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Severity of alcohol dependence and mortality after 20 years in an adult general population sample

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Abstract

Objectives: To estimate mortality on grounds of the severity of alcohol dependence which has been assessed by two approaches: the frequency of alcohol dependence symptoms (FADS) and the number of alcohol dependence criteria (NADC).

Methods: A random sample of adult community residents in northern Germany at age 18 to 64 had been interviewed in 1996. Among 4075 study participants at baseline, for 4028 vital status was ascertained 20 years later. The FADS was assessed by the Severity of Alcohol Dependence Scale among the 780 study participants who had one or more symptoms of alcohol dependence or abuse and vital status information. The NADC was estimated by the Munich Composite International Diagnostic Interview among 4028 study participants with vital status information. Cox proportional hazard models were used.

Results: The age-adjusted hazard ratio for the FADS (value range: 0–79) was 1.02 (95% confidence interval, CI: 1.016–1.028), for the NADC (value range: 0–7) it was 1.25 (CI: 1.19–1.32).

Conclusions: The FADS and NADC predicted time to death in a dose-dependent manner in this adult general population sample.

KEYWORDS
alcohol dependence severity, general population sample, mortality

1 | INTRODUCTION

Mortality is predicted by alcohol use (Rehm et al., 2017) and in addition by alcohol dependence (John et al., 2020; Roerecke & Rehm, 2013). However, the alcohol dependence diagnosis is limited to the information whether the disorder is present or absent. Ranks of the severity of alcohol dependence may provide insight into a dose-response relation between alcohol dependence and mortality. The understanding of severity of alcohol dependence had been introduced by the alcohol dependence syndrome (Edwards & Gross, 1976). Its criteria are (Edwards & Gross, 1976): narrowing of the drinking behaviour, "increased salience of drink-seeking", withdrawal, compulsion to drink and awareness thereof, alcohol tolerance (Stockwell, 2015). Additionally, the reinstatement of these criteria after a period of alcohol abstinence had been hypothesized (Edwards & Gross, 1976). Inherent was the assumption that the severity of alcohol dependence and the drinking quantity or frequency may vary independently of each other in one person to some extent (Stockwell, 2015). The alcohol dependence syndrome is a driving force of consumption which itself causes somatic or mental disorders that may infer death.

For the measurement of the severity of alcohol dependence, two approaches emerged from the alcohol dependence syndrome. One approach uses self-statements about the frequency of alcohol

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dependence symptoms (FADS). A sum score includes both the number of alcohol dependence criteria that have been fulfilled and the frequency of the symptoms. Standardized questionnaires had been developed for the assessment of the FADS on grounds of the alcohol dependence syndrome (John et al., 2003). A second approach to estimate the severity of alcohol dependence is the number of alcohol dependence criteria (NADC) according to the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM) in its versions 4 and 5 (American Psychiatric Association, 2000, 2013) and the International Classification of Diseases of the World Health Organization (ICD-10; World Health Organization, 1992). For each of the criteria, its presence or absence in a defined period of time is assessed. Both approaches, the FADS and the NADC, may be tested as predictors of mortality.

Little is known about the FADS and the NADC with respect to time to death. Even according to alcohol dependence, only a minority of studies used general population samples when predicting time to death (Laramee et al., 2015; Roerecke & Rehm, 2013). Among 81 studies, only nine included samples from the general population (Roerecke & Rehm, 2013). A study which used standardized DSM-IV 12-month diagnoses provided by a standardized psychiatric interview (Munich Composite International Diagnostic Interview) was conducted in Finland (Markkula et al., 2012) with a sample of residents 30 to under 70 years of age. Eight years later, vital status was proven. Study participants with any alcohol use disorder had a hazard ratio of 2.34 (CI 1.53–3.57) for time to death compared to those without this diagnosis.

Our aims were to analyse whether the FADS and whether the NADC may predict mortality 20 years later in a random sample of the adult general population aged below 65 at baseline according to total mortality, second among men and women, and third whether the FADS and NADC may predict specific mortality. In addition, we wanted to analyse whether the FADS and the NADC in combination with the utilization of alcohol dependence treatment may predict total mortality.

2 | METHODS

2.1 | Sample

A random adult population sample of adults aged 18–64 years had been drawn in 1995 in a northern German area that included 47 communities using the residents' registration office data in which every citizen has to be registered by law (Meyer, Rumpf, Hapke, Dilling, & John, 2000). The study area covered a total of 193,452 inhabitants at age 18–64. Among the 5829 individuals eligible for the study, 4093 (70.2%) interviews had been completed. Of these, 4075 were valid and could be analysed (Meyer, Rumpf, Hapke, Dilling, & John, 2000). The baseline study had been conducted from July 1996 until March 1997.

A mortality follow-up was realized from April 2017 until April 2018. The median number of days from the baseline interview to the assessment of vital status was 7532 (20.6 years). We used July 1, 1996, as the date of the baseline interview. Among the 4075 study participants with complete baseline data, for 47 (1.2%) vital status data could not be ascertained leaving 4028 as the final sample. These individuals are the study participants.

2.2 | Assessments

At baseline, the FADS and the NADC were assessed by self-report. We used the Severity Scale of Alcohol Dependence (SESA; John et al., 2003), a standardized questionnaire which was filled in by the study participants embedded in a standardized interview. The SESA is a standardized self-statement measure of the FADS which had been based on established assessment tools of severity of dependence according to the alcohol dependence syndrome: the Severity of Alcohol Dependence Questionnaire (Stockwell et al., 1983), the Alcohol Dependence Scale (Skinner & Allen, 1982), and the Short Alcohol Dependence Data (SADD; Davidson & Raistrick, 1986). The SESA covers the criteria of the alcohol dependence syndrome subscales and turned out to be an internally consistent and valid measure (John et al., 2003). The SESA includes the subscales: "narrowing of drinking" (value range 0–16), "somatic withdrawal symptoms" (value range 0–12), "alcohol consumption to avoid withdrawal symptoms" (value range 0–12), "craving" (value range 0–32), "increase of tolerance" (value range 0–4), "extreme increase" (value range 0–2) and "decrease of tolerance" (value range 0–4), and "reinstatement of the alcohol dependence syndrome" when drinking alcohol after having stayed abstinent 1 month or longer (value range 0–20). Questions about frequency or quantity of alcohol drinking are not part of the SESA. It includes 28 items about the frequency of alcohol dependence symptoms of which 18 were Likert-scaled ("Never", "Less than once a month", "Once a month or more often", "Once a week or more often", and "Daily"). These have been introduced by: "Please bear in mind your last drinking habits." A further 10 items about the increase of alcohol dependence symptoms over the past included the answer categories "Yes" and "No". They were introduced by "Now, please think of your entire drinking history, this means from the first until the last time when you have drunk alcohol" (John et al., 2003). A SESA sum score was calculated for these 28 items and for the SESA subscales. In addition, we used the subscale "reinstatement of the alcohol dependence syndrome" after alcohol abstinence (5 items) for those study participants who had answered the SESA questions and indicated that they had stayed alcohol abstinent for 1 month or longer after having consumed alcohol on a regular base in the past. The respondent was asked if and how fast symptoms of the criteria had been reinstated after having drunk alcohol following a period of alcohol abstinence of 1 month or longer. The answer categories were: "In the first 2 days", "In the first weeks", "In the first month", "Later or never". Eligible for the SESA were study participants who had confirmed one or more symptoms of alcohol dependence or alcohol abuse in the interview.

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The NADC was estimated as part of the standardized psychiatric interview which provided the alcohol dependence diagnosis according to DSM-IV. We used the Munich version of the Composite International Diagnostic Interview (M-CIDI; Wittchen et al., 1998). Presence of the single alcohol dependence criteria was inquired for the last 12 months prior to the interview (current alcohol dependence) and in addition for the time before the last 12 months (former alcohol dependence; Meyer, Rumpf, Hapke, & John, 2000). The seven criteria of alcohol dependence according to DSM-IV were assessed (Wittchen et al., 1998): tolerance, withdrawal, alcohol taken in larger amounts or over a longer time than intended, persistent desire or unsuccessful efforts to cut down or control the drinking of alcohol, great deal of time spent to obtain or use alcohol or recover from its effects, important activities given up or reduced because of alcohol consumption, and continued to drink alcohol despite being aware of having a problem that is likely to have been caused or exacerbated by the alcohol drinking. The two criteria for alcohol abuse were also assessed: 1) recurrent alcohol consumption resulted in failure to fulfil major role obligations or recurrent alcohol use in hazardous situations or recurrent legal problems related to alcohol consumption or having continued alcohol consumption despite problems being caused or exacerbated by alcohol consumption, 2) the symptoms have never met the criteria for alcohol dependence (American Psychiatric Association, 2000). These criteria were examined for the last 12 months prior to the interview (current alcohol abuse) and the time before the last 12 months (former alcohol abuse). Alcohol dependence was assumed if three or more of the respective DSM-IV criteria, alcohol abuse if the two respective DSM-IV criteria were fulfilled. Each study participant was counted only in one of three groups: neither alcohol dependence nor alcohol abuse, no alcohol dependence but alcohol abuse, alcohol dependence and no alcohol abuse.

Alcohol risk drinking was estimated using two ranks: 20 to less than 40 g pure alcohol per day or 65 or more grams pure alcohol once a month or more often among women with 40 to less than 60 and 100 g once a month or more often being the respective quantities for men. Fourty or more grams pure alcohol per day among women and 60 or more grams for men were assumed to indicate severe risk drinking.

Total and specific mortality were estimated by the mortality follow-up. For total mortality, we used official data files of the vital status of northern Germany residents and the residents' registration files of single communities in Germany and other countries. The data included whether the individual is alive or deceased, and if so, the date of death (for details see John et al., 2020). For specific mortality, we analysed the death certificates which are stored by local health authorities at the last place of residence of the study participant. The death certificate included health disorders which in the view of the responsible physician (a) immediately inferred death, or (b) were the main cause of death, and (c) were additional health disorders. We grouped disorders into four groups of specific mortality: cancer, cardiovascular, gastrointestinal, and respiratory disorders (Table 3).

Utilization of alcohol dependence treatment and detoxification treatment had been assessed at baseline as part of the interview. Alcohol dependence treatment in Germany is usually provided inpatient over several weeks for the purpose of supporting the motivation and power of the patient to stay abstinent from alcohol. Detoxification treatment in Germany usually has the purpose of safeguarding the vital function of the patient during the withdrawal of alcohol. Detoxification treatment in Germany is provided usually by inpatient care over several days.

2.3 | Data analysis

We included study participants with data from baseline and mortality follow-up. Cox proportional hazard models were calculated for the analysis of the prediction of time to death with hazard ratios (HRs) and 95% confidence intervals (CIs). The dependent variable is the time to death beginning at July 1, 1996. For all individuals who were alive at the date of the mortality follow-up, time was truncated at this date. In our focus was the severity of alcohol dependence. We adjusted only for age if not indicated otherwise. The reason is that causal factors next to the severity of alcohol dependence were of interest, not conditions which might be relevant to the alcohol dependence syndrome but are of no supposed causal effect.

As a precondition of the Cox proportional hazard model it was safeguarded that the minimum number of outcome events (total death cases) per predictor variable was 5 (Vittinghoff & McCulloch, 2007). We tested the proportional hazards assumption using graphical methods (Kaplan-Meier plots, log-log-plots) and Schoenfeld residuals (Bellera et al., 2010; Flynn, 2012). If the minimum number of outcome events or the proportional hazards assumption had not been met, we performed logistic regression analysis and give the odds ratio (OR) with CI.

We analysed the SESA for the total sample at first and, second, among those who had filled it in and for whom vital status data existed (780 study participants). In the total sample we took those as the reference group who had not fulfilled any criteria of alcohol abuse or dependence. We analysed the SESA using its sum score and after collapsing the value range to groups including rather equal numbers of study participants.

Fractional polynomials were tested for potential non-linear relations between the SESA as well as the number of alcohol dependence criteria and time to death (Sauerbrei et al., 2006). We included those study participants who were not eligible for filling in the SESA with a dichotomous variable in the model (Royston et al., 1999). All data analysis was performed using STATA 15.1 (StataCorp LP, 2017).

3 | RESULTS

There were 573 death cases found as certified in the residents' data files. This corresponds to 14.2% of the final sample (Table 1). Among the 152 study participants who had been identified as alcohol dependent at baseline, 48 (31.6%) were deceased at follow-up.

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3.1 | Frequency of alcohol dependence symptoms

Among the study participants who had been interviewed at baseline, 823 were eligible for the SESA, and 780 filled it in. The 28 items of the SESA included 33 missing values. This corresponds to 0.1% of the 24,360 responses to the 28 SESA items. The missing values were replaced by the mean values of the respective sex group. For the 28 items of the SESA, the data revealed a sum score range 0–79 of the possible range 0–82. Among the study participants who had responded to the 28 items of the SESA, 270 had stayed alcohol abstinent for one month or longer in the past and then returned to drinking and gave their answers in the reinstatement subscale. There were no missing values in the answers to this subsclae.

The SESA sum score including all study participants who had no symptoms of alcohol dependence or abuse turned out to predict time to death. Every rank was related to a 2% greater hazard of decrease in time to death. After adjustment for age and in addition for alcohol risk consumption, the HR for the SESA sum score was 1.01 (CI 1.005–1.02). The finding of the fractional polynomial modelling showed the linearity for the SESA sum score in predicting time to death when the SESA sum score and age are included.

Among those without any symptoms of alcohol dependence or abuse, the proportion of deceased was 13.21%, among those with a score of 5–7 it was 16.67%, among those with 21 or higher, it was 43.37%. The rank five or higher turned out to predict time to death. The highest HR was found in the group of persons with the highest rank of the SESA sum score (HR 3.44; 2.45–4.84). In addition to the study participants with a SESA sum score 5 or higher, those with a SESA sum score of 0 had an increased HR whereas persons with a SESA sum score 1 to 4 had not.

After limiting the analysis to study participants who had one or more criteria for alcohol dependence or alcohol abuse fulfilled in their life and a SESA score of 0 as the reference group, the SESA remained as a predictor of time to death. The sum score and all subscales of the SESA turned out to predict time to death except "extreme increase" of tolerance to alcohol. Among the study participants with SESA and vital status data, 270 confirmed that they had been abstinent from alcohol one month or longer and returned to alcohol consumption. Among them, 8.9% answered that they had experienced one or more symptoms of reinstatement within the first month of return to alcohol drinking, and 91.1% said that this happened to them after more than 1 month or never.

3.2 | Number of alcohol dependence criteria

Two or more alcohol dependence criteria predicted time to death with study participants as the reference who did not have any alcohol dependence criteria fulfilled. The only exception were the persons who had 3 criteria. Two alcohol dependence criteria revealed an HR 1.78 (1.11–2.86), 7 criteria an HR 5.32 (2.84–9.95). For the total NADC, the data revealed an HR 1.25 (1.19–1.32) for time to death. The relationship is linear as revealed by data of the fractional polynomial modelling with consideration of age. After adjustment for age and for alcohol risk consumption, the HR for the number of alcohol dependence criteria was 1.15 (CI 1.07–1.24). Alcohol abuse did not predict time to death.

3.3 | Men and women

Data analysis stratified by sex revealed that the higher the SESA sum score the higher the hazard of time to death was (Table 2). Among the study participants with a sum score of the SESA of 21 or higher, the HR was 2.46 (1.65–3.66) for males and the OR 9.83 (3.48–27.80) for females with those as the reference group who had no symptoms for alcohol dependence or abuse fulfilled. For six or seven alcohol dependence criteria, an HR 3.11 (1.78–5.42) among males and an OR 11.09 (3.48–35.36) among females was found. For ever having had alcohol dependence in lifetime the data revealed an HR 2.23 (1.58–3.14) among males and an HR 4.12 (2.25–7.56) among females compared to those who never had alcohol dependence or abuse in life. The data did not reveal higher HRs for females compared to males in any of the subgroups with a SESA sum one or higher, one or more alcohol dependence criteria or with ever having had alcohol dependence in lifetime. The women without any symptoms of alcohol dependence or abuse had a lower HR for time to death than the respective men (HR 0.61; CI 0.50–0.74) after adjustment for age.

3.4 | Specific mortality

Among the 573 death cases, for 28 the death certificate was not available, 7 death certificates were empty, and in 11 death certificates the cause of death was unknown. The remaining 527 (91.97%) death certificates included information about causes of death and were used for the analysis of specific mortality. The data revealed ORs 4 or higher for FADS among death cases with cancer, cardiovascular, gastrointestinal or respiratory disorders involved if the SESA sum score was higher than 20 (Table 3). Study participants with five to seven criteria of alcohol dependence fulfilled had particularly high ORs for death with cancer, cardiovascular, gastrointestinal, and respiratory disease. The OR was 6.70 (3.61–12.43) for cardiovascular disorder death. Severe risk drinking was associated with increased ORs for cardiovascular and for gastrointestinal disorder death. The OR for respiratory disorder death was 1.94 (1.02–3.69) among study participants with risk drinking.

3.5 | Utilization of treatment

Among 158 persons with three or more alcohol dependence criteria fulfilled, 38 (24.1%) had been in alcohol dependence treatment and a further 9 (5.7%) in detoxification but not in alcohol dependence treatment. Utilization of alcohol dependence or detoxification treatment was related to particularly high mean values of the FADS

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TABLE 1 Severity of alcohol dependence at baseline and deceased study participants 20 years later

		Deceased			
	N	*n*	%	HR	CI
Severity scale of alcohol dependence, sum score, total sample (n = 4028); reference: no alcohol dependence or alcohol abuse symptoms fulfilled	4028	573	14.23	1.02	1.016–1.028
Severity scale of alcohol dependence, sum score, total sample (n = 4028); reference: no alcohol dependence or alcohol abuse symptoms fulfilled; adjusted for risk drinking				1.01	1.005–1.020
Severity scale of alcohol dependence, sum score					
No alcohol dependence or alcohol abuse symptoms fulfilled	3248	429	13.21	Ref	
Score: 0	284	52	18.31	1.46	1.10–1.96
Score: 1	107	15	14.02	1.17	0.70–1.95
Score: 2	77	7	9.09	0.93	0.44–1.97
Score: 3–4	103	9	8.74	0.83	0.43–1.60
Score: 5–7	60	10	16.67	2.07	1.10–3.88
Score: 8–20	66	15	22.73	2.08	1.24–3.49
Score: 21–79	83	36	43.37	3.44	2.45–4.84
Severity scale of alcohol dependence, sum scores; persons who fulfilled one or more symptoms of alcohol dependence or alcohol abuse; reference: sum score = 0					
Severity scale of alcohol dependence, sum score	780	144	18.46	1.017	1.010–1.024
Severity scale of alcohol dependence, subscales, sum score					
Narrowing of alcohol drinking	780			1.08	1.04–1.11
Withdrawal symptoms	780			1.11	1.06–1.17
Consumption to avoid withdrawal	780			1.11	1.06–1.16
Craving	780			1.04	1.02–1.05
Tolerance increased	780			1.20	1.06–1.36
Tolerance extremely increased	780			1.37	0.97–1.92
Tolerance reversed	780			1.14	1.002–1.30
Tolerance total	780			1.13	1.05–1.22
Recurrence of criteria of alcohol dependence syndrome after alcohol abstinence	270	47	17.41	1.13	1.04–1.22
Alcohol dependence criteria, number fulfilled in lifetime before, reference: 0[a]	4028			1.25	1.19–1.32
Alcohol dependence criteria, number fulfilled in lifetime before, reference: 0; adjusted for age and alcohol risk drinking[a]				1.15	1.07–1.24
Alcohol dependence criteria, number fulfilled[a]					
0	3477	469	13.49	Ref	
1	291	35	12.03	1.08	0.77–1.53
2	102	18	17.65	1.78	1.11–2.86
3	53	9	16.98	1.69	0.87–3.26
4	33	10	30.30	2.72	1.45–5.09
5	28	11	39.29	3.41	1.88–6.21
6	29	11	37.39	3.21	1.77–5.84
7	15	10	66.67	5.32	2.84–9.95
Alcohol dependence or abuse, total sample (n = 4028)[a]					
Alcohol dependence or abuse never	3693	508	13.76	Ref	

(Continues)

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TABLE 1 (Continued)

		Deceased			
	N	n	%	HR	CI
Alcohol dependence former	98	34	34.69	2.76	1.95–3.91
Alcohol dependence current	54	14	25.93	3.36	1.97–5.73
Alcohol abuse. former[b]	140	12	8.57	0.77	0.43–1.36
Alcohol abuse. current[b]	43	5	11.63	1.53	0.63–3.70

Note: *N* number of persons at baseline.

n number of persons who had been deceased.

% proportion of of deceased among the persons at baseline who had vital status information at follow-up.

HR hazard ratio adjusted for age. Cox proportional hazard models; study participants with baseline and vital status data: 4028. The Cox Proportional hazards assumption according to the Schoenfeld criterion is fulfilled.

CI 95 %-confidence interval.

Ref reference category.

Tolerance total: sum of tolerance increased, tolerance extremely increased, and tolerance reversed.

[a]Assessed by the Munich Composite International Diagnostic Interview, lifetime.

[b]No alcohol dependence in lifetime.

and the NADC (Table 4). Both for the FADS and the NADC, HRs for time to death were greatest among those study participants who had been in detoxification but not in alcohol dependence treatment.

4 | DISCUSSION

This 20-year mortality follow-up of a random adult general population sample revealed four main findings. First, both the FADS and the NADC predicted time to death with the highest score being followed by the shortest survival time. Second, females appeared to have particularly high hazard ratios of time to death. Third, the highest ranks of the FADS and the NADC were related to increased likelihood of death after cancer, cardiovascular, gastrointestinal, and respiratory disorders. Fourth, utilization of alcohol dependence treatment was not related to longer survival time than non-utilization.

The data suggest that both the FADS and the NADC predict time to death in a dose-dependent manner. For the FADS in the total sample, this was found only for the three ranks with SESA scores of 5–79. The findings from the single subscales of the Severity of Alcohol Dependence Scale are in favor of all alcohol dependence criteria being in a dose-response relation with time to death. In addition, our data support the hypothesis that the alcohol dependence syndrome reinstates after a period of having abstained from alcohol (Edwards & Gross, 1976). With each score point the likelihood of early death was 13% higher. However, only less than 10% confirmed reinstatement within one month after having returned to drinking. The reinstatement subscale might work as a diagnostic instrument of a very high severity of alcohol dependence.

Although the findings from the Cox Proportional Hazard models and the Fractional Polynomials indicate linearity those with a SESA sum score 0 had a shorter time to death than those without any criteria of alcohol dependence or abuse. This corresponds with results according to alcohol consumption and mortality (Stockwell et al., 2016). In contrast to persons with low to moderate drinking those who said that they currently do not drink alcohol have a higher mortality according to evidence. Among them, the majority turned out to have known risk factors for early death including former alcohol or drug dependence and tobacco smoking (John et al., 2021).

According to the NADC, our data suggest that a clear dose-response relation with time to death exists. The higher the NADC the shorter the life expectancy was. The lowest NADC related to a shorter time to death compared to no criteria of alcohol dependence was two. This finding speaks in favor of the dose-response relation as it has been defined in the fifth version of the DSM (American Psychiatric Association, 2013).

Both instruments for the assessment of severity of alcohol dependence have their advantages and disadvantages. Three advantages of the SESA questionnaire are that it is cost-saving, that the sum score covers both the number of alcohol dependence criteria and the frequency of symptoms, and that the reinstatement of alcohol dependence after a period of abstinence from alcohol is included. Disadvantages of the FADS include the probability of missing values and that the time frame for answers has not been sufficiently distinct. This may have added to the finding that persons with a sum score of 0 had an increased HR of time to death while those with a sum score 1 to 4 had not.

Advantages of the NADC as part of the M-CIDI include clear inclusion rules and clear time frames both according to the last 12 months prior to the interview and the time before. One reason for the NADC showing a linear relation with time to death may be that alcohol dependence has been assessed for the entire time of life before the baseline assessment. The data suggest that the NADC might give reason for the increased HR among those with a score 0 of the FADS. Shortcomings of the NADC are the assessment costs and the lack of data about the frequency of symptoms. The NADC needs expertise and time to gather the information. However, a

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TABLE 2 Severity of alcohol dependence at baseline and deceased study participants 20 years later; men and women

	Men					Women				
		Deceased					Deceased			
	N	*n*	%	HR	CI	*N*	*n*	%	HR	CI
Severity scale of alcohol dependence, sum score, total sample; reference: no alcohol dependence or alcohol abuse symptoms fulfilled	2022	351	17.36	1.02	1.01–1.024	2006	222	11.07	1.03	1.02–1.04
Severity scale of alcohol dependence, sum score										
No alcohol dependence or alcohol abuse symptoms fulfilled	1434	234	16.32	Ref		1814	195	10.75	Ref	
Score: 0–4	423	70	16.55	1.07	0.82–1.39	148	13	8.78	1.03[a]	0.56–1.91
Score: 5–20	99	20	20.20	1.62	1.02–2.56	27	5	18.52	2.43[a]	0.84–7.01
Score: 21–79	66	27	40.91	2.46	1.65–3.66	17	9	52.94	9.83[a]	3.48–27.80
Severity scale of alcohol dependence, sum scores; persons who fulfilled one or more symptoms of alcohol dependence or alcohol abuse; reference: sum score = 0										
Severity scale of alcohol dependence, sum score	588	117	19.90	1.01	1.006–1.02	192	27	14.06	1.04[a]	1.02–1.06
Severity scale of alcohol dependence, subscales, sum score										
Narrowing of alcohol drinking	588			1.07	1.03–1.11	192			1.17[a]	1.06–1.30
Withdrawal symptoms	588			1.09	1.03–1.15	192			1.20	1.11–1.31
Consumption to avoid withdrawal	588			1.10	1.04–1.15	192			1.23[a]	1.07–1.42
Craving	588			1.03	1.01–1.05	192			1.08[a]	1.03–1.14
Tolerance increased	588			1.20	1.04–1.38	192			1.25	0.97–1.63
Tolerance extremely increased	588			1.28	0.89–1.85	192			2.07	0.82–5.25
Tolerance reversed	588			1.07	0.93–1.24	192			1.54	1.14–2.07
Tolerance total	588			1.11	1.02–1.20	192			1.23	1.05–1.43
Recurrence of alcohol dependence syndrome after alcohol abstinence	204	40	19.61	1.12	1.02–1.22	66	7	10.61	1.75	1.08–2.83
Alcohol dependence criteria, number fulfilled, reference: 0[b]	2022			1.20	1.12–1.28	2006			1.28	1.16–1.41
Alcohol dependence criteria, number fulfilled[b]										
0	1615	269	16.66	Ref		1862	200	10.74	Ref	
1–2	279	42	15.05	1.03	0.74–1.43	114	11	9.65	1.33[a]	0.67–2.60
3–5	98	27	27.55	1.93	1.30–2.87	16	3	18.75	2.17[a]	0.55–8.49
6–7	30	13	43.33	3.11	1.78–5.42	14	8	57.14	11.09[a]	3.48–35.36

(Continues)

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TABLE 2 (Continued)

	Men					Women				
		Deceased					Deceased			
	N	*n*	%	HR	CI	*N*	*n*	%	HR	CI
Alcohol dependence or abuse										
Alcohol dependence or abuse: never	1737	297	17.10	Ref		1956	211	10.79	Ref	
Alcohol dependence lifetime	122	37	30.33	2.23	1.58–3.14	30	11	36.67	4.12	2.25–7.56
Alcohol abuse lifetime[c]	163	17	10.43	0.78	0.48–1.27	20	0	0.00	na	

Note: *N* number of persons at baseline.

n number of persons who had been deceased.

% proportion of of deceased among the persons at baseline who had vital status information at follow-up.

HR hazard ratio adjusted for age. Cox proportional hazard models; study participants with baseline and vital status data: 4028. The Cox Proportional hazards assumption according to the Schoenfeld criterion is fulfilled.

CI 95 %-confidence interval.

Ref reference category.

na not applicable.

[a]Due to proportional hazards assumption not fulfilled: logistic regression with odds ratio and 95% confidence interval.

[b]Assessed by the Munich Composite International Diagnostic Interview, lifetime.

[c]No alcohol dependence in lifetime.

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TABLE 3 Alcohol dependence and risk drinking at baseline and disorders at death among deceased study participants 20 years later

	Cancer					Cardiovascular disorders					Gastrointestinal disorders					Respiratory disorders				
		Deceased					Deceased					Deceased					Deceased			
Baseline	***N***	***n***	**%**	**OR**	**CI**	***N***	***n***	**%**	**OR**	**CI**	***N***	***n***	**%**	**OR**	**CI**	***N***	***n***	**%**	**OR**	**CI**
Severity scale of alcohol dependence																				
No alcohol dependence or alcohol abuse symptoms fulfilled	2921	102	3.49		Ref	3025	206	6.81		Ref	2913	94	3.23		Ref	2901	82	2.83		Ref
Score: 0–4	510	22	4.31	1.25	0.76–2.07	541	53	9.80	1.45	1.03–2.06	506	18	3.56	1.07	0.62–1.83	501	13	2.59	0.98	0.53–1.83
Score: 5–20	105	4	3.81	1.38	0.48–3.96	110	9	8.18	1.52	0.72–3.21	103	2	1.94	0.74	0.17–3.11	105	4	3.81	1.79	0.62–5.18
Score: 21–79	58	11	18.97	4.60	2.18–9.70	70	23	32.86	5.10	2.85–9.14	55	8	14.55	4.00	1.74–9.20	54	7	2.96	4.05	1.69–9.72
Number of alcohol dependence criteria fulfilled[a]																				
0	3117	109	3.50		Ref	3236	228	7.05		Ref	3110	102	3.28		Ref	3098	90	2.91		Ref
1–2	357	17	4.76	1.56	0.89–2.71	373	33	8.85	1.43	0.94–2.18	350	10	2.86	0.96	0.48–1.90	349	9	2.58	1.04	0.51–2.13
3–4	74	7	9.46	3.01	1.27–7.11	77	10	2.99	1.91	0.90–4.05	70	3	4.29	1.40	0.42–4.74	70	3	4.29	1.63	0.48–5.54
5–7	46	6	13.04	3.46	1.36–8.81	60	20	33.33	6.70	3.61–12.43	47	7	14.89	4.82	2.00–11.62	44	4	9.09	3.16	1.06–9.35
Risk drinking and alcohol dependence[a]																				
None	3094	105	3.39		Ref	3201	212	6.62		Ref	3080	91	2.95		Ref	3069	80	2.61		Ref
Risk drinking	242	13	5.37	1.47	0.80–2.73	253	24	9.49	1.42	0.89–2.29	240	11	4.58	1.45	0.75–2.82	241	12	4.98	1.94	1.02–3.69
Severe risk drinking	132	9	6.82	1.51	0.72–3.16	147	24	16.33	2.12	1.28–3.51	133	10	7.52	2.05	1.003–4.20	129	6	4.65	1.46	0.60–3.51
Alcohol dependence lifetime[a]	116	12	10.34	3.22	1.64–6.33	134	30	22.39	4.37	2.69–7.11	113	9	7.96	3.09	1.45–6.56	111	7	6.31	2.80	1.21–6.46

N number of persons at baseline.

n number of persons who had been deceased.

% proportion of deceased among the persons at baseline who had vital status information at follow-up.

OR odds ratio. Logistic regression analysis adjusted for age and sex.

CI 95 %-confidence interval.

Ref reference group.

Cancer: brain, upper aerodigestive tract (lung, larynx, pharynx, oral cavity, esophagus), liver, colorectal tract, urothelium, bladder.

Cardiovascular disorders: myocardial infarction, coronary heart disease, arrhythmia, atrial fibrillation, cardiomyopathy, heart disease not further specified, stroke, ischemic stroke, cerebral hemorrhage, subarachnoid hemorrhage, subdural hematoma, atherosclerosis, aortic aneurysm, aneurysm, peripheral arterial disease, artery disease other or not further specified, venous thrombosis, esophageal varices, gastrointestinal hemorrhage, hemorrhagic shock.

Gastrointestinal disorders: liver cirrhosis, liver decompensation or failure, liver not further specified, gastrointestinal other (renal insufficiency or failure, gastritis, colitis, gastrointestinal not further specified).

Respiratory disorders: pulmonary emphysema or chronic bronchitis, pulmonary embolism, respiratory insufficiency, lung disorders not further specified.

Risk drinking: risk drinking but no alcohol dependence or abuse in lifetime before.

Severe risk drinking: severe risk drinking but no alcohol dependence or abuse in lifetime before.

[a]Assessed by the Munich Composite International Diagnostic Interview, lifetime.

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TABLE 4 Severity of alcohol dependence and treatment utilization at baseline and deceased study participants 20 years later

Baseline				Deceased			
	N	Mean	CI	*n*	%	HR	CI
Severity scale of alcohol dependence sum score and treatment or detoxification[a]							
Score: 0, treatment or detoxification: no	3248			429	13.21		Ref
Score: 0–4	571	2.08	1.97–2.19	83	14.54	1.07	0.84–1.37
Score: 5–79, treatment or detoxification: no	151	17.07	14.64–19.50	32	21.19	1.85	1.29–2.67
Score: 5–79, treatment	49	47.82	40.66–54.97	23	46.94	2.75	1.80–4.21
Score: 5–79, detoxification	9	43.89	28.08–59.70	6	66.67	7.16	3.20–16.04
Total	4028						
Alcohol dependence criteria[a] number and treatment or detoxification[a]							
Criteria: 0, treatment or detoxification: no	3477			469	13.49		Ref
Criteria: 1–2, treatment or detox: no	393	1.26	1.22–1.30	53	13.49	1.09	0.82–1.46
Criteria: 3–7, treatment or detox: no	111	3.96	3.76–4.17	27	24.32	2.01	1.36–2.99
Criteria: 3–7, treatment	38	5.76	5.41–6.12	18	47.37	2.83	1.76–4.54
Criteria: 3–7, detoxification	9	5.67	4.58–6.75	6	66.67	7.50	3.35–16.78
Total	4028						

Note: *N* number of persons at baseline.

Mean mean value of the SESA sum score or the number of alcohol dependence criteria.

CI 95 %-confidence interval.

n number of persons who had been deceased.

% proportion of deceased among the persons at baseline who had vital status information at follow-up.

HR hazard ratio. Cox proportional hazard models adjusted for age and sex; study participants with baseline and vital status data: 4028. The Cox Proportional hazards assumption according to the Schoenfeld criterion is fulfilled.

Ref reference category.

Treatment: alcohol dependence treatment with the aim to stay abstinent. This includes detoxification treatment.

Detoxification: inpatient detoxification treatment only, no alcohol dependence treatment.

[a]Assessed by the Munich Composite International Diagnostic Interview, lifetime.

computerized version of the CIDI is available which helps to save resources. An open question remains whether filling in a questionnaire or an expert asking the questions makes a difference. For both instruments different response bias may be assumed. The data of this study give evidence that both assessment instruments are suited to provide data about the severity of alcohol dependence as a predictor of total mortality.

The findings speak in favor of the concept of the alcohol dependence syndrome (Edwards & Gross, 1976; Stockwell, 2015). The findings are in line with those from a sample of male Vietnam veterans in which alcohol dependence and six or more criteria of alcohol dependence predicted time to death (Lundin & Mortensen, 2015), and they are in line with a community sample in Sweden in which alcoholism was inversely related to life expectancy (Lundin et al., 2015).

Alcohol abuse turned out not to be related with time to death. Alcohol abuse in the understanding of DSM-IV is a diagnosis that is largely driven by adverse consequences from alcohol consumption. Alcohol abuse criteria refer to a social context: failure to fulfil major role obligations, situations in which alcohol consumption is physically hazardous, legal, other social or interpersonal problems. Compared with the dependence criteria, the criteria for alcohol abuse are potentially more vague insofar as it might be difficult to delineate them against "normal" and socially accepted behaviour in a high alcohol consumption country such as Germany (Rehm & Room, 2017).

Women without any symptoms of alcohol dependence or abuse had a longer time to death than men. In contrast, among study participants with the highest scores of the FADS or the NADC, females tended to show a particularly high likelihood of early death although not significantly higher than among males. A meta-analysis found higher risks of death for women than for men among patients with alcohol use disorders (Roerecke & Rehm, 2013). One reason for the insignificance in our data might be that lifetime alcohol dependence had been diagnosed for just 30 women compared to 122 men.

According to specific mortality, our data revealed a relation between the severity of alcohol dependence and the likelihood of death for all four groups of health disorders involved: cancer, cardiovascular, gastrointestinal, and respiratory disorders. In each of

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these, increased ORs were found among the study participants with the highest FADS or NADC. The relation seemed to be particularly strong for cardiovascular disorders. Cardiovascular disorders could be more prevalent at rather young age whereas cancer may become apparent particularly later in life. In addition to these findings, alcohol dependence was related to the likelihood of death for all health disorders. Even alcohol risk drinking or severe risk drinking among those without alcohol dependence predicted the likelihood of cardiovascular, gastrointestinal and respiratory death. The findings suggest that both the severity of alcohol dependence and, among the general population without alcohol dependence, alcohol risk drinking are predictors of early death due to a variety of health disorders.

Treatment at first view may not have added to an increase of time to death. Persons who had utilized alcohol dependence or detoxification treatment did not show a longer survival than persons who had not. However, the utilizers also had a higher severity of alcohol dependence than non-utilizers. Our result corresponds to that of a meta-analysis. Risks of death were found to be higher among clinical than among general population samples (Roerecke & Rehm, 2013).

Our data suggest that those with a high severity of alcohol dependence are more likely to take part in alcohol dependence treatment than those with a low severity. Thus, treatment is utilized particularly by alcohol dependent patients who are at highest risk of early death. For them, treatment might have too little an effect on survival. On the other hand side, the very high HRs for those who had been in detoxification treatment only speak in favor of positive effects of alcohol dependence treatment on survival. It should be considered that only 24.1% of the study participants with alcohol dependence had been in alcohol dependence treatment. The treatment system for alcohol dependent patients in Germany is not proactive. It might offer too little to those with a low to moderate severity of alcohol dependence.

Strengths of this study include that 70.2% of the eligible persons in the general population participated in the study with complete interviews. The study participants who were diagnosed to be alcohol dependent include those who had not been in treatment and the data for alcohol dependence criteria were gathered using an internationally standardized interview. Also, the mortality follow-up with the time span of 20 years and the proportion of 98.8% with vital status information among the baseline study participants are strengths. Limitations include that our findings just show plausibility about causal relations between the severity of alcohol dependence and total mortality. The baseline data are from self-statements only. Both FADS and NADC might be underreported. There were only few female study participants with alcohol dependence in the analysis. The definition of alcohol risk drinking included high amounts of drinking. Also, it has to be kept in mind that definitions of risk drinking vary considerably. We could not provide data about further health disorders at baseline that might have added to death. We did not consider further health risk behaviors, socioeconomic status, and comorbid mental disorders. The age range of our sample is limited to adults at age below 65 years at baseline. Larger age ranges and longer follow-up periods might provide other findings according to specific mortality.

5 | CONCLUSIONS

First, the findings suggest that severity of alcohol dependence as assessed by FADS and by NADC is linearly related to time to death. Second, the data speak in favor of females more than males might be exposed to a shortening of life among those with a severe alcohol dependence. Third, the FADS and NADC were related to the entire range of common health disorders involved in death: cancer, cardiovascular, gastrointestinal, and respiratory disorders. Fourth, the severity of alcohol dependence was higher among those who had utilized alcohol dependence or detoxification treatment than among those without such treatment.

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CONFLICT OF INTEREST

All authors declared that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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