Prosjektoppgave

Article- Risk factors for idiopathic Rapid Eye Movement Disorder

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Summary

This study aims to review risk factors and additional effects on the development of idiopathic REM sleep behavior disorder (iRBD), which is closely related to α-synucleinopathies such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). This was done through a systematic review using PubMed as the only database. After a review of a large number of studies and sorting processes based on our inclusion and exclusion criteria, we ended up with 21 articles. Our main focus was to collect articles that had idiopathic RBD as a study population, in other words, exclusion of RBD second to other disorders. According to selected articles, we found that genetic components, low education, farming, blue-collar occupation, pesticide exposure, low physical activity, smoking, alcohol drinking, PTSD, depression, antidepressants, cardiovascular disease and risk factors, brain injury, and prodromal PD symptoms are risk factors for the development of iRBD. The results indicate strong similarities to the risk factor profiles of other synucleinopathies, suggesting a link between the two. However, among the selected studies some iRBD risk factors differed from the other neurodegenerative disorders.

Findings in this systematic review are of important value, seeing how this will contribute to better understanding of cognitive impairment and neurogenerative diseases.

Sammendrag:

Bakgrunn: REM-søvn adferdsforstyrrelse (RBD) er en søvnforstyrrelse som er tett forbundet med utvikling av nevrodegenerative tilstander. Omtrent 80% av denne pasientgruppen utvikler synukleinopatier, slik som Parkinsons sykdom (PD), Lewy-legemedemens, og multisystematrofi. En oversikt over litteraturen som er publisert om dette tema er interessant for å se om risikofaktorene for RBD devierer fra de for de nevrodegenerative tilstandene.

Formål: Målet med vår systematiske oversiktsstudie var å belyse risikofaktorer for utvikling av idiopatisk RBD (iRBD).

Metode: Et grundig konstruert søk ble gjennomført i PubMed 5.februar.2020. Artiklene vi satt igjen med ble nøye gjennomgått av to individuelle forfattere. Sorteringsprosessen bestod av tre faser, henholdsvis basert på: tittel, abstrakt og full tekst. Deretter ble de gjenværende artiklene sammenlignet, og forskjellene ble diskutert i plenum.

Resultater: Søket vårt resulterte i 486 artikler, hvorav 14 var relevante basert på inklusjons- og eksklusjonskriteriene våre. 7 artikler ble lagt til underveis fra andre kilder. Vi fant at ulike genetiske komponenter, lav utdannelse, gårdsbruk, blåsnipparbeider, depresjon, antidepressiva, kardiovaskulære sykdommer og risikofaktorer, hjerneskade samt prodromale PD symptomer, ble trukket frem som signifikante risikofaktorer for iRBD.

Konklusjon: Gjennom vår systematiske oversiktsstudie har vi laget en oppsummering over ulike enkeltstudier som er gjort på risikofaktorer for iRBD. Vi sitter igjen med inntrykk av at risikofaktor-profilen for iRBD stort sett likner på risikofaktorer for PD, med noen avvik. Likevel har vi oppdaget større hull i denne litteraturen, og ønsker å fremheve at flere studier burde gjennomføres i dette fagfeltet. På grunn av stor heterogenitet og små studier er det vanskelig å sammenligne resultatene, og komme med en konklusjon.

Contents

Abbreviations

RBD	Rapid Eye Movement Behavior Disorder
iRBD	Idiopathic Rapid Eye Movement Behavior Disorder
REM	Rapid Eye Movement
NREM	Non-Rapid Eye Movement
RSWA	REM Sleep Without Atonia
PD	Parkinson's Disease
AD	Alzheimers´ Disease
DLB	Dementia with Lewy Bodies
MSA	Multiple System Atrophy
MS	Multiple sclerosis
ICSD-III	International Classification of Sleep Disorders
vPSG	Video Polysomnogram
OSAS	Obstructive Sleep Apnea Syndrome

Introduction

In the 7th semester of medicine at the University of Oslo one of our main subjects was neurology. We both developed a big interest in this field, which is the reason behind our thesis´s topic. Mathias Toft, our supervisor, was one of our professors that semester. He held a lecture about neurodegenerative diseases and we found his approach to this subject appealing. Later on, we contacted him and discussed some topics for our thesis, which led to the current objective.

The main reason we decided to write the thesis together was that we shared the same interest in neurology. We have also cooperated on other projects with a positive outcome. Since we enjoy working together, this was a good opportunity that suited our schedules.

January 2020, we started our work by attending several courses, arranged by the university library. Among them were courses about literature search in different databases and EndNote as a reference tool. We constructed our search in PubMed with guidance from a librarian. Our literature search resulted in 486 articles which were carefully reviewed individually by both of us. We worked closely by frequently discussing every step of the way. We had regular meetings with our supervisor in this period. 43 articles were remaining after the initial sorting process. These were equally divided between Kiana and Tara, and read in full text. Of the remaining articles, 23 studies were divided into different risk factor categories such as Genetic, environmental, Lifestyle, Cardiovascular and Sociodemographic. We agreed upon the following distribution of categories:

Kiana → Cardiovascular, Sociodemographic, Environmental, Head and brain injuries.
Tara → Physical activity, Prodromal PD-symptoms, Psychiatric comorbidities
Mathias Toft → Genetics

Each author wrote results and discussions on their assigned topics while conversing closely. Tables, figures, method, introduction, limitations, and conclusion were written by both of us.

When writing the "kappe" we divided the following topics as such:

Kiana → “English summary", "What makes iRBD interesting?", "Setting diagnosis", "Method"
Tara → “What is iRBD?", "Epidemiology", "Pathophysiology", "Treatment", "Discussion"

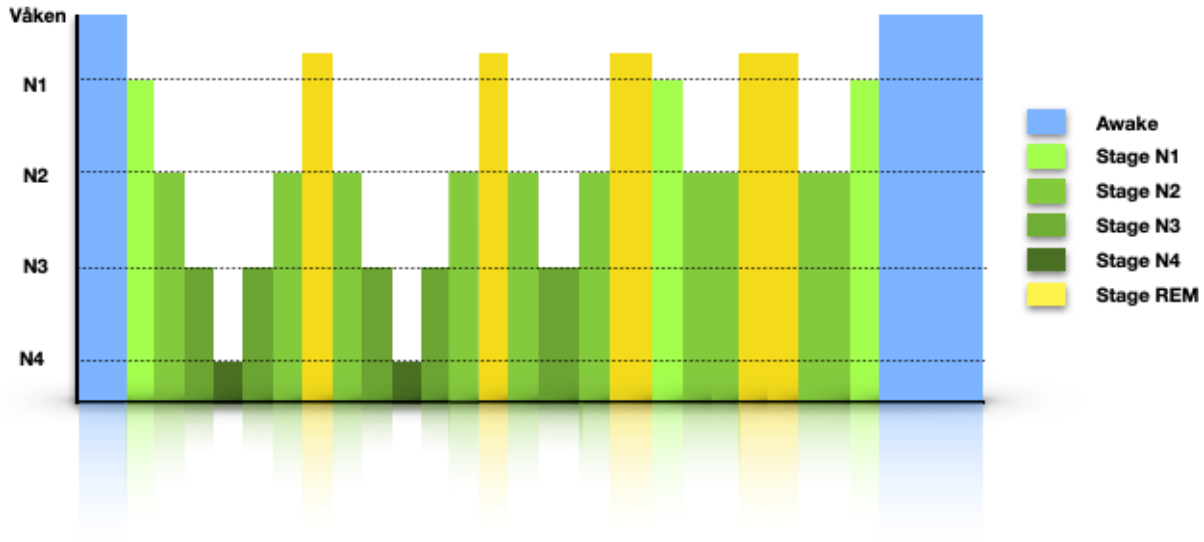
Together with Mathias Toft, we have prepared a manuscript for a scientific article to be published.

Background

What is iRBD?

Our sleep consists of four different stages: one of them is rapid eye movement sleep (REM), and the other three are non-REM sleep (NREM). NREM sleep is divided into N1, N2, N3, and N4, with stages N3 and N4 constituting the deeper sleep, also called slow-wave sleep. Over the course of a night, the brain alternates between these different stages (see figure 1). During REM sleep the body undergoes a temporary paralysis, also known as atonia (1). All muscle activity ceases, except for the ones that control eye movement and breathing. In this stage of sleep we usually dream, therefore a lack of muscle activity is thought to protect us from acting out on our dreams and getting injured.

Figure 1, sleep stages throughout the night



REM: rapid eye movement sleep. Non-REM sleep is divided into N1, N2, N3, and N4 sleep. Progression into N4 decreases throughout the course of sleep.

REM sleep behavior disorder (RBD) is a sleep disorder characterized by loss of atonia or abnormal behaviors during REM sleep. It is often discovered by the bed-partner who experiences excessive movements, vocalization, or in rare instances even injury due to the

patient's dream enactment (2). REM sleep occurs predominantly in the late hours of the night, and therefore issues arising from RBD are more frequently observed during this time.

RBD may occur in relation to brain disorders such as narcolepsy with cataplexy, MS, and the α-synucleinopathies. When a person has developed RBD without additional disorders, it's called idiopathic RBD (iRBD). This article will mainly be centered around iRBD and the risk factors involved in its development.

What makes iRBD interesting?

It is essential to increase the knowledge of risk factors leading to iRBD, since many patients with iRBD proceed to develop neurodegenerative syndromes. Among these are α-synucleinopathies such as Parkinson disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (2).

Several studies confirm the strong association between iRBD and later developing parkinsonism. In a review by Michele T.Hu, iRBD has been identified as a prodromal symptom for neurodegenerative synucleinopathies, where patients with RBD had 80% probability to develop PD, DLB, or MSA (3). A study of patients with confirmed α-synucleinopathies and RBD indicated that α-synucleinopathies might present themselves as RBD in patients up to 50 years prior to overt neurodegeneration. (2)

These findings emphasize how increasing the understanding of RBD risk factors has the potential to advance treatment and screening tools for neurodegenerative syndromes. As of today, little research has yet been conducted to find and understand these risk factors. Therefore, this article aims to present a comprehensive summary of the current research on risk factors for idiopathic RBD.

Setting a diagnosis

RBD is diagnosed according to the International Classification of Sleep Disorders (ICSD-III). To set a definite RBD diagnosis requires a video polysomnogram (vPSG) which is a diagnostic test used to assess abnormal sleep behaviors during REM sleep. The test uses

electroencephalogram, electrooculogram, and electromyogram to determine repeated episodes of REM sleep without atonia (RSWA) and dream enactment with vocalization or complex movements (4).

Research studies have also commonly used questionnaires to identify RBD in study populations. However, these questionnaires tend to overestimate the occurrence of RBD, since they most likely misclassified other conditions as RBD. The problem of low specificity is also present in the gold standard diagnostic method PSG, due to patients' symptoms not being detectable during the night of the test (5).

Furthermore, vPSG is not available at most healthcare facilities and is also a resource-demanding diagnostic method, considering time and money. This further complicates the detection of the condition in the common population, leading to a large number of cases not being discovered (5).

Epidemiology

Research in the field shows that the prevalence ranges from 1-3%, the variation is due to the different study designs and screening questionnaires (6, 7). It is frequently seen in older adults, especially those above 50 years of age.
It is rather challenging to find an estimate that reflects the true prevalence of iRBD in the population. There are several reasons for this. First of all, the vast majority of people affected by iRBD don't develop noticeable symptoms and fail to see a clinician. Secondly, iRBD is not well known in other medical fields apart from neurology and is thus underdiagnosed. Lastly, in order to confirm iRBD, vPSG is necessary, which as previously mentioned isn't always available due to the costs.

Pathophysiology

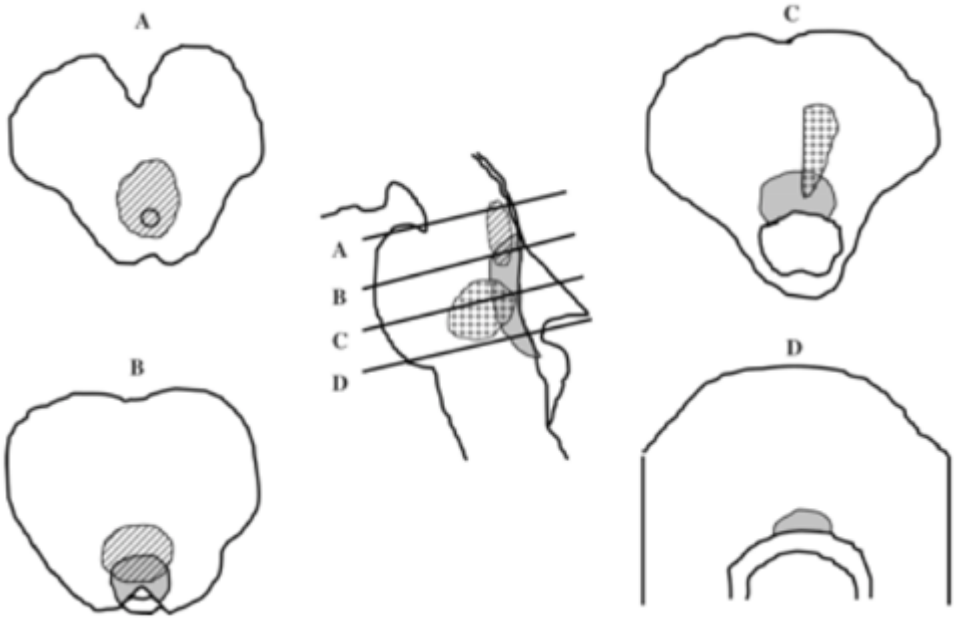
To better understand iRBD we should look to pathophysiology. The brainstem regulates a number of very important functions such as respiration, circulation, and heart rate. In addition, a number of nuclei located here control motor function, the autonomic system,

attention, sleep, and wakefulness. Thus, abnormalities that affect the physiology of the brainstem can give symptoms of RBD.

Studies suggest that there are two systems involved in muscle atonia during REM sleep(8). One leads to muscle atonia, while the other inhibits muscle activity. The induction of atonia is regulated by several nuclei in the brainstem.

In this study by Boeve et al (8), five patients were reviewed with lesions in the brainstem caused by different underlying diseases. Two of the patients had multiple sclerosis (MS) with lesions in cerebral and pontine white matter and the other in the dorsal pontine tegmentum. The other patients had a tegmental Ponto-mesencephalic cavernoma, brainstem neurinoma, and ischemic lesions in the pons. All five patients presented with the symptoms of RBD. What they all had in common was injuries on very specific parts of the brainstem (see figure 2.).

Figure 2. RBD associated with brainstem lesions shown in human brainstem template



Boeve, et al. (2) reviewed five RBD patients with lesions in the brainstem. The figure illustrates the location of the lesions, caused by different underlying diseases. A corresponding to the pontomesencephalic junction, B to the upper/mid pons, C to lower/mid pons and D just rostral to the pontomedullary junction.

In comparison, a number of patients who suffer from a-synucleinopathies such as PD, DLB, and MSA, diseases of which all are caused by various pathology in the brainstem, also present with RBD-symptoms.

It may be of interest to mention that patients with Alzheimer's disease (AD), the most common form of dementia, don't present with RBD symptoms (9). AD can affect most of the brain tissue, the strongest hypothesis for the pathology is the amyloid cascade resulting in aggregation of amyloid plaques. Yet it seems as though this dementia doesn't affect the same sites associated with RBD, as the a-synucleinopathies tend to do.

Treatment

Treatment of RBD is aimed toward symptomatic relief. The goal is to reduce dream enactment, thereby reducing the risk of injury and disturbed sleep for both the patient and the bedpartner. There are medical and non-medical treatments available. Clonazepam and melatonin are the first medical choices (10).

Clonazepam is a long-acting and potent benzodiazepine. It is the only benzodiazepine that has the desired effect on RBD, although the reason remains unknown (2). One study suggested that clonazepam increases sleep quality and reduces dream enactment even though it increases muscle activity after treatment, and does not influence the pathophysiology of RBD (10). Normal dosage starts at 0,5 mg and can be titrated up to 2mg. The drug should be taken at night. While clonazepam has a calming effect on the brain by inducing hyperpolarization of the neurons by the GABA-A receptor, melatonin's point of attack is circadian rhythm regulation. Melatonin is a hormone produced in the pineal gland, and is stimulated by darkness and inhibited by light. The level of this hormone in the body decreases as we grow older (11). Studies have shown that melatonin affects regaining atonia during REM sleep (12, 13). Another study showed that patients treated with melatonin suffered less from side effects than those treated with clonazepam (14). Initially, clonazepam and melatonin are used separately, but if neither are effective, they can be combined.

The non-medical treatments of RBD consist of safety measures, hypnosis, calming familiar voice during dream enactment, and treatment of other comorbid conditions such as OSAS (obstructive sleep apnea syndrome) . There is little research in this field and thus it's hard to establish the effect on RBD.

Objective

The aim of this article is to review available research regarding risk factors and additional effects that may impact the development of iRBD. This will be done by means of a systematic literature review.

Material and method

This is a systematic review of collected data regarding risk factors for idiopathic REM sleep behavior disorders. The studies reviewed were found by a search in the database PubMed. The following keywords and MeSH-terms used in the search were: “REM Sleep Parasomnias” [Mesh], “REM Sleep Behavior Disorder"[Mesh], “Rapid Eye Movement Sleep Behavior Disorder”, "Risk Factors"[Mesh], "population at risk", “risk scores”
To include all relevant articles available, search terms in both singular and plural forms of the keywords and MeSH-terms were added, using “OR” between synonyms.
“AND” was added between search terms to find articles concerning risk factors for iRBD. In addition, filters were added to the search to exclude Meta-analysis and reviews since the study aims to conduct a systematic review. Among other excluded articles, there were literature with children or adolescents as participants, since iRBD is frequently seen in older adults. Case reports also were excluded reason being limited data for the review. Further, only studies written in English were included in the search by adding “AND English[lang]” in the search box. Filters regarding publication year have not been used since the literature concerning risk factors for iRBD is limited. To assess further eligibility of the remaining articles, we applied our inclusion/exclusion criteria which is mentioned in our article.

Table 1: Search strategy and data extraction

Database	Keywords number	Keywords & combinations	Number data (each unfiltered search)
PubMed	1	("REM Sleep Parasomnias"[Mesh:NoExp] OR "REM Sleep Behavior Disorder"[Mesh] OR REM Sleep Behavior Disorder OR REM Sleep Behavior Disorders OR Rapid Eye Movement Sleep Behavior Disorder OR Rapid Eye Movement Sleep Behavior Disorders) AND ("Risk Factors"[Mesh] OR risk factor OR risk factors OR "population at risk" OR "populations at risk" OR risk scores OR risk score) NOT (meta-analysis[Filter] OR review[Filter] AND English[lang])	10,488
	2	("Risk Factors"[Mesh] OR risk factor OR risk factors OR "population at risk" OR "populations at risk" OR risk scores OR risk score)	1,747,331
	3	1 AND 2	654
	4	(meta-analysis[Filter] OR review[Filter])	3,016,912
	5	3 NOT 4	496
	6	(English[lang])	28,851,766
	7	5 AND 6	486

Search terms and their results. Abbreviations: MeSH: Medical Subject Headings

Search Outcome

After applying the selected keywords in various combinations, and adding filters, the literature search resulted in 486 articles. After reviewing the records identified through the database, 443 articles that weren't concerning risk factors involved in the development of iRBD/pRBD were excluded, based on their title and abstract.

The remaining 43 articles were carefully assessed by two authors for the full texts. 14 records were obtained at this stage. 7 studies were included in our literature collection by reference through other articles and studies chosen based on the author's knowledge.

Results

Please see the article.

Discussion

Please look to our paper for a discussion of our results, here we will discuss parts of our study that we haven't shed light upon in the article.

Systematic reviews have both strengths and limitations. We wished to use this study design to overview the literature regarding risk factors for the development of iRBD. Nonetheless, it is important to keep in mind that this study design has some limitations. First, it’s hard to compare the results across the studies seeing that they use different diagnostic criteria, statistical methods for analyzing the results, and are performed in different countries. Second, there is always a risk of inclusion bias for articles. We tried to minimize this bias by having two independent authors evaluate the papers by title and abstract. The discrepancies were resolved through discussion and consultation with the senior author. Third, the final constructed search in PubMed did not include all articles that were relevant to us. We know this for a fact because we included new articles from the references in our original selection. Although we frequently checked references, a possibility that some relevant articles were unidentified remains. Fourth, publication bias must also be addressed, there is always an inclination of studies with positive findings to be published rather than studies with

nonsignificant conclusions. We ought to take into consideration the risk of studies with null results not being published, and therefore not included in our systematic review.

Usually, a systematic review allows the authors to reach a conclusion on the reviewed topic. However, we weren't able to do this in our case, due to the vast heterogeneity of identified records. Some strengths that this systematic review holds, are that we were able to make a summary on the research of iRBD risk factors, and also identify a big gap in this field. A collaboration between three authors further enabled conversation and debate around the results and study topics. This increased the academic quality of our paper.

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Risk factors for idiopathic REM sleep disorder – a systematic literature study (Article)

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Tables: 2

Figures: 1

Abstract

Background: REM-sleep behavior disorder (RBD) is a parasomnia associated with the development of synucleinopathies such as Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Therefore, it is of interest to identify a risk factor profile for this parasomnia.

Methods: A systematic review was conducted on literature published by PubMed on the 5th of February 2020. The articles concerning risk factors for iRBD were initially evaluated by two independent reviewers. This was done in three phases; by title, abstract, and full text.

Results: Of 486 articles, 14 were relevant based on inclusion/exclusion criteria, while 7 additional articles were included through other sources. We identified genetic variation, low education, farming, blue-collar occupation, pesticide exposure, low physical activity, smoking, alcohol drinking, post-traumatic stress disorder(PTSD), depression, antidepressants, cardiovascular disease and risk factors, brain injury, and prodromal PD symptoms, as risk factors for the development of iRBD.

Conclusions: This systematic review summarizes the current available literature of risk factors for iRBD. Findings suggested that although the risk factor profile for iRBD had strong similarities with risk for PD, evidence also indicated that the profile for iRBD might have unique characteristics. The findings of this systematic review emphasize the need for further research on the risk factor profile for iRBD, with larger sample sizes, and less heterogeneity in the study sample.

INTRODUCTION

During rapid eye movement (REM) sleep all muscle activity ceases, except for the ones controlling eye movement and vital functions. REM sleep behavior disorder (RBD) is a sleep disorder characterized by loss of atonia during REM sleep, allowing dream enactment behavior. This consists of vocalization, excessive movements, and occasionally injury due to the patient's dream enactment(1). The patients rarely complain about the symptoms, and more often it's discovered by the bed partner.

Video polysomnography (vPSG) is required to set a concrete RBD diagnosis. vPSG is a comprehensive test used to diagnose a variety of sleep disorders. The test monitors multiple variables such as amount of airflow during sleep, breathing pattern, sound and muscle activity (2). This way the test determines episodes of dream enactments. Questionnaires have also been frequently used in multiple studies to identify RBD, in these cases the term probable RBD (pRBD) is applied.

The prevalence of iRBD in the population ranges from around 1-3% based on different screening tools. A higher prevalence has been reported in studies where RBD was diagnosed through questionnaires. Thus may be due to misclassification of other conditions than iRBD, and lower prevalence has been identified in PSG-based studies (3, 4).

Currently, there is no cure for RBD. The only existing treatment is aimed towards symptomatic relief. Clonazepam and melatonin are two available drug options(5). The underlying mechanisms in RBD patients are yet to be discovered. Both drugs appear to be equally effective in reducing dream enactment behavior. However, melatonin causes fewer side effects than clonazepam.

iRBD is a prodromal symptom for neurodegenerative synucleinopathies, and 80% of the patients will eventually develop Parkinson disease (PD), dementia with

Lewy bodies (DLB) or multiple system atrophy (MSA) (6). Therefore we wish to elucidate and better understand this prodromal stage, by looking at its risk factors. If we can recognize risk factors it will provide a window in which we can identify patients at risk of developing neurodegeneration, possibly decades earlier. By a risk factor we refer to something that increases the susceptibility for developing iRBD, be it genetics, environmental-, or lifestyle factors. This is of great value in future studies for disease modifying variables.

MATERIALS AND METHODS

The research question was answered by retrieving relevant articles through a systematic literature search in PubMed for all articles published by the 5th of February 2021. To identify relevant articles for the review, we used the following MeSH-terms: "REM sleep parasomnia", "REM sleep behavior disorder" and "Risk factors". A filter to exclude meta-analysis and reviews was added during the search. After the search words were agreed upon, our final result was as follows: ("REM Sleep Parasomnias"[Mesh:NoExp] OR "REM Sleep Behavior Disorder"[Mesh] OR REM Sleep Behavior Disorder OR REM Sleep Behavior Disorders OR Rapid Eye Movement Sleep Behavior Disorder OR Rapid Eye Movement Sleep Behavior Disorders) AND ("Risk Factors"[Mesh] OR risk factor OR risk factors OR "population at risk" OR "populations at risk" OR risk scores OR risk score) NOT (meta-analysis[Filter] OR review[Filter] AND English[lang]).

The articles were initially evaluated by two independent reviewers (TB and KS). This was done in three phases; by title, abstract and eventually full text. The

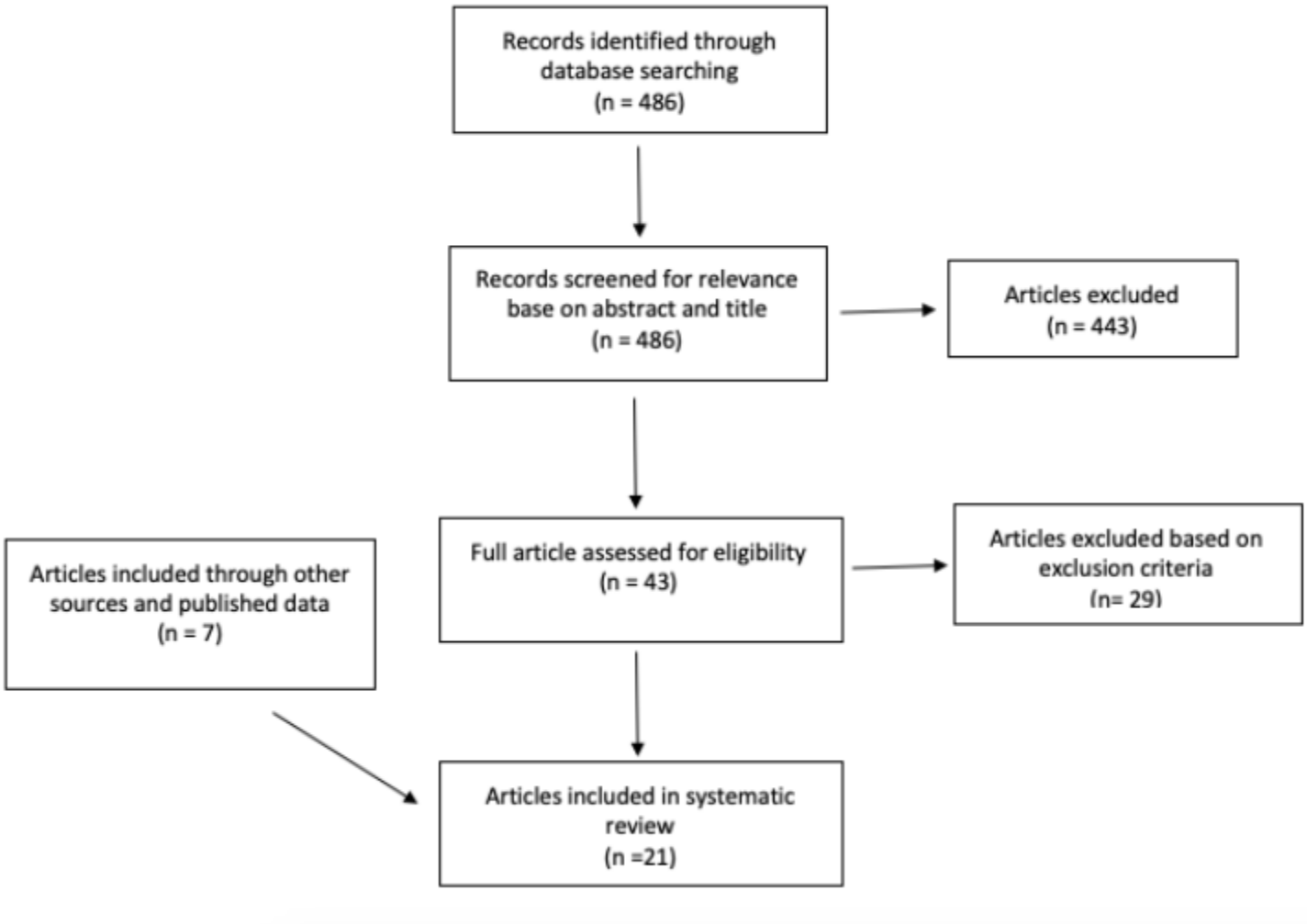
discrepancies were resolved through discussion, and consultation with the senior author (MT). A PRISMA flowchart of the search process is illustrated in figure 1.

To decrease the risk of bias in our selection of studies, we relied on inclusion- and exclusion criteria to correctly evaluate the literature. The chosen literature was included by the following criteria: Original studies whose aim was to look at both risk factors and additional effects involved in the development of iRBD/pRBD. Our article selection was limited to publications written in the English language. The exclusion criteria consisted of studies reporting RBD associated with synucleinopathies or other conditions, other parasomnias as well as disturbance of REM-sleep not caused by RBD, studies of children or adolescents, reviews, meta-analysis and case reports.

RESULTS

The literature search using the PubMed-engine resulted in 486 articles. After careful reading and evaluation using the defined inclusion and exclusion criteria, 21 articles were identified, which were highly heterogeneous with respect to study design, size and risk factors that were studied. (see figure1). Seven out of the 21 articles were identified during the literature review or were previously known by the authors.

Figure 1. Flowchart of included articles from PubMed



Abbreviations: n: number of extracted studies

Table 1. Genetic studies of idiopathic RBD

Author	Year	Design	N (number)	Diagnostic method	Associated factors with iRBD
De Francesco, Terzaghi (7)	2021	Case-control	Case n = 33, Control n = 33	ICDS III	Lower exp: - TBX21, - STAT3 - STAT4 Higher exp: - FOXp3
Mufti, Yu (8)	2021	Case-control	Case n=1039 Control n=1852	vPSG	Rare coding variants BST1 and LAMP3
Krohn, Wu (9)	2020	Case-control	Case n=1076 Control n=6155	vPSG	Variants SNCA locus
Liu, Zhang (10)	2019	Case-control	Case n = 404, Control n= 387	RBD-SQ + vPSG	Familial aggregation
Buckley, Siddique (11)	2017	Case-control	Case n = 50, Control n= 14	RBD-SQ	22q11DS
Gan-Or, Girard (12)	2015	Case-control	Case n = 261, Control n= 379	ICDS II	Negativ ass.: SCARB2 rs6812193 SNP, MAPT rs12185268 SNP
Gan-Or, Mirelman (13)	2015	Case-control	Case n = 265 Control n = 2240		GBA-mutation
Dauvilliers, Postuma (14)	2013	Case-control	Case n = 316, Control n= 316	PSG	Genetic contribution

Abbreviations: iRBD: idiopathic rapid eye movement behavior disorder; RBDSQ: REM sleep behavior disorder sleep questionnaire; ICDS III: International classification of sleep disorders - Third edition; vPSG: Video Polysomnography.

Genetic factors

In a study of familial aggregation of iRBD relatives of patients demonstrated higher levels of RBD features compared to relatives of controls (10). A multi-center case-control study of 316 patients with PSG-verified iRBD found an increased odds of

proxy-reported family history of presumed RBD among individuals with confirmed iRBD (14). Both these studies suggest the possibility of a genetic contribution to RBD. Gan-Or and colleagues genotyped nine genetic variants previously associated with PD and examined their effects (12). They found that SCARB2 rs6812193 (OR = 0.67) and MAPT rs12185268 (OR = 0.43) were associated with RBD, suggesting that RBD may be associated with PD-associated genes. In a recent study a SNCA variant (rs10005233) was associated with iRBD, and this variant is linked to variants previously found across the different synucleinopathies (9).

Genetic studies have also been performed by sequencing of candidate genes. One study sequenced the GBA gene in iRBD patients (n = 265), and compared the results to controls (n = 2240). GBA mutations carriers had an OR of 6.24 (10.2% in patients vs. 1.8% in controls) for rapid eye movement sleep behavior disorder (13). These results indicate that iRBD is associated with GBA mutations, which have previously been strongly linked to PD and DLB. Mufti et al sequenced 25 genes previously identified in genetic studies of PD in a total of 1,039 patients with iRBD and 1,852 controls (8). Using tests of genetic burden, an association between rare heterozygous nonsynonymous variants in *BST1* and *LAMP3* were found.

Table 2. Remaining studies of idiopathic RBD

Author	Year	Design	n (number)	Diagnostic method	Associated factors with iRBD
Zhang, Gu (3)	2020	Cohort	n = 7,225	RBD-SQ	Hyperlipidaemia, Smoking, Pesticide exposure, Prodromal symptoms of PD, Positive family history of dementia or PD, CO poisoning, Smoking Alcohol drinkers
Elliott, Opel (15)	2020	Cross section	n = 394	vPSG	PTSD, Traumatic brain injury
Park, Han (16)	2020	Prospective cohort	n = 245, 2 year follow-up n = 146	RBD-SQ	Small volume of pineal gland
Hughes, Gao (17)	2019	Cohort	n = 46,272	RBD-SQ	Lower physical activity
Yao, Fereshtehnejad (4)	2018	Cross section	n = 30,097	RBD-SQ	Male sex, low education, heavy drinking, smoking, antidepressant, depression, anxiety, PTSD, marriage/ long-term relationship
Lerche, Gutfreund (18)	2018	Cross section Longitudinal	n = 667 n = 513	RBD-SQ	Low physical activity
Shrestha, Kamel (19)	2018	Cohort	n = 20,591	RBD-SQ	PD symptoms Smoking Alcohol drinking Marital status Pesticides
Haba-Rubio, Frauscher (20)	2018	Cohort	n = 1,997	vPSG	Antidepressants, Antipsychotics Smoking
Ma, Qiao (21)	2017	Cross section	n = 3,635	RBD-SQ	Previous head injury, Lower education, SSRIs,

					Benzodiazepines, Alcoholic beverages, Atrial fibrillation, Hyperlipidaemia, Constipation, PD non-motor symptoms
Wong, Li (22)	2016	Cross section	n = 12,784	RBD-SQ	Lower education level, Coal occupation Lower physical activity level Diabetes Low BMI Head injury, cardiovascular risk factors, Olfactory and taste dysfunction
Frauscher, Jennum (23)	2014	Case control	Case n = 318, Control n= 318	RBD-SQ	Depression, Antidepressants, Ischemic heart Disease, Inhaled glucocorticoids
Postuma, Montplaisir (24)	2012	Case control	Case n= 347 Control n = 347	vPSG	Head injury, Pesticide exposure, Low education, Working as a farmer, Cigarette smoking
Verma, Anand (25)	2007	Retrospective cohort	n = 60	vPSG	Chronic traumatic brain injury

Abbreviations: iRBD: idiopathic rapid eye movement behavior disorder; ICDS III: International classification of sleep disorders - Third edition; RBDSQ; REM sleep behavior disorder sleep questionnaire; vPSG: Video Polysomnography; PD: Parkinson's disease; CO: carbon monoxide; PTSD: post-traumatic stress disorder; SSRI: selective serotonin reuptake inhibitors; BMI: body mass index.

Socioeconomic factors

Socioeconomic factors that were associated with higher risk of having iRBD was lower education level and being in a long-term relationship or marriage. Wong et al included lower education level as a significant risk factor for pRBD (22). In a Canadian longitudinal study with one of the largest number of participants, iRBD was more common among subjects with lower education level(4). Ma et al (21) and Postuma, et al (24) disclose the same association.

Even though sex and age in the majority of studies were adjusted, Yao et al (4) found significant association between male sex and pRBD with an OR= 2.24 (1.78-2.44), while other studies in our collection found no difference in RBD-risk between sexes (20-22).

Environmental factors

Many found some environmental risk factors such as occupational and nonoccupational pesticides exposure to be a contributor to the higher risk of RBD development. The cohort study among a population of farmers by Shresthaet al found a significant association for pesticides and dream enacting behaviors (DEB) (19). Zhang et al also included exposure to industrial aerosols and chemicals among blue-collar workers as a significant risk factor for pRBD (3).

Lifestyle factors

Regarding lifestyle factors, both protective and risk factors were reported. The studies provided different results on the effect of physical activity on the risk for iRBD. Two large studies, one from the United States (17) (OR=0,85) and another from China (22) (OR=0,60), concluded with physical activity being a protective factor against

development of iRBD. In a German study, baseline physical active participants were less affected by symptoms of iRBD, although six years later the effect was indifferent (18). A small cross-sectional study in China could not find any association between iRBD and physical activity (21). However, in the latter, their small population was a limitation for the identification of a possible effect of physical activity.

Multiple studies looked at the effect of alcohol consumption and development of iRBD. Some found no association (22, 24), while others as Zhang et al (3), Yao et al (4), Ma et al (21), and Shrestha et al (19) found a positive association with alcohol usage and iRBD with ORs in the range of 1.25 to 2.16..

Although the findings for cigarette smoking varied in the studies, an important common feature was that neither found smoking to be a protective component. Two community-based studies from China, found no connection between iRBD and smoking (21, 22). One the other hand, four studies found significant associations between smoking and iRBD(3, 19, 20, 24). Interestingly Zhang et al found that both smokers (OR=2,02) and passive smokers (OR=2,37) were more at risk of having iRBD(3).

Psychiatric comorbidities

Psychiatric comorbidities have been assessed in several studies, and evidence suggests that there is a strong coherence with iRBD. Depression was frequently identified as a risk factor, both Yao et al (4) and Fraucher et al (OR=2,0) (23) found this to be significant. Further, the studies that were reviewed also show that antidepressants such as SSRIs ((OR=2,2) (23), (OR=2,77) (4),(OR=4,56) (20)), benzodiazepines (OR=2,68) (21) and antipsychotics (OR=5,61) (20) are associated with development of iRBD.

Yao et al. suggested PTSD as a notable risk factor (OR=2,68) (4), this was again confirmed in 2020 by Elliot et al. in a study conducted on veterans with iRBD(15).

Cardiovascular risk factors

In a clinical case-control study a possible association between different comorbid conditions and iRBD was investigated(23). The results showed that patients with iRBD were more likely to report ischemic heart disease. They were however not able to find significant associations to cardiovascular risk factors such as obesity, diabetes mellitus, hypercholesterolemia, and hypertension (23)

In a cross-section study of community cohorts in Shanghai, the authors found atrial fibrillation, hyperlipidemia, coronary disease, and chronic diabetes to be significantly associated with higher risk for iRBD development (21).

In addition, in one of the largest studies with a sample of 12,784 adults diagnosed with pRBD, Wonget al (22), reported that higher LDL level, a history of diabetes and other cardiovascular risk factors were detected more frequently in iRBD patients and could therefore be described as potential risk factors for this parasomnia.

Hyperlipidemia has also been reported more often among pRBD subjects compared to healthy participants in a longitudinal cohort study from Beijing (3).

Head trauma and brain pathologies

Several studies have found an association between head injuries and a higher risk of developing iRBD (15, 21, 22, 24). Wong et al found an increased risk for RBD in individuals with previous head injury, with an adjusted OR of 3.02 (CI 95% 2.2-4.12) (22). Elliot et al. showed 5% increased prevalence of RBD (OR= 1.12) among

veterans with traumatic brain injury (15). Yet they were limited by their small sample size to assess more accurate data. In another prospective cohort design Verma et al. found 24% increased risk of RBD after 2 years of ongoing TBI (25).

In addition to head injury, a prospective cohort study indicated that smaller visual pathway glioma (VPG) and volume of pineal parenchyma (VPP) could possibly be a future biomarker of isolated RBD in cognitively normal elderly (16).

Prodromal PD-symptoms

Since iRBD in the majority of patients converts into a parkinsonian disorder, RBD is considered a prodromal symptom for these disorders. Other prodromal symptoms for PD have been assessed in a number of reports. Ma et. al. looked specifically at PD non-motor symptoms such as constipation, urinary disturbance, olfactory disturbance, and imbalance, of which all were found to be associated with iRBD (21). A Chinese cross-sectional study on 12,784 participants also found olfactory dysfunction to be a risk factor for iRBD(22). While a cohort study from 2020 saw a strong association with both non-motor symptoms such as constipation(OR=3,8) , olfactory dysfunction(OR=2,16), daytime sleepiness(OR=2,40), and motor symptoms as inexpressive face(OR=2,28), clumsy arms/legs(OR=4,40), reduced arm swing(OR=2,01) and falls (OR=2,04) (3).

A study on male farmers in the United States also found higher prevalence of motor and non-motor symptoms among participants presenting with dream enactment behavior (19).

DISCUSSION

This systematic review of risk factors for development of iRBD is, to our knowledge, the first of its kind. Our search on PubMed provided 21 relevant articles after careful review of a large number of studies. We focused solely on patients with iRBD, RBD secondary to other disorders (e.g. PD, dementia) were excluded. The results are of important value seeing how some risk factors differed, but most were similar to the risk of PD development. This is especially interesting for understanding the prodromal phases of neurodegeneration and PD. Of the observed risk factors, genetic components, low education, farming, blue collar occupation, pesticide exposure, low physical activity, smoking, alcohol drinking, PTSD, depression, antidepressants, cardiovascular disease and risk factors, brain injury and prodromal PD symptoms were significant.

A genetic component to risk for iRBD is indicated by the identification of familial aggregation (10, 14). Sequencing of the GBA gene found a clear overrepresentation of mutations in this gene in iRBD compared to controls (13). Such mutations are strong risk factors for both PD and DLB, and the link also to iRBD is compatible with high conversion rate from iRBD to synucleinopathies. Genetic association studies are dependent on large samples sizes, which are not available for iRBD. Thus, no major unbiased genome-wide association study of this trait has been performed to date. A smaller study indicated that some of the PD-associated genetic variants were also linked to iRBD, but the power of this study was very limited(12) . A larger study of the SNCA locus, encoding the α-synuclein protein, found a clear association also here (9). Interestingly, this study found a distinct pattern of association at the SNCA locus in RBD as compared to PD, indicating only partly overlap between genetic risk for the two conditions. In total very limited data is

available on the genetic risk factors predisposing to iRBD, and larger studies are needed to shed further light on this interesting topic.

Large studies from the United States(17) and China(22), including 59,056 participants in total, found physical activity as a positive disease modifier, and protective factor. Their results are of considerable worth, yet some degree of caution must be addressed in interpretation of their results. Causality between RBD and level of physical activity in the patients can be challenging to determine. The American cohort did not assess prodromal features at baseline, and the Chinese cross section is limited to the study design's momentarily snapshot of the situation. 80% of iRBD patients will eventually develop an synucleinopathy (6), therefore one can assume that these patients might have some level of ongoing neurodegeneration. Early dopaminergic loss can result in imbalanced motivation for physical activity, or early PD-symptoms such as rigidity, bradykinesia or poor balance which all can result in less physical activity.

In other words, evidence suggests that physical activity has merit for patients suffering from iRBD, but more thorough research is preferable to further understand this relationship.

Our findings point towards smoking as a significant risk factor for development of iRBD. This is of great importance, because smoking is inversely associated with PD (26), and this implies divergent risk factor profiles for the diseases. This divergence is interesting, and the underlying mechanism behind the link between smoking and iRBD remains uncertain. A possible explanation might be that smoking usually is associated with other suggested risk factors such as alcohol consumption, lower physical activity, and cardiovascular disease.

In several case-control studies cardiovascular diseases have been found to be more prevalent in iRBD patients than controls. In fact, Frauscher et al (23) also found a CVD association that remained after adjustments for CV risk factors, which strengthened this link. However, they hypothesized that this finding might have been affected by healthy participant bias, since the association was less prominent when compared to sleep center controls. This association might on the other hand have been affected by the introduction of sleep apnea, a known risk factor for CVD, into the control group. Among frequent CV risk factors that have been linked to iRBD, hyperlipidemia, chronic diabetes and atrial fibrillation has been mentioned. The etiology of CVD as a risk factor for iRBD is not fully understood. Yet one can assume that cerebrovascular disease, such as vascular parkinsonism, may be caused by CVD or its risk factors. Some reports confirmed a strong link between CVD and other associated factors and PD (21). This would make CVD and its risk factors a common contributor for both PD and iRBD.

Some of the studies in our collection indicated that head trauma and traumatic brain injury (TBI) is a risk factor for iRBD. The same risk factors have been found to be associated with PD, making TBI a common disease modifier (27). The causality of this association may be due to the fact that TBI could cause damage in multiple nuclei in the brainstem, which are responsible for control of motor function and atonia during sleep.

Being in a long-term relationship or marriage has been shown to be one of the risk factors for having pRBD according to a cross section and cohort studies (4), (19). Their findings are significant and of interest. This identified risk factor might be due to the fact that those with bedpartners are more likely to be told about their dream enactments, while participants without a bed partner are left unaware of their

parasomnia. Further PSG- diagnostic method and larger cohorts are needed to better elucidate the association of this risk factor.

Of the potential environmental risk factors associated with higher risk of developing iRBD, pesticides and other chemical exposure have been identified. Several case-control studies have found pesticides exposure, mainly among farmers, to be an associative factor for iRBD (19). One of the limitations in some of these studies is the fact that duration and dose of pesticide exposure is not fully quantified, contributing to the level of bias in this case. Further it has been reported that coal mining workers have a significantly higher risk of developing iRBD, possibly due to exposure to different sorts of industrial aerosols (22). Interestingly, there have been found similarities between a neurotoxin (MPTP) which contributes to PD development and some chemical structures in pesticides, indicating common risk factors in both PD and iRBD (28).

Psychiatric conditions are closely linked to iRBD, but also here it is challenging to determine causality. Depression might be a prior sign of neurodegeneration and is a known prodromal symptom of PD. Patients suffering from depression may have physical manifestation of their mental issues, such as sleep problems, and might therefore be more prone to development of iRBD (29). Antidepressants seemed to have a stronger association with iRBD than depression(23). A prospective cohort study revealed that iRBD patients taking antidepressants had lower risk of developing neurodegenerative synucleinopathies, yet they also exhibited markers of neurodegeneration(30). It has been implied that especially selective serotonin reuptake inhibitors (SSRIs) can trigger an earlier clinical progression of RBD. PTSD is exhibited as a risk factor for developing iRBD. Some suggest that this evident association might be due to intense night-mares that

result in dream enactment (4) (31), but Elliot et al. did a PSG based study that revealed the same association(15). The authors also pointed out that PTSD and RBD share some similarities when it comes to their pathophysiology.

Prodromal PD-symptoms were linked to the development of iRBD in our study, both motor symptoms and non-motor symptoms as constipation and olfactory disturbance. Because of the strong link between iRBD and PD, we were notsurprised to see this association. This might imply some similarities in their pathological mechanism. iRBD combined with these symptoms, especially olfactory and motor dysfunction, has proved to be a strong indicator for conversion to neurodegenerative diseases in the near future (32, 33). This specific subgroup of patients with both iRBD and prodromal symptoms could be of interest in future trials for prevention of neurodegeneration.

Our results must be interpreted while taking into account some limitations. First, most of our included studies used screening questionnaires instead of PSG to confirm iRBD. iRBD prevalence determined through PSG studies was 1,06% (20), but in a number of the studies using questionnaires the prevalence of iRBD was around 3% (3, 4). This indicates that other parasomnias which mimic iRBD (e.g. OSAS, restless leg syndrome) may also have been included. Hence, this might have affected the outcome. Nevertheless, use of questionnaires allows inclusion of large samples which cannot be done with PSG. Second, although we only included studies that looked at iRBD it is important to be aware of the fact that some patients with an early non-diagnosed PD could have been included. Third, causality has been problematic to determine throughout the suggested risk factors. Fourth, we run at a risk of selection bias due to our strict inclusion criteria to only use English articles

published on PubMed. Lastly, the small sample size makes it difficult to map out significant and trustworthy results. The great variation in methods and study designs also makes it hard to compare results across the studies. It is challenging to single out the iRBD population, as they seldom present with troublesome symptoms and seek a physician.

Conclusions:

In this systematic review, according to the 24 included articles, we found that genetic components, low education, farming, collar occupation, pesticide exposure, low physical activity, smoking, alcohol drinking, PTSD, depression, antidepressants, cardiovascular disease and risk factors, brain injury and prodromal PD symptoms are risk factors for development of iRBD. In spite of similarities in risk factor profile between PD and iRBD, research also suggests that there may be an independent risk factor composition for iRBD. Our findings can provide clinicians with important information about modifiable interventions and the prodromal phase of neurodegeneration. Small sample sizes, variation in study methods and criteria, makes it hard to draw a final conclusion. We want to emphasize that further studies on risk factors for development of iRBD are needed to clarify this relation.

Author Roles

The study was designed by MT. TB and KS carried out the literature search, analyzed the data and drafted the manuscript. MT supervised the study. All authors critically revised the manuscript for intellectual content and approved the final version for publication.

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