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TITLE PAGE

Title: Gait Ataxia in Alcohol Use Disorder: A Systematic Review

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Author disclosures

Contributors

NM, AM, and LC were involved in the conceptualization of the systematic review, whereas NM, LC, DN collaborated in the screening and review process as well as the quality assessment. NM wrote the first version of the manuscript with help from LC and AM. The manuscript was revised after being reviewed by AM, and the second revision was proof-read and edited by LS. The final revision was later approved by all the authors.

Conflicts of interest

The authors declare no conflicts of interest.

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Abstract

Objective: A severe and long-term alcohol use can have adverse effects on lower limb function. Over time, some individuals may develop gait ataxia, which refers to the impairment of controlled lower-body movements that are important for walking and maintaining proper gait. Gait ataxia is well-documented in patients who have been diagnosed with alcohol related Wernicke-Korsakoff syndrome (WKS), however, less is known on how common ataxia is among patients with alcohol use disorder (AUD) without WKS. To date, no study has systematically reviewed the evidence focusing on patients suffering only from AUD. Our aim was to perform a qualitative synthesis of the existing literature examining behavioural signs of gait ataxia among abstinent patients with AUD.

Method: Two facets were created encompassing keywords for "alcohol use disorder" and "measures of gait ataxia". Databases including EMBASE, PsychInfo, Medline, and Cochrane Library were searched for studies, and a quality assessment was performed.

Results: Ten studies were identified ($37 \geq ns \leq 247$), which were all rated as being of moderate ($N = 7$) to good quality ($N = 3$). The age range was 31.4-53.4 years (weighted mean age: 53.6 years), and 78.3% of the participants were male. Eight studies found that patients with AUD and without WKS exhibited behavioural signs of gait ataxia.

Conclusions: Although there is evidence of gait ataxia among patients with AUD, heterogeneous results and methodological shortcomings such as lack of screening for neurocognitive deficits deems these findings preliminary and highlights the need for more research in the future.

Keywords: alcohol use disorder, alcohol dependence, gait ataxia, cerebellar ataxia, lower limb ataxia

Public health significance: The lack of knowledge on whether gait ataxia is present among patients with alcohol use disorder, can delay an early diagnosis and impede on the treatment of the motor dysfunction. This systematic review provides important insights to the nature of gait ataxia among patients with alcohol use disorder.

Gait Ataxia in Alcohol Use Disorder: A Systematic Review

Alcohol use disorder (AUD) is associated with growing disability and mortality rates affecting both the individual and society as a whole and contributes significantly to the global burden of disease (Mathers et al., 2008; Peacock et al., 2018; Whiteford et al., 2013). Impaired cognitive and motoric functions may mediate this increasing disability among patients with AUD, who often experience both functional and socio-occupational impairments in their everyday activities (Bates et al., 2002; Samokhvalov et al., 2010; Stavro et al., 2013). In recent years, cognitive dysfunctions in AUD have been receiving increasing attention in the literature (Crowe et al., 2019; Le Berre, 2019; Le Berre et al., 2017; Stavro et al., 2013), while fewer resources have been dedicated to exploring the nature of the impaired motor functions in AUD. Thus, the impact of impaired motor function in AUD as well as treatment pathways targeting these dysfunctions are not well understood.

The alcohol-related impairment of lower limb function or motor function can be denoted as *ataxia*, which is defined as lack of coordination of muscle movements that subserve the ability to walk and maintain a proper gait (Araujo et al., 2021; Mitoma et al., 2021). This type of ataxia is also defined as *cerebellar ataxia* due to the structural changes in the cerebellum, including atrophy in the anterior superior portion of the vermis (Andersen, 2004; Gilman et al., 1990) and aberrations in the corpus callosum (Fein et al., 2009; Pfefferbaum et al., 2006). It has been hypothesized that long-term alcohol use can lead to cerebellar neurodegeneration, which may be mediated by neuropathological factors such as glutamatergic excitotoxicity, oxidative stress, and thiamine (vitamin B1) deficiency (Harper et al., 1986; Isenberg-Grzeda et al., 2012; Kohnke & Meek, 2021). The latter is often a result of severe, long-term alcohol use and poor dietary intake, which in turn may lead to acute Wernicke encephalopathy (WE), and if untreated, this can gradually lead to Wernicke-Korsakoff syndrome (WKS; Araujo et al., 2021). There is consensus that ataxia is one of the

clinical manifestations of WKS, whereas less is known about ataxia and how common it is in patients with AUD who have not developed WKS (Nutt et al., 2021; Ridley et al., 2013). However, ataxia has been documented among patients with AUD who do not have WKS (Fein & Greenstein, 2013; Gilman et al., 1990; Sullivan, Deshmukh, et al., 2000), which points to a need for understanding ataxia as a general sequala related to long-term alcohol use rather than being exclusive to a diagnosis of WKS (Mitoma et al., 2021).

We aimed to examine whether patients with AUD and without a diagnosis of WKS show behavioural signs of gait ataxia by conducting a qualitative synthesis of the existing evidence. Although there is evidence that patients with AUD do suffer from gait ataxia, no one has disentangled these findings from reports of patients with both AUD and WKS, and to date, no systematic review has focused on examining gait ataxia exclusively in patients with AUD.

In this systematic review, we only focused on studies that explicitly reported an abstinence period of no less than two weeks, which should reduce the risk of including AUD patients with withdrawal symptoms or uncompleted pharmacological treatment that could have an unwanted effect on motor function. Furthermore, we excluded patients with other substance use disorders as we wanted to examine the effects of alcohol and to include a population that is closely associated with patients suffering from alcohol-related WKS. Due to the narrow field of research on gait ataxia, we did not have any a priori evidence to support a distinction between the aetiology in patients with AUD and in AUD patients with a co-dependence of caffeine and/or nicotine, thus, we chose not to exclude these patients. Finally, we also narrowed the scope of the review by only including studies with behavioural measures, where the gait ataxia can be objectively evaluated by the researchers with standardized assessment batteries for ataxia.

Methods

Protocol and registration

This systematic review was prospectively registered through the online database PROSPERO (ID: CRD42021238748) on March 25 and amended on November 13, 2021. The review was conducted in accordance with the PICOS framework (Patient [*P*], Investigated condition [*I*], Comparison condition [*C*], Outcome [*O*], and Study type [*S*]) and it followed the guidelines from the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA; Moher et al., 2009).

Eligibility criteria

Inclusion criteria. Studies were eligible if they: (1) included an abstinent, a non-treatment seeking, a subclinical, or a clinical sample comprising individuals with a confirmed diagnosis of AUD (*P*); (2) assessed gait function (*O*) using behavioural measures of ataxia (*I*); (3) included a control group consisting of healthy participants (*C*); (4) used an observational study designs (e.g., cohort or cross-sectional studies; [*S*]); (5) examined participants aged 18 years or older; (5) were published in peer-reviewed journals; and (6) were written in English.

Exclusion criteria. Studies were excluded if they: (1) included samples with animals; (2) only included patients suffering from alcohol-related disorders that were not AUD (e.g., WKS); (3) examined individuals with medical conditions (e.g., arthritis, tendonitis, infections), neurological disorders (e.g., stroke, traumatic brain injury, cerebral palsy, Parkinson's disease), severe psychiatric comorbidities (e.g., psychotic disorder), or substance use disorders (SUD; except for nicotine and caffeine dependence) that could have an impact on motor function (i.e., gait function); and (4) either did not report period of abstinence or did not at any given time point (i.e., at baseline or follow-up) assess patients whose period of abstinence was equal to or more than two weeks.

Search for standardized assessment of gait ataxia. The current search strategy only included studies that assessed gait ataxia among patients using behavioural measures, but the strategy did not focus on any standardized assessment batteries for ataxia a priori. However, it was expected that one of the oldest assessment batteries, the *Fregly-Graybiel Ataxia Test Battery* (Fregly et al., 1972; Fregly & Graybiel, 1968; Graybiel & Fregly, 1966) or variations of it, would be used to assess gait function among patients with AUD. This test battery consists of three subtests, which are performed twice, the first time with eyes open and the second time with eyes closed. One subtest called *The Stand-One-Leg* requires the individual to first stand on his/her right foot (for a maximum 30 seconds) and then do the same with the left foot (maximum 30 seconds). The *Sharpened Romberg* subtest (maximum time 60 seconds) requires the person to stand with feet placed heel-to-toe and to simultaneously place his/her arms across the chest. In the last subtest called *Walk-A-Line*, the person must walk heel-to-toe on a straight line (maximum 10 steps) whilst simultaneously placing his/her arms across the chest (Fregly et al., 1972; Fregly & Graybiel, 1968; Graybiel & Fregly, 1966).

Information sources

The PICOS framework was used to guide the search methodology. Medical Subject Headings (MeSH) and their relevant synonyms were explored in PubMed and in the Cochrane Library, and keywords were mapped to subject headings in PsycInfo and EMBASE. This process resulted in two facets (see supplementary material for detailed search methodology), one of which consisted of terms related to “alcohol use disorder” (Facet 1) and the other comprised keywords for “gait ataxia” (Facet 2).

Search strategy

The search string was generated by combining the two facets using the Boolean operator “AND” (i.e., Facet 1 AND Facet 2), and this search was limited to records with human beings and to records in English (see supplementary material). A block search was

performed using EMBASE (via Ovid), PsycInfo (via Ovid), Medline (via PubMed), and Cochrane Library. Additionally, a search for grey literature was performed by looking for records in Google Scholar, trial registries, and unpublished articles on Research Gate. Finally, a chain search was performed in which the reference lists of eligible studies were scrutinized to identify other relevant studies.

Study selection

An automatic and manual duplicate removal was performed using Covidence (Veritas Health Innovation, 2019). The remaining studies were screened and reviewed by two independent research assistants (DN and NM), and any disagreements between the assessors were discussed before reaching an agreement.

Data extraction

The following data were extracted from the eligible studies: (1) surname of author(s), publication year and country information (i.e., alpha-2 country codes according to the 3166-standard of the *International Organization for Standardization* [ISO]); (2) study design; (3) sample size (across and within groups) and gender (percentage of males) and age of the participants (mean [*M*] and standard deviation [*SD*]); (4) patient and control groups; (5) primary diagnosis and the diagnostic manual used; inclusion of clinical or subclinical populations; (6) state of the patients (i.e., abstinence period, in- or outpatient-status, alcohol usage, and onset of AUD); (7) comorbid disorders (e.g., depression or anxiety); (8) measures of ataxia; (9) follow-up period; and (10) main findings (if the authors detected impaired gait function relative to the control group). The data extraction was performed by two independent researchers (NM and LC), and any disagreements between the assessors were discussed before reaching consensus.

Risk of bias assessment

A proxy measure for the risk of bias assessment was performed using the *Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies*, which consists of 14 items measuring the internal validity of studies (National Heart, Lung, and Blood Institute [NHLBI], 2019). Each study was rated (i.e., with either a yes or no) by two independent researchers (LC and NM), and any disagreements were discussed before finalizing the quality assessment. The responses were tallied and sorted into three categories (i.e., “Focus and Recruitment”, “Exposure” and “Results and Measurement”). A perfect score with five yes responses for a domain was rated as "very high", four yes responses was rated as "high", three yes responses was rated as "moderate", two yes responses was rated as "good", and one or zero yes responses were rated as "low" and "critically low", respectively. An overall percentage of the quality assessments was calculated to offer approximations of the risk of bias for each study. Here, a percentage between 95-100% indicated "high quality", between 80-95% indicated "moderate quality", between 70-80% indicated "good quality", and below 70% indicated "low quality".

Results

Study inclusion

The most recent block search was performed on July 1, 2023, which yielded 2,212 hits. A total of 570 duplicates were removed after an automatic and manual search (see figure 1). The remaining 1,642 records were screened, and 1,618 records were deemed irrelevant by the two independent researchers. Full-text review was conducted on 24 studies. Twelve of these studies were excluded due to the use of non-behavioural measures of ataxia and two studies were re-analyses of samples already included in the synthesis. The remaining ten studies were deemed eligible for the qualitative synthesis by the two researchers. Scrutinizing these studies by conducting a chain search did not result in any additional records.

[FIGURE 1]

Study characteristics

The ten included studies were conducted between 1993 and 2021 (see table 1). Nine studies were carried out by American research groups and the remaining study by researchers from Australia (Fitzpatrick et al., 2012). Seven studies used a cross-sectional design (Fitzpatrick et al., 2012; Smith & Fein, 2011; Sullivan, Rosenbloom, et al., 2000; Sullivan et al., 2002, 2004, 2010, 2021), and the remaining three studies were longitudinal (Bauer, 1993; Rosenbloom et al., 2007; Schmidt et al., 2014). The sample sizes (i.e., across experimental and control groups) ranged from 37 to 247. Five studies included small samples (i.e., $37 \leq n\text{s} \leq 78$; Bauer, 1993; Fitzpatrick et al., 2012; Rosenbloom et al., 2007; Sullivan, Desmond, et al., 2002; Sullivan et al., 2004), while the remaining five studies had a moderate sample size (i.e., $145 \leq n\text{s} \leq 247$; Schmidt et al., 2014; Smith & Fein, 2011; Sullivan et al., 2010, 2021; Sullivan, Rosenbloom, et al., 2000). Seven studies were conducted on samples consisting of more males than females (Bauer, 1993; Fitzpatrick et al., 2012; Smith & Fein, 2011; Sullivan, Rosenbloom, et al., 2000; Sullivan et al., 2004, 2010, 2021), one study was well-balanced in terms of gender (Rosenbloom et al., 2007), whereas the remaining two studies included more females than males (Schmidt et al., 2014; Sullivan et al., 2002). Across all patients with AUD, the gender distribution was as follows: 78.3% male and 21.7% female. The mean age of the patient groups (i.e., total sample of $N = 573$) ranged from 34.1 years (youngest sample; Bauer, 1993) to 53.4 years (oldest sample; Fitzpatrick et al., 2012), and the weighted mean age was 53.6 years. Three studies assessed the patients at multiple time points, including at 12-weeks (Bauer, 1993), 34-weeks (Schmidt et al., 2014), and two-year follow-up (Rosenbloom et al., 2007), whereas the remaining seven studies either did not disclose information on time of follow-up or only assessed the patients at baseline.

Regarding clinical characteristics, nine studies (Bauer, 1993; Fitzpatrick et al., 2012; Rosenbloom et al., 2007; Schmidt et al., 2014; Smith & Fein, 2011; Sullivan et al., 2002,

2004, 2010, 2021) confirmed that the included patients had a primary diagnosis of AUD (i.e., alcohol dependence [AD] according to previous diagnostic nomenclature) using criteria from the third, fourth, or fifth editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III/IV//DSM-5; American Psychiatric Association [APA], 2013), and the last study (Sullivan, Rosenbloom, et al., 2000) used the *Research Diagnostic Criteria* (RDC) to confirm the diagnosis of AUD (Spitzer et al., 1978).

[TABLE 1]

Eight studies reported abstinence periods among the included patients lasting three to 37 weeks (Bauer, 1993; Fitzpatrick et al., 2012; Rosenbloom et al., 2007; Schmidt et al., 2014; Smith & Fein, 2011; Sullivan et al., 2000, 2004, 2010, 2021), and one study included long-term abstinent patients with a mean abstinence of 2.2 years and another study included patients with an abstinence of a minimum of seven years (Smith & Fein, 2011; Sullivan et al., 2002). Three studies assessed the patients for gait ataxia at multiple time-points: one study conducted assessments at one-week, three-weeks, and 12-weeks follow-up (Bauer, 1993), the second study assessed patients at five-weeks and 34-weeks follow-up (Schmidt et al., 2014), and the third study assessed the patients at an average of 2-years follow-up (Rosenbloom et al., 2007). The remaining studies only assessed the patients for gait ataxia one time (Fitzpatrick et al., 2012; Smith & Fein, 2011; Sullivan et al., 2000, 2002, 2004, 2010, 2021). Regarding patient status, two studies only included inpatients (Bauer, 1993; Sullivan, Rosenbloom, et al., 2000), two studies only included outpatients (Fitzpatrick et al., 2012; Schmidt et al., 2014), and one study included both in- and outpatients (Sullivan et al., 2002). The remaining studies did not disclose information on patient status (Rosenbloom et al., 2007; Smith & Fein, 2011; Sullivan et al., 2004, 2010, 2021). Comorbid Axis I disorder was reported in one of the studies (Rosenbloom et al., 2007), whereas four studies (Rosenbloom

et al., 2007; Schmidt et al., 2014; Sullivan et al., 2010, 2021) reported that 176 of the patients with AUD were smokers (136 non-smokers).

Qualitative synthesis of results

Fregly-Graybiel Ataxia Test Battery. Eight studies (Rosenbloom et al., 2007; Schmidt et al., 2014; Smith & Fein, 2011; Sullivan et al., 2000, 2002, 2004, 2010, 2021) used the Fregly-Graybiel Ataxia Test Battery (Fregly et al., 1972; Fregly & Graybiel, 1968; Graybiel & Fregly, 1966) to assess gait function among patients with AUD. The earliest of the included studies examined ataxia in clinical samples consisting of either inpatients or both in- and outpatients (Sullivan et al., 2002; Sullivan, Rosenbloom, et al., 2000). In the study by Sullivan and colleagues (2000), a subgroup of inpatients (n = 53) who had been abstinent for four weeks showed worse performance on a composite score for balance and gait relative to healthy controls (HCs) after controlling for age, premorbid intelligence quotient (IQ), and years of education. Another study conducted on patients (n = 24) who had been abstinent for 29 weeks revealed an impaired performance relative to HCs on composite scores for subtests requiring the patients to have eyes open and eyes closed (Sullivan et al., 2004). This effect was also demonstrated by in- and outpatients (n = 39) who had been abstinent for even longer periods (mean abstinence period: 2.2 years), but the authors only found a lower overall performance among male patients relative to sex-matched HCs (Sullivan et al., 2002). Two of the largest and most recent studies by Sullivan and colleagues (2010, 2021) which included short-term abstinent patients (11 weeks and 37 weeks of abstinence, respectively) demonstrated impairments on various subdomains of the Fregly-Graybiel Ataxia Test Battery requiring eyes to be closed and open among patients with AUD (i.e., n = 95 and n = 151, respectively) relative to HCs.

Lastly, three studies assessed the patients either at multiple time points (Rosenbloom et al., 2007; Schmidt et al., 2014) or by including groups with different abstinence periods

(Smith & Fein, 2011). In one of these studies (Schmidt et al., 2014), smoking (n = 59) and non-smoking outpatients with AUD (n = 41), with a mean abstinence period of five weeks, exhibited impaired gait function relative to the matched control groups (n = 35 and n = 39, respectively). This pattern of impairment was also displayed by both patient groups after 34 weeks. In the study by Rosenbloom and colleagues (2007), patients with AUD (n = 15) were found to no longer exhibit gait ataxia at two-year follow-up when compared to HCs (n = 26) despite showing impaired performance at baseline (i.e., 16 weeks of abstinence). Finally, a study that examined two groups of patients with AUD, one with short-term abstinence (i.e., 6-15 weeks of abstinence; n = 70) and the other with long-term abstinence (i.e., > 7 years; n = 82), found that both groups exhibited lower performance relative to HCs after controlling for age (Smith & Fein, 2011). The authors also compared the two AUD groups in terms of gait function and found that the long-term abstinent patients performed better on the subtests of the Fregly-Graybiel battery compared to the short-term abstinent patients.

Miscellaneous assessment tools for ataxia. Two studies differed from the rest of the included studies due to the choice of assessment tools. One of these studies (n = 78) conducted by Fitzpatrick and colleagues (2012) assessed ataxia in a sample of outpatients (n = 49) using the *International Cooperative Ataxia Rating Scale* (ICARS), which is a test to quantify cerebellar ataxia symptoms across four domains, including posture and gait, limp, oculomotor, and speech function (Trouillas et al., 1997). The patients had been abstinent for eight weeks on average and they displayed impaired performance (i.e., higher scores) on the posture and gait domains as well as the kinetic domain when compared to healthy controls (HCs). Finally, the last study (n = 37) assessed body sway using a transduction method, where the inpatients (n = 6) had to balance on their dominant foot on a force-sensitive platform (Bauer, 1993). Although the patients did display more body sway relative to HCs (n = 15) at baseline (i.e., after one week of abstinence), this pattern was not present at the

second time of testing (i.e., after three weeks of abstinence).

Quality assessment

Nine of the ten studies were rated as high to very high quality (i.e., four out of five yes-responses and five out of five yes-responses, respectively) in terms of the recruitment process (Fitzpatrick et al., 2012; Rosenbloom et al., 2007; Schmidt et al., 2014; Smith & Fein, 2011; Sullivan, Rosenbloom, et al., 2000; Sullivan et al., 2002, 2004, 2010, 2021), whereas one study (Bauer, 1993) was rated as moderate quality (i.e., three out of five yes-responses) due to missing power calculations and poor description of the recruitment of patients (see table 2). All studies were rated as high to very high quality in terms of exposure assessment, different levels of exposure (e.g., dose-response relationship), and assessment of repeated exposure. Regarding the final domain, nine studies were rated as moderate quality (Bauer, 1993; Fitzpatrick et al., 2012; Schmidt et al., 2014; Smith & Fein, 2011; Sullivan et al., 2000, 2002, 2004, 2010, 2021) (Bauer, 1993; Fitzpatrick et al., 2012; Schmidt et al., 2014; Sullivan, Rosenbloom, et al., 2000; Sullivan et al., 2002, 2004, 2010, 2021), and one study was rated as low quality (Rosenbloom et al., 2007; Smith & Fein, 2011), which raised concerns regarding lack of adjustment for potential confounding variables.

[TABLE 2]

In terms of the overall percentage of positive responses, seven studies were rated as moderate quality (i.e., > 80 %; Fitzpatrick et al., 2012; Schmidt et al., 2014; Sullivan et al., 2002, 2004, 2010, 2021; Sullivan, Rosenbloom, et al., 2000), which indicates a lower risk of bias. In contrast, the three remaining studies (Bauer, 1993) had the lowest quality assessment (i.e., < 80 %), and they all raised some concerns in terms of an increased risk of bias.

Discussion

The findings of the present review suggest that patients with AUD and without WKS exhibit behavioral signs of gait ataxia. All the included studies reported some degree of gait

abnormalities among patients with AUD in the early phases of sobriety when compared to healthy control participants. Although these results are inconclusive, they might provide preliminary support for the notion that gait ataxia may be a general sequalae of long-term alcohol use (Araujo et al., 2021; Fein & Greenstein, 2013; Gilman et al., 1990; Sullivan, Deshmukh, et al., 2000). While it is still debated, it has been proposed that the age of onset and the duration of alcohol abuse mediate the severity of dysfunctions across a wide range of neurocognitive domains (Binder et al., 2017; Brennan et al., 2020; Ridley et al., 2013; Xu et al., 2017) and alcohol cerebellar degeneration (Fitzpatrick et al., 2008, 2012). In keeping with this hypothesis, a longer duration of AUD would allow for the neurotoxic effects of alcohol to exert more widespread and prominent damage to the brain (Araujo et al., 2021). Although only a few studies reported the age of onset of AUD, most of the patients were between 20-30 years old at the time of AUD onset (Fitzpatrick et al., 2012; Schmidt et al., 2014; Sullivan et al., 2010, 2021), and the period with heavy alcohol use from AUD onset to entering the study may have mediated some of the impairments in their lower motor function. Others have also suggested that the processes of the aging brain and the normal decline in cognitive and motor functions can be accelerated in individuals with early onset of AUD and years of heavy alcohol use (Nutt et al., 2021; Sullivan, Rosenbloom, et al., 2000). Nevertheless, in the studies that reported on AUD onset or years with heavy drinking (Fitzpatrick et al., 2012; Schmidt et al., 2014; Sullivan et al., 2010, 2021) the patients had suffered from AUD for up to 20 years, thus it cannot be fully determined whether the lower motor dysfunctions would be displayed by patients with a shorter duration of alcohol abuse. Furthermore, most of the studies included middle-aged patients, and only one study included a sample of patients aged less than 40 years old (Bauer, 1993), which makes it unclear whether gait ataxia is present in younger clinical populations as well.

All the included studies were conducted on patients with a confirmed diagnosis of AUD, and except for the studies by Sullivan and colleagues (2004) and Rosenbloom and colleagues (2007), they excluded patients with any other neurological and medical conditions. Still, no single study used objective measures such as cognitive screening to ensure that the included patients did indeed not suffer from conditions other than AUD. When relying exclusively on clinical records and on self-reported alcohol use and duration, one could neglect the presence of more severe alcohol-related disorder and subsyndromal alcohol-related WKS. Comparisons between patients with AUD and patients with WKS point to that the observable signs of gait ataxia do not differ between the two diagnostic groups, which also suggests that one cannot simply rely on the severity of gait ataxia to distinguish the two (Ritz et al., 2021). In keeping with this notion, the same authors also discovered that the two diagnoses only differed in terms of verbal fluency and episodic memory dysfunctions, which were only evident in the patients with WKS (Ritz et al., 2021). Thus, neurocognitive dysfunctions may be a valid predictor of other alcohol-related disorders such as WKS. The lack of screening for neurocognitive dysfunctions in previous studies highlights an important conceptual as well as a methodological issue when conducting studies examining the nature of gait ataxia in AUD.

Limitations

The studies included in the synthesis have several limitations, which impedes on the ability to draw firm conclusions in the current review. First, the preliminary evidence of gait ataxia among patients with AUD, is limited by the methodological inconsistencies and sample characteristics of the included studies. The behavioral measurements of gait ataxia vary across the studies, which in turn provides heterogeneous results and makes it difficult to compare the individual studies. In addition, most of the studies included more male than female participants (Bauer, 1993; Fitzpatrick et al., 2012; Smith & Fein, 2011; Sullivan et al.,

2004, 2010, 2021; Sullivan, Rosenbloom, et al., 2000), therefore, generalizing the findings to female patients with AUD should be done with caution. Although Sullivan and colleagues (2002) did include more women than men in their study, they still found that only the male participants exhibited decreased performance on a range of ataxia measures, which could suggest potential gender differences in gait ataxia. Lastly, only a few studies included information on race and ethnicity (Bauer, 1993; Rosenbloom et al., 2007; Sullivan et al., 2021), while it is uncertain how this may affect the symptoms of gait ataxia, it should be noted that this may preclude the results from be generalized to a wider population. Nonetheless, the inconsistent ways of assessing gait ataxia, the disproportionate number of studies with samples consisting of male patients with AUD as well as the lack of information on ethnicity highlights the need for conducting studies that use more homogeneous assessment batteries and that are more balanced in terms of gender, race, and ethnicity.

Second, though a diagnosis of SUD was an exclusion criterion in the current review and that most studies screened for SUD before the patients were included (Fitzpatrick et al., 2012; Schmidt et al., 2014; Smith & Fein, 2011; Sullivan et al., 2000, 2004), there were still studies which included patients using other substances, while not fulfilling criteria for SUD (Bauer, 1993; Sullivan et al., 2021), included patients without explicitly excluding or reporting on SUD (Sullivan et al., 2002, 2010), and studies with patients who had previously been diagnosed with SUD (Rosenbloom et al., 2007; Schmidt et al., 2014; Sullivan et al., 2004). There is some evidence of long-term effects of illicit substance use on motor function (Deik & Saunders-Pullman, 2014), thus, it may have had a mediating effect on symptoms of gait ataxia in the studies which included patients who are using or have used other substances in the past. This limitation stresses the importance of more strict criteria on whether patients are allowed to use other substances than alcohol and screening for SUD prior to including the patients in the study.

Third, the included studies did not control for nutritional status. The evidence of long-term thiamine deficiency being the cause of WKS as well as being associated with structural findings of cerebellar degeneration (Araujo et al., 2021; Nutt et al., 2021) emphasizes the importance of controlling for nutritional status prior to the inclusion of patients. Thus, it is possible that patients with AUD in some of the reviewed studies may have suffered from B1 deficiency and potentially WKS that went undetected during clinical examinations.

Finally, most of the reviewed studies were cross-sectional, whereas only a few assessed the patients at different time points. This makes it challenging to assess the effects of long-term abstinence on gait ataxia and whether the underlying aetiologic processes that mediate the clinical presentation of gait ataxia could be reversible. The studies that included multiple assessments of gait ataxia had follow-up times ranging from five weeks to two years, and they showed that the effects of prolonged duration of abstinence increased participants' overall performance on the assessments of lower motor function (Bauer, 1993; Rosenbloom et al., 2007; Schmidt et al., 2014). Similarly, other studies have demonstrated partial recovery of neurocognitive functions after long-time abstinence in patients with AUD (Crowe et al., 2019; Le Berre et al., 2017; Stavro et al., 2013). However, the present findings can only be deemed preliminary, and more longitudinal studies on the effects of long-term abstinence on gait ataxia in patients with AUD are needed.

Conclusion and future implications

There is preliminary evidence to support that AUD patients without WKS exhibit impaired motor function, which can be expressed as gait ataxia. This behavioral manifestation could point to common aetiologic mechanisms for the development of gait ataxia in patients with AUD and in patients with alcohol related WKS, which might suggest that our current conceptual framing demarcating these disorders as distinct entities should be put under more scrutiny in the future. However, the limited number of studies, heterogenous

results as well as several methodological shortcomings of the included studies prevent bold inferences to be drawn on the association between gait ataxia and AUD, and thus the existence of common pathways between alcohol related WKS and AUD.

Large-scaled longitudinal studies examining younger individuals with AUD at risk for developing cerebellar ataxia should be conducted. These studies should screen for other clinical symptoms of WKS, including neurocognitive deficits such as impaired verbal fluency and episodic memory, and it is important to control for SUD and thiamine deficiency prior to the inclusion of the patients with AUD. Future studies could uncover aetiologic pathways and the mechanisms mediating the development of gait ataxia and its expression in patients with AUD and how these compare to patients with other alcohol related disorders such as WKS. This evidence might provide valuable insights into whether ataxia in AUD and WKS could the result of unique etiology or whether it is part of a general sequalae of long-term and severe alcohol use.

References

Agabio, R., Pisanu, C., Gessa, G. L., & Franconi, F. (2017). Sex Differences in Alcohol Use Disorder. *Current Medicinal Chemistry*, *24*(24). https://doi.org/10.2174/0929867323666161202092908

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders: DSM-5* (5th ed.). American Psychiatric Association.

Andersen, B. B. (2004). Reduction of Purkinje cell volume in cerebellum of alcoholics. *Brain Research*, *1007*(1), 10–18. https://doi.org/10.1016/j.brainres.2004.01.058

Araujo, I., Henriksen, A., Gamsby, J., & Gulick, D. (2021). Impact of Alcohol Abuse on Susceptibility to Rare Neurodegenerative Diseases. *Frontiers in Molecular Biosciences*, *8*, 643273. https://doi.org/10.3389/fmolb.2021.643273

Bates, M. E., Bowden, S. C., & Barry, D. (2002). Neurocognitive Impairment Associated With Alcohol Use Disorders: Implications for Treatment. *Experimental and Clinical Psychopharmacology*, *10*(3), 193–212. https://doi.org/10.1037/1064-1297.10.3.193

Bauer, L. O. (1993). Motoric signs of CNS dysfunction associated with alcohol and cocaine withdrawal. *Psychiatry Research*, *47*(1), 69–77. https://doi.org/10.1016/0165-1781(93)90056-M

Binder, N., Manderscheid, L., & Schumacher, M. (2017). The combined association of alcohol consumption with dementia risk is likely biased due to lacking account of death cases. *European Journal of Epidemiology*, *32*(7), 627–629. https://doi.org/10.1007/s10654-017-0252-0

Brennan, S. E., McDonald, S., Page, M. J., Reid, J., Ward, S., Forbes, A. B., & McKenzie, J. E. (2020). Long-term effects of alcohol consumption on cognitive function: A systematic review and dose-response analysis of evidence published between 2007 and 2018. *Systematic Reviews*, *9*(1), 33. https://doi.org/10.1186/s13643-019-1220-4

Crowe, S. F., Cammisuli, D. M., & Stranks, E. K. (2019). Widespread Cognitive Deficits in Alcoholism Persistent Following Prolonged Abstinence: An Updated Meta-analysis of Studies That Used Standardised Neuropsychological Assessment Tools. *Archives of Clinical Neuropsychology*, *2019*(1), 1–15. https://doi.org/10.1093/arclin/acy106

Fein, G., & Greenstein, D. (2013). Gait and Balance Deficits in Chronic Alcoholics: No Improvement from 10 Weeks Through 1 Year Abstinence. *Alcoholism: Clinical and Experimental Research*, *37*(1), 86–95. https://doi.org/10.1111/j.1530-0277.2012.01851.x

Fein, G., Shimotsu, R., Di Sclafani, V., Barakos, J., & Harper, C. (2009). Increased White Matter Signal Hyperintensities in Long-Term Abstinent Alcoholics Compared with Nonalcoholic Controls. *Alcoholism: Clinical and Experimental Research, 33*(1), 70–78. https://doi.org/10.1111/j.1530-0277.2008.00812.x

Fitzpatrick, L. E., Jackson, M., & Crowe, S. F. (2008). The relationship between alcoholic cerebellar degeneration and cognitive and emotional functioning. *Neuroscience & Biobehavioral Reviews*, *32*(3), 466–485.

Fitzpatrick, L. E., Jackson, M., & Crowe, S. F. (2012). Characterization of Cerebellar Ataxia in Chronic Alcoholics Using the International Cooperative Ataxia Rating Scale (ICARS). *Alcoholism: Clinical and Experimental Research*, *36*(11), 1942–1951. https://doi.org/10.1111/j.1530-0277.2012.01821.x

Fregly, A. R., & Graybiel, A. (1968). *An Ataxia Test Battery Not Requiring the Use of Rails*. U.S. Naval Aerospace Medical Institute, U.S. Naval Aviation Medical Center.

Fregly, A. R., Graybiel, A., & Smith, M. J. (1972). *Walk on Floor Eyes Closed (WOFEC): A New Addition to an Ataxia Test Battery* (1st ed.). Naval Aerospace Medical Research Laboratory, Naval Aerospace Medical Institute, Naval Aerospace and Regional Medical Center.

Gilman, S., Adams, K., Koeppe, R. A., Berent, S., Kluin, K. J., Modell, J. G., Kroll, P., & Brunberg, J. A. (1990). Cerebellar and frontal hypometabolism in alcoholic cerebellar degeneration studied with positron emission tomography. *Annals of Neurology*, *28*(6), 775–785. https://doi.org/10.1002/ana.410280608

Graybiel, A., & Fregly, A. R. (1966). *A New Quantitative Ataxia Test Battery*. U.S. Naval School of Aviation Medicine.

Harper, C., Giles, M., & Finlay-Jones, R. (1986). Clinical signs in the Wernicke-Korsakoff complex: A retrospective analysis of 131 cases diagnosed at necropsy. *Journal of Neurology, Neurosurgery & Psych*Bauer, L. O. (1993). Motoric signs of CNS dysfunction associated with alcohol and cocaine withdrawal. *Psychiatry Research*, *47*(1), 69–77. https://doi.org/10.1016/0165-1781(93)90056-M

Deik, A., & Saunders-Pullman, R. (2014). *Substances of abuse and movement disorders: Complex interactions and comorbidities*.

Fitzpatrick, L. E., Jackson, M., & Crowe, S. F. (2012). Characterization of Cerebellar Ataxia in Chronic Alcoholics Using the International Cooperative Ataxia Rating Scale (ICARS). *Alcoholism: Clinical and Experimental Research*, *36*(11), 1942–1951. https://doi.org/10.1111/j.1530-0277.2012.01821.x

Rosenbloom, M. J., Rohlfing, T., O'Reilly, A. W., Sassoon, S. A., Pfefferbaum, A., & Sullivan, E. V. (2007). Improvement in memory and static balance with abstinence in alcoholic men and women: Selective relations with change in brain structure. *Psychiatry Research: Neuroimaging*, *155*(2), 91–102. https://doi.org/10.1016/j.pscychresns.2006.12.019

Schmidt, T. P., Pennington, D. L., Durazzo, T. C., & Meyerhoff, D. J. (2014). Postural Stability in Cigarette Smokers and During Abstinence from Alcohol. *Alcoholism:*

Clinical and Experimental Research, *38*(6), 1753–1760. https://doi.org/10.1111/acer.12409

Smith, S., & Fein, G. (2011). Persistent but Less Severe Ataxia in Long-Term Versus Short-Term Abstinent Alcoholic Men and Women: A Cross-Sectional Analysis. *Alcoholism: Clinical and Experimental Research*, *35*(12), 2184–2192. https://doi.org/10.1111/j.1530-0277.2011.01567.x

Sullivan, E. V., Desmond, J. E., Lim, K. O., & Pfefferbaum, A. (2002). Speed and Efficiency but Not Accuracy or Timing Deficits of Limb Movements in Alcoholic Men and Women. *Alcoholism: Clinical and Experimental Research*, *26*(5), 705–713. https://doi.org/10.1111/j.1530-0277.2002.tb02595.x

Sullivan, E. V., Rohlfing, T., & Pfefferbaum, A. (2010). Pontocerebellar volume deficits and ataxia in alcoholic men and women: No evidence for "telescoping." *Psychopharmacology*, *208*(2), 279–290. https://doi.org/10.1007/s00213-009-1729-7

Sullivan, E. V., Rosenbloom, M. J., & Pfefferbaum, A. (2000). Pattern of Motor and Cognitive Deficits in Detoxified Alcoholic Men. *Alcoholism: Clinical and Experimental Research*, *24*(5), 611–621. https://doi.org/10.1111/j.1530-0277.2000.tb02032.x

Sullivan, E. V., Rosenbloom, M. J., & Pfefferbaum, A. (2004). Balance and Gait Deficits in Schizophrenia Compounded by the Comorbidity of Alcoholism. *American Journal of Psychiatry*, *161*(4), 751–755. https://doi.org/10.1176/appi.ajp.161.4.751

Sullivan, E. V., Zahr, N. M., Sassoon, S. A., & Pfefferbaum, A. (2021). Disturbed sensory physiology underlies poor balance and disrupts activities of daily living in alcohol use disorder. *Addiction Biology*, *26*(4). https://doi.org/10.1111/adb.12966

iatry, *49*(4), 341–345.

Isenberg-Grzeda, E., Kutner, H. E., & Nicolson, S. E. (2012). Wernicke-Korsakoff-syndrome: Under-recognized and under-treated. *Psychosomatics, 53*(6), 507–516.

Kohnke, S., & Meek, C. L. (2021). Don't seek, don't find: The diagnostic challenge of Wernicke's encephalopathy. *Ann Clin Biochem*, *58*(1), 38–46. https://doi.org/10.1177/0004563220939604

Le Berre, A.-P. (2019). Emotional processing and social cognition in alcohol use disorder. *Neuropsychology, 33*(6), 808–821. https://doi.org/10.1037/neu0000572

Le Berre, A.-P., Fama, R., & Sullivan, E. V. (2017). Executive Functions, Memory, and Social Cognitive Deficits and Recovery in Chronic Alcoholism: A Critical Review to Inform Future Research. *Alcoholism: Clinical and Experimental Research*, *41*(8), 1432–1443. https://doi.org/10.1111/acer.13431

Mathers, C., Fat, D. M., Boerma, T., & World Health Organization (Eds.). (2008). *The global burden of disease: 2004 update* (2nd ed.). World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/43942/9789241563710_eng.pdf?sequence=1&isAllowed=y

Mitoma, H., Manto, M., & Shaikh, A. G. (2021). Mechanisms of Ethanol-Induced Cerebellar Ataxia: Underpinnings of Neuronal Death in the Cerebellum. *International Journal of Environmental Research and Public Health*, *18*(16), 8678. https://doi.org/10.3390/ijerph18168678

Moher, D., Liberati, A., Tetzlaff, J., Altman, D., & The Prisma Group. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLOS Medicine*, *6*(7), 1–6. https://doi.org/10.1371/journal.pmed.1000097

National Heart, Lung, and Blood Institute [NHLBI]. (2019). *Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies*. NIH. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Nutt, D. J. (2008). Relationship of neurotransmitters to the symptoms of major depressive disorder. *The Journal of Clinical Psychiatry*, *69 Suppl E1*, 4–7.

Nutt, D. J., Hayes, A., Fonville, L., Zafar, R., Palmer, E. O. C., Paterson, L., & Lingford-Hughes, A. (2021). Alcohol and the Brain. *Nutrients*, *13*(11), 3938. https://doi.org/10.3390/nu13113938

Peacock, A., Leung, J., Larney, S., Colledge, S., Hickman, M., Rehm, J., Giovino, G. A., West, R., Hall, W., Griffiths, P., Ali, R., Gowing, L., Marsden, J., Ferrari, A. J., Grebely, J., Farrell, M., & Degenhardt, L. (2018). Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. *Addiction*, *113*(10), 1905–1926. https://doi.org/10.1111/add.14234

Pfefferbaum, A., Adalsteinsson, E., & Sullivan, E. V. (2006). Dysmorphology and microstructural degradation of the corpus callosum: Interaction of age and alcoholism. *Neurobiology of Aging*, *27*(7), 994–1009. https://doi.org/10.1016/j.neurobiolaging.2005.05.007

Ridley, N. J., Draper, B., & Withall, A. (2013). Alcohol-related dementia: An update of the evidence. *Alzheimer's Research & Therapy*, *5*(1), 3. https://doi.org/10.1186/alzrt157

Ritz, L., Laniepce, A., Cabé, N., Lannuzel, C., Boudehent, C., Urso, L., Segobin, S., Vabret, F., Beaunieux, H., & Pitel, A. (2021). Early Identification of Alcohol Use Disorder Patients at Risk of Developing Korsakoff's Syndrome. *Alcoholism: Clinical and Experimental Research*, *45*(3), 587–595. https://doi.org/10.1111/acer.14548

Rosenbloom, M. J., Rohlfing, T., O'Reilly, A. W., Sassoon, S. A., Pfefferbaum, A., & Sullivan, E. V. (2007). Improvement in memory and static balance with abstinence in alcoholic men and women: Selective relations with change in brain structure. *Psychiatry Research: Neuroimaging*, *155*(2), 91–102. https://doi.org/10.1016/j.pscychresns.2006.12.019

Samokhvalov, A. V., Popova, S., Room, R., Ramonas, M., & Rehm, J. (2010). Disability Associated with Alcohol Abuse and Dependence. *Alcoholism: Clinical and Experimental Research*, *34*(11), 1871–1878. https://doi.org/10/dfx5hd

Schmidt, T. P., Pennington, D. L., Durazzo, T. C., & Meyerhoff, D. J. (2014). Postural Stability in Cigarette Smokers and During Abstinence from Alcohol. *Alcoholism: Clinical and Experimental Research*, *38*(6), 1753–1760. https://doi.org/10.1111/acer.12409

Smith, S., & Fein, G. (2011). Persistent but Less Severe Ataxia in Long-Term Versus Short-Term Abstinent Alcoholic Men and Women: A Cross-Sectional Analysis: PERSISTENT BUT LESS SEVERE ATAXIA. *Alcoholism: Clinical and Experimental Research*, *35*(12), 2184–2192. https://doi.org/10.1111/j.1530-0277.2011.01567.x

Spitzer, R. L., Endicott, J., & Robins, E. (1978). Research diagnostic criteria: Rationale and reliability. *Archives of General Psychiatry*, *35*(6), 773–782. https://doi.org/10.1001/archpsyc.1978.01770300115013

Stavro, K., Pelletier, J., & Potvin, S. (2013). Widespread and sustained cognitive deficits in alcoholism: A meta-analysis: Alcoholism and cognition. *Addiction Biology*, *18*(2), 203–213. https://doi.org/10.1111/j.1369-1600.2011.00418.x

Sullivan, E. V., Deshmukh, A., Desmond, J. E., Lim, K. O., & Pfefferbaum, A. (2000). Cerebellar volume decline in normal aging, alcoholism, and Korsakoff's syndrome: Relation to ataxia. *Neuropsychology*, *14*(3), 341–352. https://doi.org/10.1037/0894-4105.14.3.341

Sullivan, E. V., Desmond, J. E., Lim, K. O., & Pfefferbaum, A. (2002). Speed and Efficiency but Not Accuracy or Timing Deficits of Limb Movements in Alcoholic Men and

Women. *Alcoholism: Clinical and Experimental Research*, *26*(5), 705–713. https://doi.org/10.1111/j.1530-0277.2002.tb02595.x

Sullivan, E. V., Rohlfing, T., & Pfefferbaum, A. (2010). Pontocerebellar volume deficits and ataxia in alcoholic men and women: No evidence for "telescoping." *Psychopharmacology*, *208*(2), 279–290. https://doi.org/10.1007/s00213-009-1729-7

Sullivan, E. V., Rosenbloom, M. J., & Pfefferbaum, A. (2000). Pattern of Motor and Cognitive Deficits in Detoxified Alcoholic Men. *Alcoholism: Clinical and Experimental Research*, *24*(5), 611–621. https://doi.org/10.1111/j.1530-0277.2000.tb02032.x

Sullivan, E. V., Rosenbloom, M. J., & Pfefferbaum, A. (2004). Balance and Gait Deficits in Schizophrenia Compounded by the Comorbidity of Alcoholism. *American Journal of Psychiatry*, *161*(4), 751–755. https://doi.org/10.1176/appi.ajp.161.4.751

Sullivan, E. V., Zahr, N. M., Sassoon, S. A., & Pfefferbaum, A. (2021). Disturbed sensory physiology underlies poor balance and disrupts activities of daily living in alcohol use disorder. *Addiction Biology*, *26*(4). https://doi.org/10.1111/adb.12966

Trouillas, P., Takayanagi, T., Hallett, M., Currier, R. D., Subramony, S. H., Wessel, K., Bryer, A., Diener, H. C., Massaquoi, S., Gomez, C. M., Coutinho, P., Ben Hamida, M., Campanella, G., Filla, A., Schut, L., Timann, D., Honnorat, J., Nighoghossian, N., & Manyam, B. (1997). International Cooperative Ataxia Rating Scale for pharmacological assessment of the cerebellar syndrome. The Ataxia Neuropharmacology Committee of the World Federation of Neurology. *Journal of the Neurological Sciences*, *145*(2), 205–211. https://doi.org/10.1016/s0022-510x(96)00231-6

Veritas Health Innovation. (2019). *Covidence systematic review software* (2.0) [Groove]. Veritas Health Innovation. https://www.covidence.org

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., Charlson, F. J., Norman, R. E., Flaxman, A. D., Johns, N., Burstein, R., Murray, C. J., & Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *The Lancet*, *382*(9904), 1575–1586. Elsevier. https://doi.org/10.1016/S0140-6736(13)61611-6

Xu, W., Wang, H., Wan, Y., Tan, C., Li, J., Tan, L., & Yu, J.-T. (2017). Alcohol consumption and dementia risk: A dose–response meta-analysis of prospective studies. *European Journal of Epidemiology*, *32*(1), 31–42. https://doi.org/10.1007/s10654-017-0225-3

Table 1

Summary of results

Author	Study design	*N* participants (% males/females)	Groups (*n*); M_{age} (SD)	Diagnosis	State	Comorbidity	Measures of ataxia	Follow-up	Main findings
Bauer (1993) [US]	Longitudinal	37 (100/0)	AUD (*n* = 6), 34.1 (1.9) HC (*n* = 15), 32.3 (1.2)	AUD or SUD (DSM-III-R)	28 (2.2) days of alcohol use the preceding month; Abstinence > 3 weeks; Inpatients	No	Body sway transduction with force-sensitive platform Assessment performed at baseline and follow-ups	1, 3, and 12 weeks	Patients with AUD did not exhibit more body sway relative to HCs.
Fitzpatrick et al. (2012) [AU]	Cross-sectional	78 (65/35)	AUD (*n* = 49), 53.4 (9.5) HC (*n* = 29), 54.9 (7.3)	ADD (DSM-IV-R)	33.8 (9.9) years of heavy drinking; Total lifetime alcohol consumption of 2160.5 (1105.7) kg; Mean abstinence of 8 weeks; Outpatients	No	ICARS Assessment performed only once	N/A	Patients with AUD performed significantly worse on the ICARS battery relative to HCs.
Rosenbloom et al. (2007) [US]	Longitudinal	41 (48/52)	AUD (*n* = 15), 48.8 (8.6) HC (*n* = 26), 52.8 (10.6)	AD (DSM-IV)	Total lifetime alcohol consumption of 760.7 (471.6) kg; Abstinence > 16 weeks	Axis-I-disorder (*n* = 3); Nicotine dependence (*n* = 9)	Fregly-Graybiel Ataxia Battery Assessment performed at baseline and at follow-up	2 years	Patients with AUD performed significantly worse on the ataxia battery relative to HCs.
Schmidt et al. (2014) [US]	Longitudinal	174 (12/88)	nsAUD (*n* = 41), 52.0 (10.0) sAUD (*n* = 59), 49.0 (9.0) nsHC (*n* = 39), 45.0 (9.0) sHC (*n* = 35), 49.0 (9.0)	AD (DSM-IV-TR)	Age for heavy drinking onset for nsAUD 28 (11.0) years and sAUD 22 (7.0) years; Lifetime average alcoholic drinks per month for nsAUD 170 (104.0) and sAUD 267 (121.0); Mean abstinence of 5 weeks; Outpatients	Nicotine dependence (*n* = 22)	Fregly-Graybiel Ataxia Battery Assessment performed at baseline and at follow-ups	5 and 34 weeks	Both AUD groups performed significantly worse on the ataxia battery relative to HCs. The sAUD group performed worse compared to all three groups.
Smith & Fein (2011) [US]	Cross-sectional	204 (57/43)	staAUD (*n* = 70), 45.1 (N/A) ltaAUD (*n* = 48), 48.4 (N/A) HC (*n* = 52), 47.8 (N/A)	AD (DSM-IV-R)	staAUD: 6-15 weeks of abstinence; ltaAUD: < 7 years of abstinence	No	Fregly-Graybiel Ataxia Battery Assessment only performed once	N/A	Correcting for age, both staAUD and ltaAUD performed significantly worse on the ataxia battery relative to HCs.
Sullivan et al. (2000) [US]	Cross-sectional	145 (100/0)	AUD (*n* = 71), 44.5 (9.4) HC (*n* = 67), 45.1 (13.7)	AUD (RDC)	Total lifetime alcohol consumption of 1356.0 (882.7) kg; Abstinence > 4 weeks; Inpatients	No	Fregly-Graybiel Ataxia Battery Assessment only performed once	N/A	Patients with AUD performed significantly worse on the ataxia battery relative to HCs.
Sullivan et al. (2002) [US]	Cross-sectional	60 (36/64)	AUD (*n* = 39), 47.4 (33.5) HC (*n* = 21), 50.3 (30.0)	AD (DSM-IV)	Total lifetime alcohol consumption of 767 (655) kg; Mean abstinence of 2.2 years; In- and outpatients	No	Fregly-Graybiel Ataxia Battery Assessment performed only once	N/A	Patients with AUD did not perform significantly worse on the ataxia battery relative to HCs. Only a male subgroup of patients showed worse performance relative to sex-matched HCs.

Sullivan et al. (2004) [US]	Cross-sectional	71 (100/0)	AUD (*n* = 24), 49.1 (11.1) HC (*n* = 27), 47.9 (11.6)	AUD (DSM-III-R)	Total lifetime alcohol consumption of 1288.1 (787.3) kg; Median abstinence of 29 weeks	No	Fregly-Graybiel Ataxia Battery Assessment performed only once	N/A	Patients with AUD performed significantly worse on the ataxia battery relative to HCs.
Sullivan et al. (2010) [US]	Cross-sectional	200 (57/43)	AUD (*n* = 95), 49.1 (25.2) HC (*n* = 105), 48.9 (26.5)	AD (DSM-IV)	AUD onset age at 29.5 (10.6) years; Total lifetime alcohol consumption of 775 (605) kg; Mean abstinence of 11 weeks	Nicotine dependence (*n* = 46)	Fregly-Graybiel Ataxia Battery Assessment performed only once	N/A	Patients with AUD performed significantly worse on the ataxia battery relative to HCs.
Sullivan et al. (2021) [US]	Cross-sectional	247 (67/33)	AUD (*n* = 151), 50.1 (10.3) HC (*n* = 96), 50.3 (13.8)	AD/AUD (SCID)	AUD onset age at 25.1 (9.4); Total lifetime alcohol consumption of 1221 (959.4) kg; Mean abstinence of 37 weeks	Nicotine dependence (*n* = 99)	Fregly-Graybiel Ataxia Battery Assessment performed only once	N/A	Patients with AUD performed significantly worse on the ataxia battery relative to HCs.

Note. AD, alcohol dependence; AU, Australia; AUD, alcohol use disorder; DSM-III-R/DSM-IV/DSM-5, the third/fourth/fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (Revised); HC, healthy control; ICARS, International Cooperative Ataxia Rating Scale; ltaAUD, long-term abstinent alcohol use disorder; nsAUD, non-smoking AUD; nsHC, non-smoking healthy control; RDC, Research Diagnostic Criteria; SCID, Structured Clinical Interview for DSM-IV-R and DSM-5; sHC, smoking healthy control; sAUD, smoking alcohol use disorder; staAUD, short-term abstinent alcohol use disorder;

Table 2

Summary of the risk of bias of the included studies

Study	Focus and Recruitment	Exposure	Results and Measurement	Sum (%)
Bauer (1993)	3/5	5/5	3/4	78.57%
Fitzpatrick et al. (2012)	5/5	4/5	3/4	85.71%
Rosenbloom et. al (2007)	4/5	4/5	2/4	71.43%
Schmidt et al. (2014)	5/5	5/5	3/4	92.86%
Smith & Fein (2011)	4/5	3/5	3/4	71.43%
Sullivan et al. (2004)	5/5	4/5	3/4	85.71%
Sullivan et al. (2021)	5/5	4/5	3/4	85.71%
Sullivan, Desmond, Lim & Pfefferbaum (2002)	5/5	4/5	3/4	85.71%
Sullivan, Rohlfing, & Pfefferbaum (2010)	5/5	4/5	3/4	85.71%
Sullivan, Rosenbloom, & Pfefferbaum (2000)	5/5	4/5	3/4	85.71%

Note: The first five questions are categorized as the domain "Focus and Recruitment", the next five questions are included in the domain denoted as 'Exposure', and the remaining four questions are included in the domain "Results and Measurement" (NHLBI, 2019). The number of yes-responses are inserted for each of the domains, and a final sum is calculated as the percentage (%) of the total number yes-responses.

Figure 1

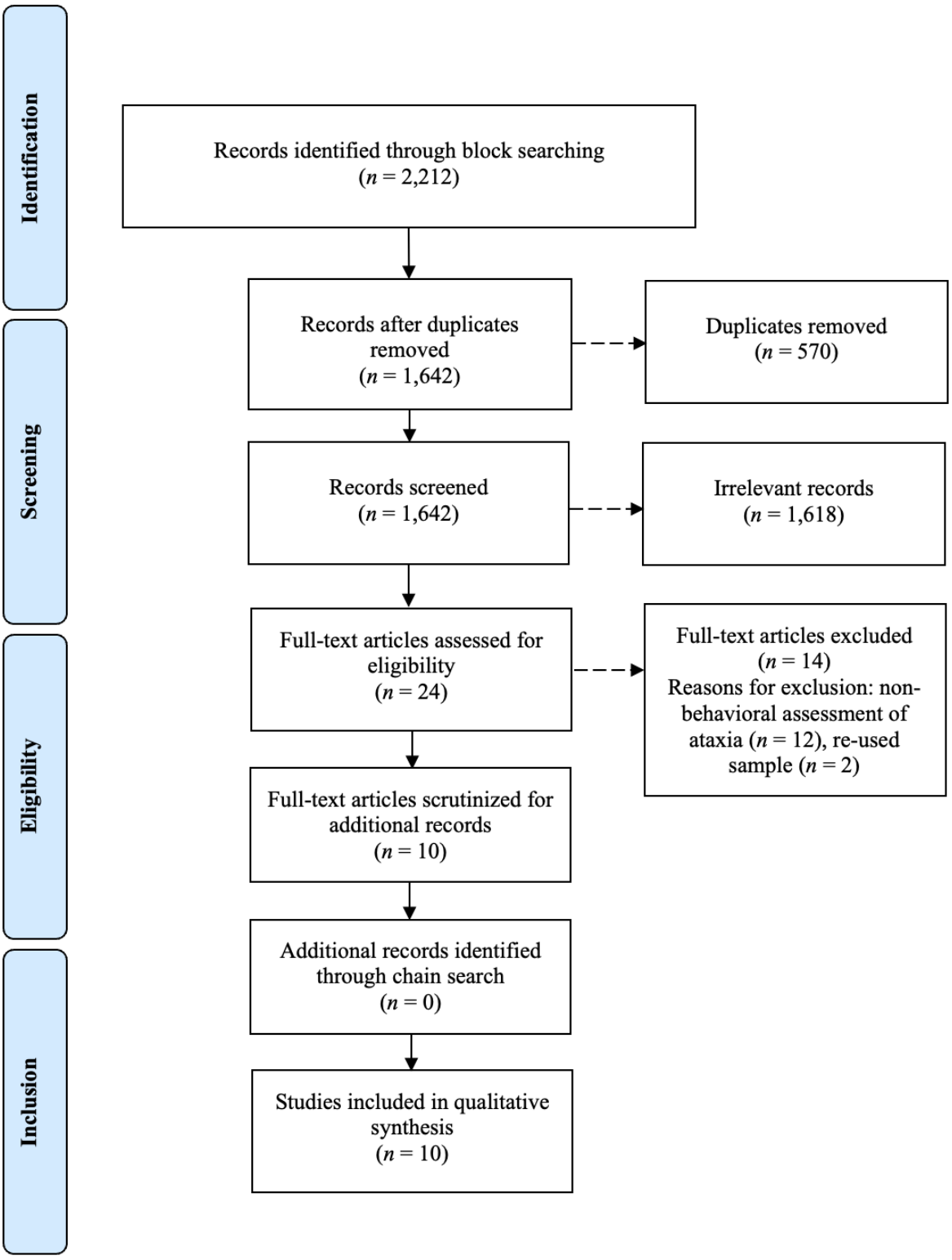

Figure 1. The flow chart of the various stages of the literature search. The figure is adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher et al., 2009, p. 3).

Supplementary table