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REVIEW

ADDICTION SSA

The risk relationships between alcohol consumption, alcohol use disorder and alcohol use disorder mortality: A systematic review and meta-analysis

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Abstract

Background and aims: Increasing levels of alcohol use are associated with a risk of developing an alcohol use disorder (AUD), which, in turn, is associated with considerable burden. Our aim was to estimate the risk relationships between alcohol consumption and AUD incidence and mortality.

Method: A systematic literature search was conducted, using Medline, Embase, PsycINFO and Web of Science for case–control or cohort studies published between 1 January 2000 and 8 July 2022. These were required to report alcohol consumption, AUD incidence and/or AUD mortality (including 100% alcohol-attributable deaths). The protocol was registered with PROSPERO (CRD42022343201). Dose–response and random-effects meta-analyses were used to determine the risk relationships between alcohol consumption and AUD incidence and mortality and mortality rates in AUD patients, respectively.

Results: Of the 5904 reports identified, seven and three studies from high-income countries and Brazil met the inclusion criteria for quantitative and qualitative syntheses, respectively. In addition, two primary US data sources were analyzed. Higher levels of alcohol consumption increased the risk of developing or dying from an AUD exponentially. At an average consumption of four standard drinks (assuming 10 g of pure alcohol/standard drink) per day, the risk of developing an AUD was increased sevenfold [relative risk (RR) = 7.14, 95% confidence interval (CI) = 5.13–9.93] and the risk of dying fourfold (RR = 3.94, 95% CI = 3.53–4.40) compared with current non-drinkers. The mortality rate in AUD patients was 3.13 (95% CI = 1.07–9.13) per 1000 person-years.

Conclusions: There are exponential positive risk relationships between alcohol use and both alcohol use disorder incidence and mortality. Even at an average consumption of 20 g/day (about one large beer), the risk of developing an alcohol use disorder (AUD) is nearly threefold that of current non-drinkers and the risk of dying from an AUD is approximately double that of current non-drinkers.

KEYWORDS
Alcohol, alcohol use disorder, dose–response, incidence, meta-analysis, mortality

INTRODUCTION

Alcohol use disorder (AUD) is characterized by an impaired ability to control alcohol intake and compulsive alcohol use over extended periods of time [1, 2]. Affected individuals display escalating patterns of drinking that may result in serious consequences on both their physical and mental health and within their social environments [1, 3]. Thus, AUDs are highly disabling and potentially lethal [4, 5]. However, despite their potential for disability or death they are among the most undertreated mental disorders, with fewer than one in five individuals with an AUD receiving treatment for the condition/episode at the time of onset [1, 3, 6].

AUDs rank as one of the most prevalent mental disorders globally [7, 8]. Previously they have been shown to predominantly affect men, although sex differences in prevalence are narrowing over time, due to a global increase in the number of women drinking at higher risk levels since 2000 [9, 10]. In 2016, 8.6% of adult men and 1.7% of adult women were affected by AUDs globally [11]. Variations in prevalence of AUDs are also apparent for other factors, including country income-level and geographic region [12]. The rising prevalence of AUDs contribute tremendous risks to both health and social life and are associated with considerable burden [13]. In 2016, for example, alcohol use led to a loss of 117.2 million disability-adjusted life years (DALYs) and 2.0 million premature deaths globally [14], and AUD specifically caused health harms that accounted for 145 000 deaths [15].

With higher levels of alcohol intake, the risk of developing or dying from an AUD increases [16–18]. This exposure–outcome relationship seems intuitive, but little is known about the shape of the underlying dose–response relationship connecting the level of alcohol use to AUD incidence or mortality. Additionally, these risk relationships are probably dependent upon several factors, including age, sex, race/ethnicity and socio-economic status (SES). Relative to men, women drink less often and consume less alcohol, but are more susceptible to specific alcohol-related problems and are less likely to receive help for these problems [19, 20]. Furthermore, among women themselves, there are racial/ethnic disparities in access to treatment and the quality of care that they receive [21]. For instance, in the United States, both Black and Latina women have a significantly lower likelihood than White women to access speciality treatment for AUD [21]. Additionally, previous research suggests that socio-economic inequalities are approximately two times higher for 100% alcohol-attributable deaths compared to all-cause mortality [22]. As a result, alcohol use may not relate to AUD incidence or mortality in the same way throughout socio-demographic subgroups.

The aim of this study was to disentangle the complex associations between alcohol use, AUD and AUD mortality by analyzing three risk relationships separately. We conducted a systematic review and meta-analysis, which was additionally supported by two primary data analyses [described in more depth in the 'Alcohol use and AUD mortality (ii)' section] exploring the risk relationships of: (i) the level of alcohol use and AUD incidence (use- > AUD inc.); (ii) the level of alcohol use and AUD mortality (use- > AUD mort.); and (iii) having an AUD and dying from an AUD (AUD- > AUD mort.) (Figure 1). Given substantial differences in drinking patterns and AUD prevalence throughout socio-demographic groups, we also aimed to account, where possible, for the effects of age, sex, race/ethnicity and SES on each of these relationships.

METHODS

Search strategy

A systematic literature search was conducted on 8 July 2022 via Medline, Embase and PsycINFO (via OVID) and Web of Science to find studies regarding the associations between alcohol use, incidence of AUD and AUD mortality, with no language restrictions applied. The electronic databases were searched from 1 January 2000 to 8 July 2022 for original, observational studies using search terms including the study design ('case–control' or 'cohort'), outcome ('incidence' or 'mortality') and exposure ('alcohol use' or 'alcohol consumption' and 'alcohol dependence' or 'alcohol abuse') (see Supporting information, Table S3). Screening of the references was conducted first at title and abstract and then at full text by three reviewers (T.C., L.L.F., C.K.). Every reference was screened by two independent reviewers and inter-rater reliability among the reviewers was determined using Cohen's kappa statistic [23]. Backward and forward citation tracking was performed for each of the included articles, in addition to a systematic grey literature search (see Supporting information, eMethods 5).

Studies were included in the review if they met the following criteria: (a) participants were at least 18 years of age; (b) the study used a prospective or retrospective cohort design drawn from the general population [for risk relationships (i) (use- > AUD inc.) and (ii) (use- > AUD mort.)] or a sample of AUD patients [for risk relationship (iii) (AUD- > AUD mort.)] or a case–control design with a sample of cases of AUD incidence or mortality and controls; (c) they reported at least one of the three risk relationships between average alcohol consumption level, AUD and AUD mortality (Figure 1), using either odds ratios (OR), risk ratios (RR) or hazard ratios (HR) with corresponding confidence intervals (CI), or mortality rates [risk-relationship (iii) only] or sufficient data to calculate respective quantitative results (for excluded studies, see Supporting information Table S2). AUD was

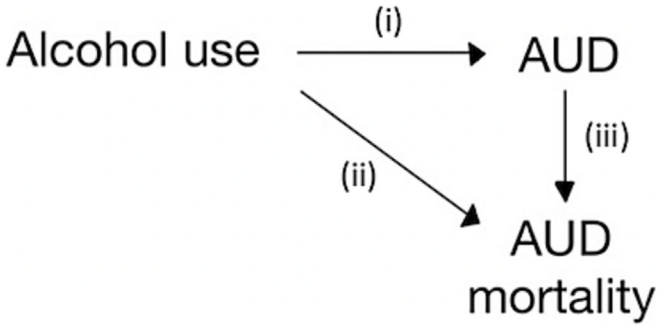

FIGURE 1 Display of the three risk relationships to be evaluated in this review. AUD = alcohol use disorder.

defined according to Roerecke & Rehm's criteria: AUD diagnosed by a medical professional (physician or psychiatrist), participated in an AUD treatment programme, drove while intoxicated or registered at a temperance board and/or met criteria for AUD on a standardized and validated questionnaire [4]. AUD mortality was defined as dying from mental and behavioural disorders due to the use of alcohol (F10), according to the International Classification of Diseases, 10th revision (ICD-10) criteria [24]. Studies that included causes of death that are 100% alcohol-attributable and that are probably the result of an AUD characterized by heavy alcohol use over time (e.g. alcoholic liver cirrhosis), in addition to AUD mortality, were also eligible for inclusion. This is because registration of the cause of death as a 100% alcohol-attributable category rather than F10 may be mainly a reflection of coding practices with an AUD being the underlying driver. Thus, the following ICD-10 codes were included: E24.4, G31.2, G62.1, G72.1, I42.6, K29.2, K70–70.4, K70.9, K85.2, K86.0, R78.0, X45–X45.9, X65, Y15–Y15.9, Y90, Y91, Y91.0–Y91.3 and Y91.9 when reported grouped together with F10–F10.9 (see Supporting information, Table S4). Studies were excluded if they employed an experimental or cross-sectional design, if they represented a specific subgroup or if they reported results for AUD incidence and mortality combined. The review protocol was registered with PROSPERO under the ID number CRD42022343201, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were applied [25] (see Supporting information, Table S1).

Data extraction

From all included articles the following details were extracted by one reviewer (T.C.) and checked by another independent reviewer (C.P. or A.L.): authors' names, year of publication, country, design and duration of study, follow-up years, age, sex, number of participants and events (AUD incidence/AUD mortality), operationalization of alcohol use/AUD/cause of death, adjustments used and OR/RR/HR with corresponding CIs or mortality rates [relationship (iii)]. When stratified by the covariates of interest, estimates of RR and their CIs were additionally extracted. Any inconsistencies were discussed and decided by consensus between reviewers. When information required for analysis was not available, the authors were contacted to obtain the necessary results. Data were additionally extracted from two US data sources, including the longitudinal National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) and the National Health Interview Survey (NHIS) linked to mortality data.

Secondary data sources

We used secondary data from two US studies that allowed us to perform primary analyses. (1) Two longitudinal waves of the NESARC survey, conducted in 2001/202 and 2004/05, were used to calculate point estimates for the risk of developing an AUD at various levels of alcohol consumption (for the logistic regression model refer to Supporting information, Table S9). (2) NHIS 1997–2018 data linked to the 2019 National Death Index data were used to calculate HRs of dying from an AUD at different levels of alcohol use (Cox's proportional hazard model). Greater detail surrounding the methodology can be found in Supporting information, eMethods 9 and 10.

Statistical analysis

One-stage random-effects dose–response meta-analyses were used to explore the nature of the dose–response risk relationships between alcohol use and AUD incidence (i) (use- > AUD inc.) and mortality (ii) (use- > AUD mort.) at various levels of alcohol use in grams per day (g/day) [26]. Alcohol consumption in average grams of pure alcohol per day served as the exposure variable. When alcohol consumption was not reported in grams of pure alcohol per day, it was estimated from the reported quantity in standard drinks and frequency. If the study provided a range for quantity or frequency estimates (e.g. three to five standard drinks per occasion) the mid-point was taken, and if there was no upper bound to the highest category (e.g. six or more standard drinks per occasion), 75% of the width of the previous range was added to the lower bound of the highest level to represent the point estimate for this category (e.g. in our example, 8.25 standard drinks). The country-specific definition of a standard drink provided in the respective study was used when converting standard drinks to grams of pure alcohol. The outcome variable was AUD incidence for (i) (use- > AUD inc.) and AUD mortality for (ii) (use- > AUD mort.). Two models (linear and quadratic) were tested for each of the dose–response relationships, and optimal fit was determined based on the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), with the lowest value indicating the best fit to the data.

In risk relationship (iii) (AUD- > AUD mort.), we were interested in the AUD mortality risk of people with AUD. The outcome of interest was AUD mortality rate per person-years (PY). When PY were not provided, they were estimated as follows: if provided with the total number of all-cause deaths and the all-cause mortality rate per PY within the target population (AUD patients), these values were divided to obtain the PY. For one study by Haver *et al.* [27], PY were estimated based on a survival plot by extracting the survival rates at various time-points and multiplying these figures by the number of people in the sample. The total number of survivors at each time-point was summed together to get the total PY. In this study, a random-effects meta-analysis was conducted using single mortality rates to obtain the weighted average of the mortality risk of people with an AUD.

To evaluate the between-study heterogeneity, Cochran's Q and the I^2 statistic were used, such that a significant Q-value was indicative of substantial heterogeneity, together with an I^2 value of ≥75%. $I^2 > 25\%$ and $< 75\%$ represented moderate heterogeneity and $I^2 \leq 25\%$ represented low heterogeneity.

A qualitative summary was performed where a study met the inclusion criteria, but the way in which alcohol consumption was reported did not allow for accurate conversion into grams per day. For

example, one study, by Zaridze *et al*. [28], assessed consumption in terms of only one beverage (vodka), making it relatively incomparable to other studies, even when the grams of pure alcohol per day were obtained.

Statistical analyses were conducted in R version 4.2.1, using the dosresmeta package for (i) and (ii) [29] and the meta package for (iii) [30].

Risk of bias assessment

The Newcastle–Ottawa Scale (NOS) for case–control and cohort studies was adapted to assess the risk of bias of the selected studies (see Supporting information, Tables S7, S8) [31]. Risk of bias was assessed using three subcategories by two independent reviewers per study and any conflicts were resolved through deliberation among the reviewers. Results were reported on a scale of 0–4 for the selection category, where the risk of bias was high if rated a score of ≤ 1, moderate if rated a 2 or 3 and low if rated a 4. All cohort studies that used mortality rates (iii) (AUD- > AUD mort.) were scored one point lower on a scale of 0–3 points, with 3, 2 and ≤ 1 representing low, moderate and high risk of bias, respectively, as one item within the selection category was not applicable (no comparison to an unexposed cohort). The same scale was used for the outcome category. For the comparability category, which reported results on a scale of 0 to 2, risk of bias was low if rated a 2, moderate if rated a 1 and high if rated a 0.

RESULTS

Of the initial 5904 records screened for inclusion, a total of 10 studies were included in the systematic review, seven of which were eligible for quantitative synthesis [27, 32–37], in addition to two secondary US data sources (i.e. NESARC and NHIS) (Figure 2). A substantial

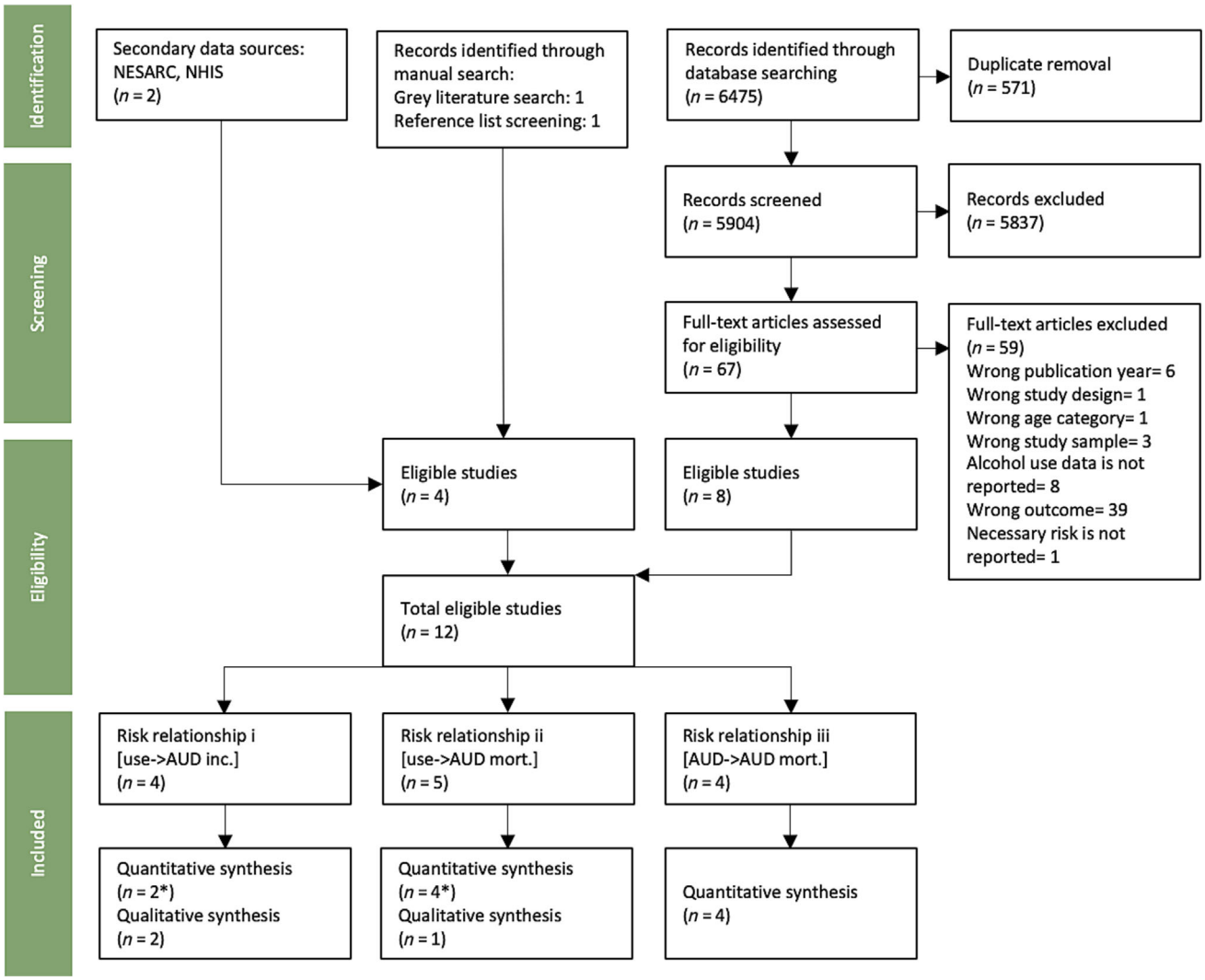

FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart of study selection. *One study informed two risk relationships. NESARC = National Epidemiologic Survey of Alcohol and Related Conditions; NHIS = National Health Interview Survey.

reviewer agreement of Kappa ranging between 0.60 and 0.69 was achieved among the reviewers for both the screening of titles and abstracts as well as full texts. In total, the included studies (quantitative analysis only) reported on results from Sweden (three), the United States (two), Brazil (one), Finland (one), Iceland (one) and Norway (one), with 3760 alcohol-related events (AUD incidence and mortality cases) observed overall in the quantitative analysis. For most of the studies (n = 6) a longitudinal cohort design was employed, with record linkage to register data. One study was of case–control design and used matched general population controls with data from a cause of death registry (Table 1). Reports that provided sex- and age-stratified estimates were limited; however, for risk relationship (ii) (use- > AUD mort.), three studies contributed male-specific estimates of AUD deaths ([33, 34] NHIS), and for risk relationship (iii) (AUD- > AUD mort.) two studies contributed female-specific estimates of AUD deaths for those with an AUD [27, 35]. None of the included studies investigated the role of age, SES or race/ethnicity on any of the three risk relationships, nor was it possible to explore sex-specific dose–response relationships between alcohol use and AUD incidence.

Risk of bias assessment

Four studies, including the two secondary data sources, achieved the maximum rating, indicative of a low risk of bias. All these studies observed the relationship between alcohol use and AUD mortality, except for NESARC, which informed the relationship between alcohol use and AUD incidence. Three other reports received a moderate risk of bias in the category of comparability due to the absence of additional control variables (i.e. race/ethnicity or SES). Within the remaining reports, descriptions of their cohort/case selection criteria or comparability controls were lacking; thus, they achieved the lowest ratings in these categories and had the highest risk of bias. For category-specific ratings, see Table 1.

Alcohol use and AUD incidence (i)

Quantitative summary

In total, two identified studies reported 2566 AUD incident cases (limited to one per individual) of 57 460 individuals. The dose–response relationship between alcohol use and AUD incidence was best described by a model including a quadratic term (formula and AIC/BIC values available in Supporting information, eMethods 11 and eResults 12). The quadratic dose–response relationship between alcohol use and the risk of AUD incidence (non-log scale) is shown in Figure 3 (for log scale, see Supporting information, eResults 13). Overall, the risk of incident AUD increases immediately and exponentially as alcohol use surpasses 0 g/day (Table 2). At 20 g/day, the RR is 2.74 (95% CI = 1.48–5.08) and at 40 g/day, the RR is 7.14 (95% CI = 5.13–9.93), relative to 0 g/day. In other words, a person drinking 40 g of pure alcohol per day has a 7.1-fold increased risk of developing an AUD compared to non-drinkers. Beyond this point, the RR begins to increase more drastically, and as consumption surpasses 60 g/day the RR increases by more than 1 for every 1-g increase in the amount of pure alcohol consumed (Figure 3). However, given the low number of point estimates for high levels of consumption, the dose–response relationship at high levels of consumption is subject to large uncertainty.

Qualitative summary

Two additional studies explored the relationship between alcohol consumption and the risk of AUD incidence, in which alcohol use was assessed using frequency of 'binge' or 'risky' drinking. Although they reported an average level of consumption over a given time, this could not be converted accurately into a grams of pure alcohol per day measurement. This rendered them ineligible for inclusion in the quantitative analysis (Table 3).

Tavolacci *et al.* [38] is a retrospective case–control study that investigated the association between binge drinking during the ages of 18–25 years and AUD in adulthood, using data from a sample of adults who sought treatment for AUD in France (13.3% women, mean age = 34.6 years). They included 83 cases of AUD (13.3% women) and 83 matched controls (13.3% women). The study assessed frequency and prevalence of consumption and binge drinking, with binge drinking defined as consumption of four/five or more alcoholic drinks in a single day for women/men, respectively, and frequent binge drinking (> twice a month). Frequent binge drinking in early adulthood was a risk factor for AUD in adulthood with threefold increased odds compared to those who did not report binge drinking or reported occasional binge drinking in early adulthood. The frequency of binge drinking occasions between ages 18 and 25 years were significantly higher in AUD cases relative to controls.

Dawson *et al.* [39] investigated the association between the frequency of risky drinking (defined as five or more alcoholic drinks in a single day for men and four or more for women) and the incidence of adverse outcomes (including AUD) approximately 3 years later, using US NESARC waves 1 and 2 data (n = 22 122, 38.1% women, mean age = 38.9 years). Individuals were categorized into four groups depending on their frequency of risky drinking and the incidences of AUD were presented as OR, adjusted for several factors including age, sex, race/ethnicity, SES (marital status, education, employment) and health status. The findings suggested that baseline risky drinking led to a significantly increased risk of incident AUD; even when risky drinking occasions occurred at low frequency (< 1/month), the ORs for incident 'alcohol abuse' and 'alcohol dependence' were 1.59 (95% CI = 1.25–2.02) and 1.35 (95% CI = 1.05–1.73), respectively. The adjusted ORs increased steadily with the frequency of risky drinking occasions up to 3.93 (95% CI = 2.40–6.44) for 'alcohol abuse' and 7.23 (95% CI = 4.75–11.00) for 'alcohol dependence' at the highest frequency of daily/near-daily.

Together, the studies reported an overall increased risk of incident AUD when binge drinking occasions, regardless of the number of occasions per month, occurred 3+ years prior to AUD diagnosis. This was compared to matched controls or those who never engaged in binge

TABLE 1 Characteristics of studies and data sources included in quantitative analysis.

men	Country	Study years	Mean follow-up years (range)	Study design	Sample size	Sex	Mean age or range at baseline
Risk relationships (i) and (ii): (use- > AUD inc.) and (use- > AUD mort.)							
Laatikainen *et al.*, 2013 [34] (ii)	Finland	1987–97	7.3 (5-10)	Longitudinal cohort study, with record linkage to national mortality register	5092	100% men	42.1 (heavy drinkers), 45.5 (no heavy drinking)
Romelsjö *et al.*, 2012 [33] (ii)	Sweden	1969–2004	N/A (1-35)	Longitudinal cohort study, with record linkage to mortality data	48 716	100% men	18–20
Thern *et al.*, 2021 [32] (i and ii)	Sweden	2002–07	13.3 (1-16)	Longitudinal cohort study, with record linkage to national registers	37 484	45.6% men, 54.4% women	25–70
[a]NESARC (see Supporting information, eMethods 3) (i)	United States	2001–05	3 (N/A)	Longitudinal study	24 581	33.9% men, 66.1% women	NA
[a]NHIS (see Supporting information, eMethods 3) (ii)	United States	1997–2018	10.5 1-22	Longitudinal study	562 042	43.8% men, 56.2% women	50.3
Risk relationship (iii): (AUD- > AUD mort.)							
da Roza *et al.*, 2022 [36]	Brazil	2002–16	11.3 (0-14)	Longitudinal study, with database linkage	803	54.8% men, 45.2% women	35
Gunnarsdottir *et al.*, 2014 [35]	Iceland	2002–08	N/A (1-7)	Prospective cohort study, with record linkage to a national cause-of-death registry	107 237	53.3% men, 46.7% women	41.5
Haver *et al.*, 2009 [27]	Sweden	1981–2007	N/A (0-25)	Case–control study between patients and matched GP controls, with data from cause of death register	357	100% women	42.5
Hjemsaeter *et al.*, 2019 [37]	Norway	1997–2016	N/A (1-19)	Prospective, longitudinal cohort study, with record linkage to cause of death registry	102	72% men, 28% women	45.8

Abbreviations: AUD = alcohol use disorder; AUDADIS-4 = Alcohol Use Disorder and Associated Disabilities Interview Schedule, Diagnostic and Statistical Manual of Mental Disorders, 4th version; GP = general population; NA = not applicable; NESARC = National Epidemiologic Survey of Alcohol and Related Conditions; NHIS = National Health Interview Survey.

[a]Secondary data sources analyzed by the authors.

TABLE 1 (Continued)

men	Number of cases	Alcohol consumption/ exposure	Reference category	Outcome	Adjustments	Risk of bias (selection/ comparability/ outcome)
Risk relationships (i) and (ii): (use- > AUD inc.) and (use- > AUD mort.)						
Laatikainen *et al*., 2013 [34] (ii)	32	Heavy drinking pattern	No heavy drinking occasions	100% alcohol-attributable mortality; ICD-10	NA	4/2/3
Romelsjö *et al*., 2012 [33] (ii)	210	Alcohol consumption (g/day)	Abstainers (0 g/ day)	100% alcohol-attributable mortality; ICD-10	NA	4/0/3
Thern *et al*., 2021 [32] (i and ii)	1301 (i), 67 (ii)	Alcohol consumption (g/day)	Light drinkers (6 g/day)	AUD incidence (including identical ICD-10 codes as for mortality), standardized questionnaire; ICD-10 (Swedish index of alcohol-related diagnoses) 100% alcohol-attributable mortality; specifically, AUD, alcohol-related liver cirrhosis, alcohol poisoning; ICD-10	Age, sex, country of birth	4/2/3
[a]NESARC (see Supporting information, eMethods 3) (i)	1265	Alcohol consumption (g/day)	Life-time abstainers	AUD incidence; AUDADIS-4 interview; DSM-IV	Age, sex, education, race/ethnicity	4/2/3
[a]NHIS (see Supporting information, eMethods 3) (ii)	825	Alcohol consumption (g/day)	Life-time abstainers	100% alcohol-attributable mortality; ICD-10	Sex, education, race/ethnicity, marital status, survey year, survey design	4/2/3
Risk relationship (iii): (AUD- > AUD mort.)						
da Roza *et al*., 2022 [36]	14	AUD diagnosis (F10)	NA	100% alcohol-attributable mortality; ICD-10	Age and sex	3/0/2
Gunnarsdottir *et al*., 2014 [35]	18	AUD diagnosis (F10)	NA	100% alcohol-attributable mortality and alcoholic liver disease mortality; ICD 10	Age, sex, number of visits, year of entrance, mental and behavioural disorders at discharge	3/1/3
Haver *et al*., 2009 [27]	20	AUD diagnosis	NA	100% alcohol-attributable mortality; alcohol explicitly mentioned in diagnostic category	NA	2/2/2
Hjemsaeter *et al*., 2019 [37]	17	AUD diagnosis	NA	100% alcohol-attributable mortality; ICD-10	NA	3/1/3

Abbreviations: AUD = alcohol use disorder; AUDADIS-4 = Alcohol Use Disorder and Associated Disabilities Interview Schedule, Diagnostic and Statistical Manual of Mental Disorders, 4th version; GP = general population; NA = not applicable; NESARC = National Epidemiologic Survey of Alcohol and Related Conditions; NHIS = National Health Interview Survey.
[a]Secondary data sources analyzed by the authors.

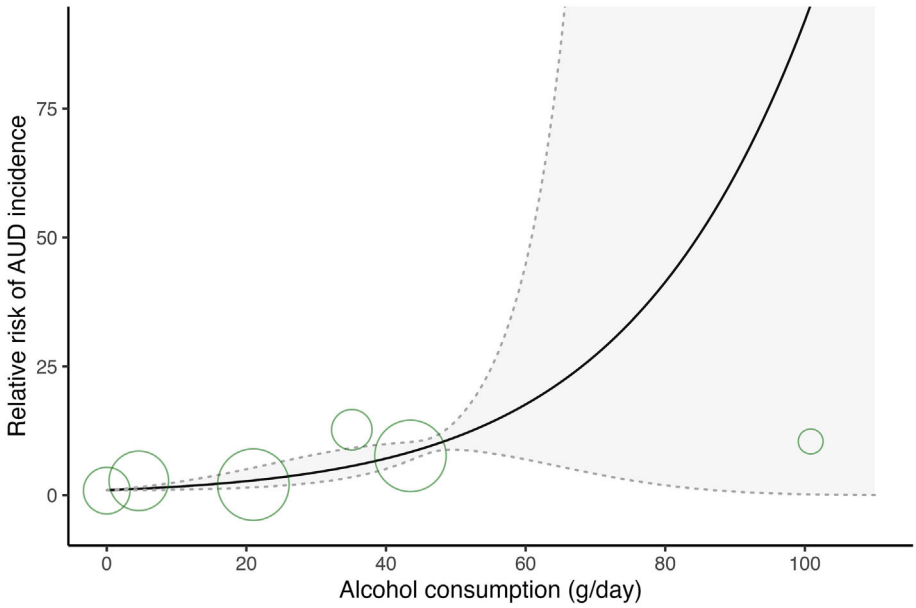

FIGURE 3 Dose–response relationship between the average level of alcohol consumption and the relative risk of developing an AUD based on a dose–response meta-analysis with two studies ([32], NESARC). Bubble size indicate inverse variance weights. The dashed line and grey area indicate the 95% confidence interval of the dose–response relationship. All data points are based off of a sample including men and women. AUD = alcohol use disorder; g/day = average grams of pure alcohol consumed per day; NESARC = National Epidemiologic Survey of Alcohol and Related Conditions.

TABLE 2 Relative risk of incident AUD for increasing levels of alcohol use.

Grams of pure alcohol per day	Relative risk	95% confidence interval
10	1.67	1.09–2.54
20	2.74	1.48–5.08
40	7.14	5.13–9.93
60	17.64	6.95–44.76

Abbreviation: AUD = alcohol use disorder.

drinking. These results support our findings that AUD incidence risk increases with greater quantities and frequencies of alcohol consumption.

Alcohol use and AUD mortality (ii)

Quantitative summary

A total of four identified studies included 612 964 individuals who reported their alcohol consumption, 1134 individuals later died from an AUD. For the dose–response relationship between alcohol use and AUD mortality, the linear model showed the best fit (formula and AIC/BIC values available in Supporting information, eMethods 11 and eResults 12). Figure 4 displays the linear dose–response relationship between the level of alcohol use (average grams of pure alcohol per day) and the log-RR of dying from an AUD for men, women and all participants on a non-log scale (for log scale, see Supporting information, eResults 13). As alcohol consumption increases, the risk of AUD mortality increases in an accelerated manner. As shown in Table 4, at 20 g/day the RR is 1.99 (95% CI = 1.88–2.10), increasing to 3.94 (95% CI = 3.53–4.40) at 40 g/day. Similarly, as consumption increases from 60 to 80 g/day, the RR increases from 7.82 (95% CI = 6.63–9.22) to 15.52 (95% CI = 12.46–19.34). Two studies included men only, and among this group the RR of AUD mortality increases with every 20-g increase in consumption in a similar manner to the values reported above for the combined men, women and all participants (see Supporting information, eResults 14).

Qualitative summary

One study similarly observed the RR of death from AUDs and alcohol poisoning (F10, X45, Y15) at varying levels of alcohol intake per week, reported by proxy (spouse/partner, sibling, parent, adult offspring or other adult relative) (Table 3) [28]. In this report by Zaridze *et al*. [28], alcohol consumption was presented in half-litre bottles of vodka or equivalent for men and women separately (n = 48 557, 35.1% women, age range = 15–74.) A fixed-effect model was used to combine estimates for men and women to create an 'all participants' category with 'reference drinkers' defined as 16 g of pure alcohol per day as the reference category. Despite these efforts, data from the study could not be used because consumption patterns in Russia vary significantly from the rest of the world. For example, alcohol intake was measured at significantly higher doses (0 to approximately 300 g/day) in this study relative to the other included studies.

AUD and AUD mortality (iii)

Quantitative summary

Among all four identified studies, 60 AUD deaths were observed in 22 216 PY of follow-up. The mortality rate due to AUD for those with an AUD for each study, as well as the weighted average by sex, is displayed in Figure 5. Participants were grouped into three categories.

TABLE 3 Characteristics of studies included in the qualitative analysis.

Study	Country	Study years	Follow-up years	Study design	Sample size	Sex	Mean age (years)	Alcohol consumption/ exposure	Reference category	Outcome
Tavolacci *et al.*, 2019 [38]	France	2017	NA	Retrospective case–control study	166	86.7% men, 13.3% women	34.6	Alcohol consumption (frequency of binge drinking before age 18, between 18 and 25 and between 25 and 45)	Non-alcohol-dependent (AUDIT score < 8) (controls)	AUD incidence
Dawson *et al.*, 2008 [39]	United States	2001–05	3	Prospective cohort study	22 122	61.9% men, 38.1% women	38.9	Alcohol consumption (frequency of risk drinking in year preceding wave 1 interview)	No risky drinking	AUD incidence; AUDADIS-4 interview; DSM-IV
Zaridze *et al.*, 2009 [28]	Russia	2001–05	Deaths occurred from 1990 to 2001. Data collected by proxy from 2001 to 2005	Case–control study, reported by proxy	48 557	64.9% men, 35.1% women	15.74	Alcohol consumption (half-liter bottles of vodka, or equivalent, by usual weekly intake)	Usual weekly consumption always < 0.5 bottles of vodka or equivalent, and maximum consumption of spirits in 1 day always < 0.5 bottles	100% alcohol-attributable mortality; ICD-10 (X45, Y15, F10)

Abbreviations: AUD = alcohol use disorder; AUDADIS-4 = Alcohol Use Disorder and Associated Disabilities Interview Schedule, Diagnostic and Statistical Manual of Mental Disorders, 4th version; NA = not applicable.

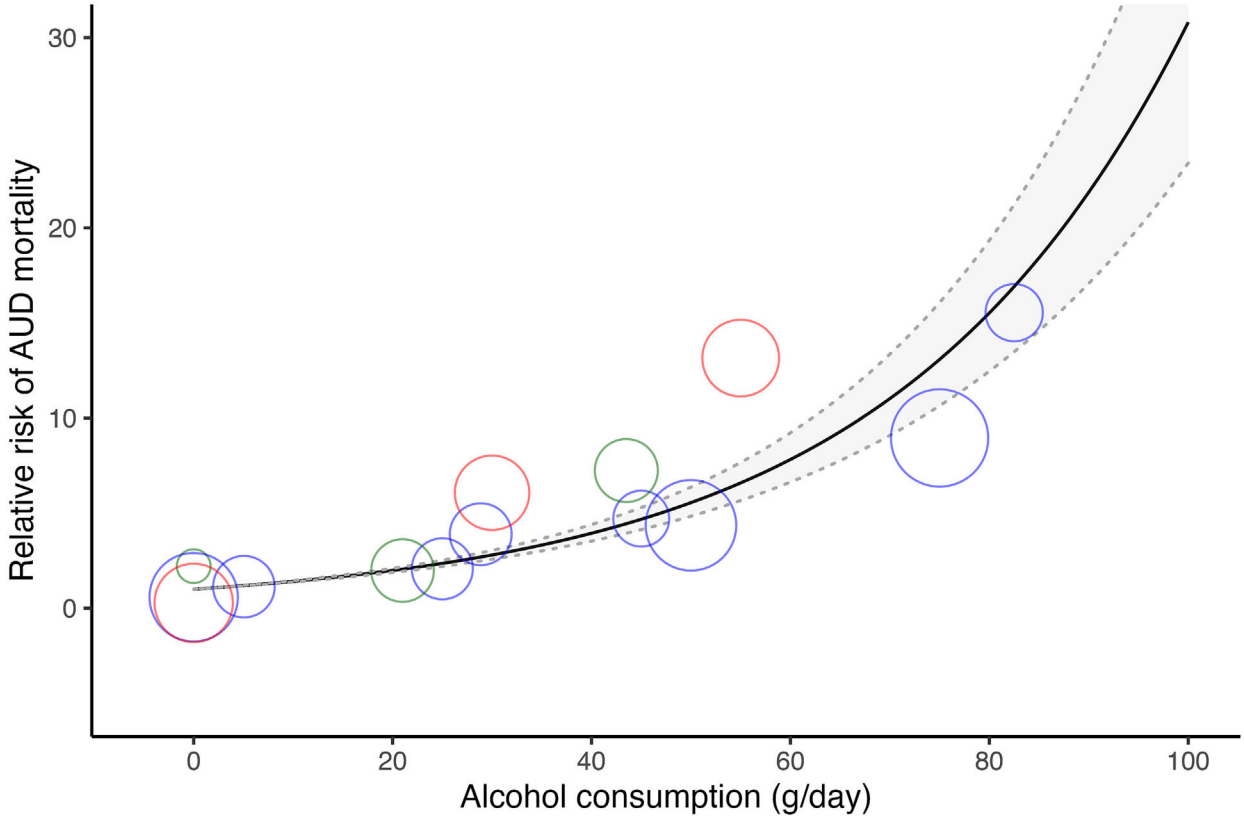

FIGURE 4 Dose–response relationship between the average level of alcohol consumption and the relative risk of death due to an AUD based on a dose–response meta-analysis, including four studies ([32–34], NHIS). Inverse variance weights are indicated by bubble size. Men are represented by the blue bubbles, women by red and 'all participants' are indicated by green. The 95% confidence interval of the resulting dose–response relationship is indicated by dashed lines and the grey area. AUD = alcohol use disorder; g/day = average grams of pure alcohol consumed per day; NHIS = National Health Interview Survey.

TABLE 4 Relative risk of AUD mortality for all participants at increasing levels of alcohol use.

Grams of pure alcohol per day	Relative risk	95% confidence interval
20	1.99	1.88–2.10
40	3.94	3.53–4.40
60	7.82	6.63–9.22
80	15.52	12.46–19.34
100	30.81	23.41–40.56

The 'all participants' category was comprised of overall estimates for all participants in the study, while the 'women' and 'men' categories included estimates that were stratified by sex. The overall mortality rate per 1000 PY was 3.13 for all participants (95% CI = 1.07–9.13), 2.17 (95% CI = 1.09–4.35) for men and 1.50 (95% CI = 0.33–6.78) for women with an AUD, respectively. Between-study heterogeneity was substantial for the 'all participants' category, in which Hjemsaeter *et al.* [37] produced a significantly higher mortality rate than the other included studies. For the sex-specific risk estimates, the interpretation is limited by the fact that only one and two studies provided estimates for men and women, respectively. A leave-one-out analysis was performed for each study to determine if studies contributed substantial leverage to estimated results (see Supporting information, eResults 15).

DISCUSSION

To our knowledge, this is the first study to describe the risk relationships between alcohol use, AUD and AUD mortality, which are imperative for understanding the harmful effects of alcohol consumption and preventing associated harms. The study identified exponential risk relationships between alcohol use and both AUD incidence and death. Moreover, even at an average consumption of 20 g/day (about one large beer), the risk of developing an AUD is nearly threefold that of current non-drinkers. At this level of consumption, the risk of dying from an AUD is approximately double that of current non-drinkers. Among men and women with diagnosed AUD, the average AUD mortality rate was found to be 3.1 per 1000 PY overall. This means if we would observe 500 individuals for 2 years, we would expect approximately three AUD deaths. Importantly, the studies were based on very young samples with an average age of approximately 30 years; hence, AUD mortality rates are expected to be higher in samples with

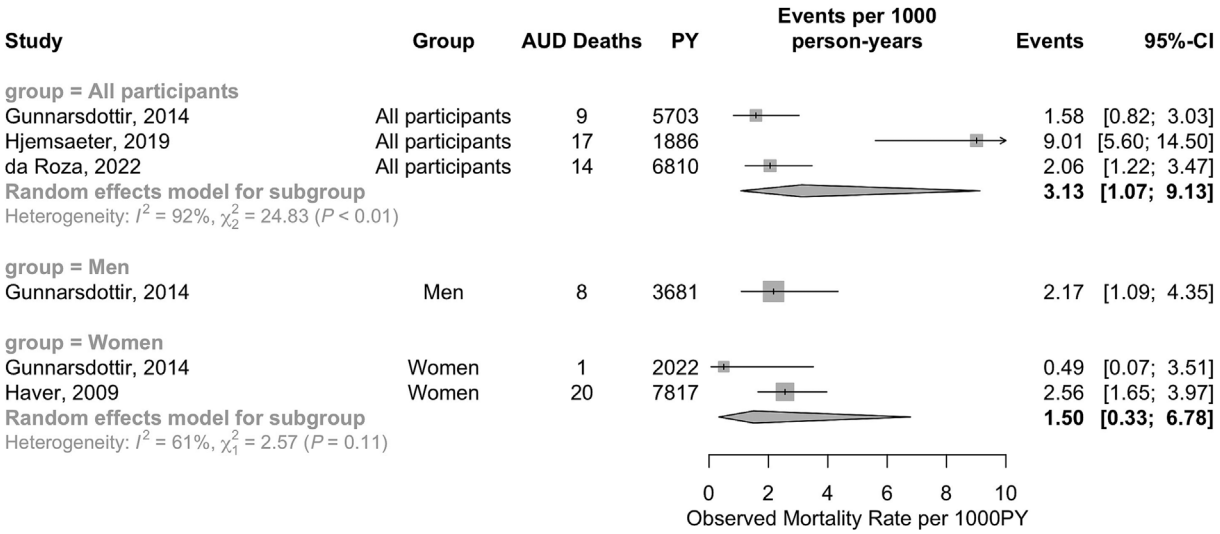

FIGURE 5 Observed mortality rate per 1000 PY, due to an AUD, in individuals previously diagnosed with an AUD based on four studies [27, 35–37]. AUD = alcohol use disorder; CI = confidence interval; PY = person-years.

an older mean age. For each of the studied risk relationships the effect modification by age, race/ethnicity and SES could not be accounted for, due to a lack of available evidence. Insufficient data of this type can have significant consequences. Failure to consider variations in alcohol use and health outcomes throughout racial/ethnic and SES groups can further perpetuate or worsen existing health disparities and, in particular, limit the accessibility or effectiveness of treatment for more vulnerable populations. Future studies should seek to address these key research gaps by investigating the risk relationships individually and how they vary by age, sex, race/ethnicity and SES, as well as by levels and patterns of alcohol use, as an important foundation for a targeted public health strategy to reduce the burden of disease related to AUD.

Our data suggest that the risk of developing and dying from AUD may differ by sex. However, the availability of sex-specific data was limited and gender-specific data were not available. There are several explanations for potential sex differences. For example, drinking patterns and beverage preferences among men may lead to increased risks of AUD incidence and mortality compared to women. Men are more likely to engage in heavy and frequent drinking, with a higher consumption of spirits, which could explain higher mortality rates among men [20, 40]. Furthermore, there is a potential excess risk associated with spirits consumption due to rapid ethanol intake and intoxication which may contribute to elevated risks among men [40]. Conversely, several factors may contribute to higher risks among women. First, at the same level of alcohol intake, women tend to have higher blood alcohol concentrations and may experience more progressive liver damage [41], potentially contributing to higher AUD incidence and mortality rates among women. Moreover, women with AUD may face more barriers to learning about AUD treatment options [42] and to receiving treatment [43, 44].

Overall, our results are consistent with previous findings, suggesting that the prevalence of AUD increases significantly with the level of consumption and the frequency of heavy episodic drinking [45]. However, data on the specific levels of consumption at which the risk increases are still limited, both for AUD incidence and mortality. According to our findings, a reduction in daily average consumption from 60 to 40 g/day may lower the RR from approximately 18 to 7 for developing an AUD, and from 8 to 4 for dying from an AUD. Similarly, the risks are approximately halved when reducing an average consumption from 40 to 20 g/day.

While this is currently the most comprehensive review, to our knowledge, on the risk relationships between alcohol use, AUD and AUD mortality there are some limitations to consider when interpreting its results. First, the outcome of AUD mortality was defined by both acute and chronic causes of death under the assumption that they are 100% alcohol-attributable, which reflects a broader definition of AUD mortality. As recording of AUD as an underlying cause of death is subject to coding practices that vary by country and over time, and is probably subject to stigmatization that may introduce further variation [46], we believe that this approach provides a clearer and more realistic estimate of AUD mortality. However, this introduced some heterogeneity in the included causes of death among the included studies. Furthermore, none of the included studies used lifetime abstainers as the reference category for exposure to alcohol use, which makes our estimates prone to the 'sick quitters' effect and a potential underestimation of the observed risk relationships [47]. These estimates may have additionally been affected by our use of the mid-point of an alcohol exposure range; it is possible that participants consumed on average at the lower end of a given range, as alcohol consumption generally follows a right-skewed distribution [48].

The majority of these studies relied upon self-reported alcohol use, which is likely to be under-reported due to drinkers' recall bias and the use of surveys employing simple quantity–frequency indices that may not accurately reflect consumption habits [49]. In addition, the risk relationship between AUD and AUD mortality was based

upon a select group of individuals who attended treatment for an AUD. This may have led either to an underestimation of the risks as the included individuals received AUD treatment or to an overestimation based on the inclusion of a group of individuals with greater severity of AUD. We expect that our findings most effectively reflect an overestimation of risk, as previous studies have demonstrated that those treated for an AUD compared to those with an AUD in the general population have significantly greater all-cause mortality rates, with RRs of 3.38 (95% CI = 2.98–3.84) for men and 1.91 (95% CI = 1.51–2.42) for women, due probably to greater severity of dependence and higher rates of comorbidities [4]. We were also unable to comment on the latency period of exposure to outcome, as is true with many chronic conditions. However, given the included longitudinal studies that used HR for survival analysis and accounted for time of follow-up, the bias should have been minimized. Due to a gap in available research, the total number of studies included in the review was low. As a result, we had to combine research findings reporting on both men and women with those referring to men only, as was used for risk relationship (ii) (use- > AUD mort.). This may have resulted in RR values that more clearly represent the (potentially higher) mortality risk of alcohol use on men, rather than only women. Finally, most studies included in this review were from high-income countries, limiting the generalizability of our findings.

In conclusion, there is a clear dose–response relationship between levels of alcohol consumption and the risk of AUD incidence and mortality. Further research is needed to validate and explore these risks, particularly regarding subgroup analyses, to gain a more comprehensive understanding of AUD incidence and mortality in relation to alcohol consumption levels and patterns. This will have important implications for public health and policy implementation. By understanding the risks associated with the level of alcohol use, individuals can make informed decisions regarding their drinking habits, seek earlier interventions and adhere more effectively to treatment plans. At the same time, policies can focus on improving public awareness of alcohol-related risks, while providing interventions that strive to reduce alcohol-related harms, in order to improve public health outcomes.

AUTHOR CONTRIBUTIONS

Tessa Carr: Conceptualization (equal); data curation (lead); formal analysis (lead); investigation (lead); methodology (equal); validation (lead); visualization (lead); writing—original draft (lead); writing—review and editing (lead). **Carolin Kilian:** Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); validation (supporting); visualization (supporting); writing—review and editing (supporting). **Laura Llamosas-Falcón:** Conceptualization (supporting); data curation (supporting); methodology (supporting); writing—review and editing (supporting). **Yachen Zhu:** Formal analysis (supporting); writing—review and editing (supporting). **Aurélie M. Lasserre:** Data curation (supporting); writing—review and editing (supporting). **Klajdi Puka:** Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); project administration (supporting); supervision (supporting); visualization (supporting); writing—review and editing (supporting). **Charlotte Probst:** Conceptualization (lead); data curation (supporting); formal analysis (supporting); funding acquisition (lead); investigation (supporting); methodology (lead); project administration (lead); supervision (lead); validation (supporting); visualization (supporting); writing—review and editing (supporting).

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DECLARATION OF INTERESTS

None to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study, as well as all associated R scripts are openly available in the Figshare respiratory at https://doi.org/10.6084/m9.figshare.25254538 (data) and https://doi.org/10.6084/m9.figshare.25254541 (R code).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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