. Inexpensive, non-invasive biomarkers predict Alzheimer's transition using machine learning analysis of the Alzheimer's disease neuroimaging (ADNI) database. *PLoS ONE.* (2020) 15:e0235663. doi: 10.1371/journal.pone.0235663

80. Delenclos M, Jones DR, McLean PJ, Uitti RJ. Biomarkers in Parkinson's disease: advances and strategies. *Parkinsonism Relat Disord.* (2016) 22:S106–10. doi: 10.1016/j.parkreldis.2015.09.048

81. Miller DB, O'Callaghan JP. Biomarkers of Parkinson's disease: present and future. *Metabolism.* (2015) 64 (3 Suppl. 1):S40–6. doi: 10.1016/j.metabol.2014.10.030

82. Mattsson N, Zetterberg H, Blennow K. Lessons from multicenter studies on CSF biomarkers for Alzheimer's disease. *Int J Alzheimers Dis.* (2010) 2010:610613. doi: 10.4061/2010/610613

83. Tysnes O-B, Storstein A. Epidemiology of Parkinson's disease. *J Neural Trans.* (2017) 124:901–5. doi: 10.1007/s00702-017-1686-y

84. Marek K, Jennings D, Lasch S, Siderowf A, Tanner C, Simuni T, et al. The parkinson progression marker initiative (PPMI). *Prog Neurobiol.* (2011) 95:629–35. doi: 10.1016/j.pneurobio.2011.09.005

85. Global Parkinson's Genetics Program. *Understanding the Genetic Architecture of Parkinson's Disease.* Available online at: https://parkinsonsroadmap.org/gp2/ (accessed May 20, 2021).

86. Wolters FJ, Chibnik LB, Waziry R, Anderson R, Berr C, Beiser A, et al. Twenty-seven-year time trends in dementia incidence in Europe and the United States. *Alzheimer Cohorts Consort.* (2020) 95:e519–31. doi: 10.1212/WNL.0000000000010022

87. Heinzel S, Lerche S, Maetzler W, Berg D. Global, yet incomplete overview of cohort studies in Parkinson's disease. *J Parkinsons Dis.* (2017) 7:423–32. doi: 10.3233/JPD-171100

88. Weuve J, Proust-Lima C, Power MC, Gross AL, Hofer SM, Thiébaut R, et al. Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. *Alzheimers Dement.* (2015) 11:1098–109. doi: 10.1016/j.jalz.2015.06.1885

89. *Parkinson Alliantie Nederland.* (2021). Available online at: https://parkinsonalliantie.nl/ (accessed May 20, 2021).

90. *Dutch Parkinson Scientists - the Dutch Association for Parkinson's Researchers.* (2021). Available online at: https://www.dutchparkinsonscientists.nl/en/about-us/ (accessed May 20, 2021).

91. Cannon JR, Greenamyre JT. Gene-environment interactions in Parkinson's disease: specific evidence in humans and mammalian models. *Neurobiol Dis.* (2013) 57:38–46. doi: 10.1016/j.nbd.2012.06.025

92. Fleming SM. Mechanisms of gene-environment interactions in Parkinson's disease. *Curr Environ Health Rep.* (2017) 4:192–9. doi: 10.1007/s40572-017-0143-2

93. Jacobs BM, Belete D, Bestwick J, Blauwendraat C, Bandres-Ciga S, Heilbron K, et al. Parkinson's disease determinants, prediction and gene–environment interactions in the UK Biobank. *J Neurol Neurosurg Psychiatry.* (2020) 91:1046–54. doi: 10.1136/jnnp-2020-323646

94. Vance JM, Ali S, Bradley WG, Singer C, Di Monte DA. Gene–environment interactions in Parkinson's disease and other forms of parkinsonism. *NeuroToxicology.* (2010) 31:598–602. doi: 10.1016/j.neuro.2010.04.007

95. Goldman SM, Kamel F, Ross GW, Bhudhikanok GS, Hoppin JA, Korell M, et al. Genetic modification of the association of paraquat and Parkinson's disease. *Mov Disord.* (2012) 27:1652–8. doi: 10.1002/mds.25216

96. Berg D, Borghammer P, Fereshtehnejad S-M, Heinzel S, Horsager J, Schaeffer E, et al. Prodromal Parkinson disease subtypes — key to understanding heterogeneity. *Nat Rev Neurol.* (2021) 17:349–61. doi: 10.1038/s41582-021-00486-9

97. Barber TR, Lawton M, Rolinski M, Evetts S, Baig F, Ruffmann C, et al. Prodromal Parkinsonism and neurodegenerative risk stratification in REM sleep behavior disorder. *Sleep.* (2017) 40:zsx071. doi: 10.1093/sleep/zsx071

98. De Pablo-Fernández E, Lees AJ, Holton JL, Warner TT. Prognosis and neuropathologic correlation of clinical subtypes of Parkinson disease. *JAMA Neurol.* (2019) 76:470–9. doi: 10.1001/jamaneurol.2018.4377

99. Lin Y-Q, Chen S. RBD: a red flag for cognitive impairment in Parkinson's disease? *Sleep Med.* (2018) 44:38–44. doi: 10.1016/j.sleep.2018.01.006

100. Borghammer P, Van Den Berge N. Brain-first versus gut-first Parkinson's disease: a hypothesis. *J Parkinsons Dis.* (2019) 9:S281–95. doi: 10.3233/JPD-191721

101. Horsager J, Andersen KB, Knudsen K, Skjærbæk C, Fedorova TD, Okkels N, et al. Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. *Brain.* (2020) 143:3077–88. doi: 10.1093/brain/awaa238

102. Durcan R, Wiblin L, Lawson RA, Khoo TK, Yarnall AJ, Duncan GW, et al. Prevalence and duration of non-motor symptoms in prodromal Parkinson's disease. *Eur J Neurol.* (2019) 26:979–85. doi: 10.1111/ene.13919

103. Chen H, Shrestha S, Huang X, Jain S, Guo X, Tranah GJ, et al. Olfaction and incident Parkinson disease in US white and black older adults. *Neurology.* (2017) 89:1441–7. doi: 10.1212/WNL.0000000000004382

104. Sauerbier A, Aris A, Lim EW, Bhattacharya K, Ray Chaudhuri K. Impact of ethnicity on the natural history of Parkinson disease. *Med J Aust.* (2018) 208:410–4. doi: 10.5694/mja17.01074

105. Ben-Joseph A, Marshall CR, Lees AJ, Noyce AJ. Ethnic variation in the manifestation of Parkinson's disease: a narrative review. *J Parkinsons Dis.* (2020) 10:31–45. doi: 10.3233/JPD-191763

106. Lekoubou A, Echouffo-Tcheugui JB, Kengne AP. Epidemiology of neurodegenerative diseases in sub-Saharan Africa: a systematic review. *BMC Public Health.* (2014) 14:653. doi: 10.1186/1471-2458-14-653

107. Adams HHH, Evans TE, Terzikhan N. The uncovering neurodegenerative insights through ethnic diversity consortium. *Lancet Neurol.* (2019) 18:915. doi: 10.1016/S1474-4422(19)30324-2

108. Khalil H, Chahine L, Siddiqui J, Aldaajani Z, Bajwa JA. Parkinson's disease in the MENASA countries. *Lancet Neurol.* (2020) 19:293–4. doi: 10.1016/S1474-4422(20)30026-0

109. Zabetian CP, Mata IF, on behalf of the Latin American Research Consortium on the Genetics of PD. LARGE-PD: examining the genetics of Parkinson's disease in Latin America. *Mov Disord.* (2017) 32:1330–1. doi: 10.1002/mds.27081

110. Williams U, Bandmann O, Walker R. Parkinson's disease in Sub-Saharan Africa: a review of epidemiology, genetics and access to care. *J Mov Disord.* (2018) 11:53–64. doi: 10.14802/jmd.17028

111. Dekker MCJ, Coulibaly T, Bardien S, Ross OA, Carr J, Komolafe M. Parkinson's disease research on the African continent: obstacles and opportunities. *Front Neurol.* (2020) 11:512. doi: 10.3389/fneur.2020.00512

112. Olanow CW, Obeso JA. The significance of defining preclinical or prodromal Parkinson's disease. *Mov Disord.* (2012) 27:666–9. doi: 10.1002/mds.25019

113. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *Br Med J.* (2018) 362:k601. doi: 10.1136/bmj.k601

114. Kobylecki CJ, Nordestgaard BG, Afzal S. Plasma urate and risk of Parkinson's disease: a mendelian randomization study. *Ann Neurol.* (2018) 84:178–90. doi: 10.1002/ana.25292

115. Noyce AJ, Bandres-Ciga S, Kim J, Heilbron K, Kia D, Hemani G, et al. The Parkinson's disease Mendelian randomization research portal. *Mov Disord.* (2019) 34:1864–72. doi: 10.1002/mds.27873

116. Smit RAJ, Trompet S, Dekkers OM, Jukema JW, le Cessie S. Survival bias in Mendelian randomization studies: a threat to causal inference. *Epidemiology.* (2019) 30:813–6. doi: 10.1097/EDE.0000000000001072

117. Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. *Int J Epidemiol.* (2017) 45:1866–86. doi: 10.1093/ije/dyw314

118. Pearce N, Vandenbroucke JP, Lawlor DA. Causal inference in environmental epidemiology: old and new approaches. *Epidemiology.* (2019) 30:311–6. doi: 10.1097/EDE.0000000000000987

119. Labrecque JA, Swanson SA. Target trial emulation: teaching epidemiology and beyond. *Eur J Epidemiol.* (2017) 32:473–5. doi: 10.1007/s10654-017-0293-4

120. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol.* (2016) 183:758–64. doi: 10.1093/aje/kwv254

121. Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology.* (2008) 19:766–79. doi: 10.1097/EDE.0b013e3181875e61

122. Cain LE, Saag MS, Petersen M, May MT, Ingle SM, Logan R, et al. Using observational data to emulate a randomized trial of dynamic treatment-switching strategies: an application to antiretroviral therapy. *Int J Epidemiol.* (2016) 45:2038–49. doi: 10.1093/ije/dyv295

123. García-Albéniz X, Hsu J, Hernán MA. The value of explicitly emulating a target trial when using real world evidence: an application to colorectal cancer screening. *Eur J Epidemiol.* (2017) 32:495–500. doi: 10.1007/s10654-017-0287-2

124. Andrew JA, John PD, Jonathan DC, David RJ, Derek WR, Aaron MJ, et al. Emulating a novel clinical trial using existing observational data. Predicting results of the PreVent study. *Ann Am Thorac Soc.* (2019) 16:998–1007. doi: 10.1513/AnnalsATS.201903-241OC

125. Didelez V. Commentary: should the analysis of observational data always be preceded by specifying a target experimental trial? *Int J Epidemiol.* (2016) 45:2049–51. doi: 10.1093/ije/dyw032

126. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol.* (2016) 79:70–5. doi: 10.1016/j.jclinepi.2016.04.014