

Alcohol-A Risk Factor of Mood Disorders? A Review of General Population Studies According to the Criteria of Hill

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Abstract

Objective: Mood disorder is considered a risk factor of alcoholism in the general population. The aim of this review is to evaluate whether the reverse is true, that alcohol is a risk factor of mood disorder.

Methods: Pub med, Psych Net, and Cochrane library were searched for relevant publications. Longitudinal general population studies of alcohol use disorders and mood disorders according to DSM-IV and studies with other criteria of drinking, e.g. amount of alcohol consumed were chosen. Evaluations were made according to Hill's criteria, i.e. Consistency, temporal sequence of events, strength of association, dose-response relationship, specificity and biological criteria.

Results: Seven studies were found. Five showed a significant, positive association between alcohol and later Mood Disorder. There was no consistency for age and gender. The strength of the associations was moderate.

A positive dose-response relationship was found in two studies. The specific effect of alcohol on mood disorder was difficult to evaluate, since other possible confounding factors were not always accounted for. Biological criteria could not be evaluated.

Conclusion: When evaluated according to the criteria of Hill, the majority of the selected population studies indicated that alcohol may cause or trigger mood disorders according to DSM-IV. An indirect effect due to confounding factors, in particular social ones, could not be entirely excluded. Future studies should focus on estimates that quantify alcohol consumption more precisely.

Keywords: Alcohol; Depression; Depressive; Mood

Introduction

There is a considerable comorbidity of alcohol and mood disorders in the general population [1-7]. The Epidemiologic Catchment Area Study (ECA Study), a prospective longitudinal population study, estimated the life time prevalence of DSM-III disorders in a representative sample of 20291 persons. Those with a life-time diagnosis of any Alcohol disorder had an almost two-fold risk of having also any Affective disorder compared with those having no Alcohol disorder; vice versa, those with a life time prevalence of any Affective Disorder had an almost two-fold risk of having also any Alcohol Disorder compared with those without any Affective disorder [8]. Data from the 2001-2002 given by The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) including 43093 persons showed that 13.7% of those with a past year Alcohol Use Disorder (AUD) according to DSM-IV also had a past year Major Depressive Episode (MDE), compared to a 7.2% base rate of past year MDE [9]. Moreover, 16.4% of those with a past year MDE had a past year AUD, compared to an 8.5% base rate of past year AUD [10]. When assessing Major Depressive Disorder (MDD) instead of MDE, Hasin et al. [2], found that 40.3% of those with a lifetime MDD also had a lifetime AUD.

Alcohol and its related conditions is a major challenge to public health. Mental and substance use disorders have been found to be the leading cause of years lived with disability (YLDs) worldwide. Furthermore, the burden of mental and substance use disorders increased by 37.6% between 1990 and 2010, which for most disorders was driven by population growth and ageing [11]. Alcohol disorders have been found to worsen the prognosis severely in subjects with mood disorders and lead to illicit drug use and violent acts including suicide. Hence about 45% of all suicides are considered to be related to alcohol [4,12-18].

It is, however, unclear how alcohol and mood disorders are related, and, if there is a causal relation, which of the conditions that causes the other [19,20]. Some studies have found mood disorders to be a risk factor of alcoholism [6,21]; one explanation given for this is that alcohol is a self-medication that relieves depressive symptoms [22-26].

Based on the DSM-III diagnostics, The ECA Study investigated the risk of either Major Depression or Alcohol Dependence being followed by the other disorder after one year of follow-up. Major Depression at baseline did not increase the odds ratio for developing alcohol dependence, while Alcohol Dependence at base-line significantly increased the risk of major depression in both genders [27]. Accordingly, it seems that alcohol may cause mood disorders, in particular depression, as well. However, another prospective population study found a relationship, though not significant, between alcohol use disorder and first incidence major depression, when studying predictors of first incidence psychiatric disorders acc. to DSM-III-R [28].

The aim of the present study is to review whether alcohol consumption can be considered a risk factor of mood disorders in

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the general population, by assessing the Hill criteria of cause-effect relationships.

Methods

The data bases Pub med, Psych Net, and Cochrane library were searched for relevant publications. The searches were limited to titles and/or abstracts in English between the years 1994-2017.

Prospective and retrospective longitudinal population studies also including adolescents and other selected groups were chosen.

The diagnoses studied were Alcohol Use Disorders (AUD) including the sub-diagnoses Alcohol Abuse (AA) and Alcohol Dependence (AD), and mood disorders according to The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) 1994 [29]. Dealing with predefined criteria reduces biases due to diagnostic differences. However, to be able to study the specific effect of alcohol, we included also studies with other criteria of drinking habits, such as the amount of alcohol consumed.

In order to study a possible cause-effect relation between alcohol consumption and primary mood disorders, we applied what is often called Hill's criteria: Consistency of the observed association, Temporal sequence of events, Strength of association, Dose-response relationship and Specificity of the association. The criterion 'Biological plausibility' of the association was not studied [30,31].

The selected studies were evaluated independently by the two authors. In case of disagreement, problems were solved by consensus discussion.

Results

Seven relevant longitudinal population studies were found, In six of them mood disorders applied to Major Depressive Disorder (MDD) (Tables 1 and 2) [29].

Studies Where Alcohol Significantly Predicted Mood Disorders Prospective studies

The Lundby study (Risk factors for depressive disorders in the Lundby cohort a 50 year prospective follow-up (Mattisson et al. [32])

Alcoholism according to the Lundby definition approximates the diagnosis AUD according to DSM-IV. The study included cases with medium or severe impairment of depression, corresponding to a GAF score of 60 and below. Most of the cases met criteria of MDD according to DSM-IV. Due to the specific study design the data were considered as two cohorts, one from 1947 to 1997 and the other from 1957 to 1997. For both ways of looking at the cohorts it was found, by means of Cox regressions, that alcoholism significantly predicted depression; odds ratio: 1.56 (95% CI: 1.02-2.38) and odds ratio: 1.67 (95% CI: 1.14-2.45), respectively . The effects changed slightly in multivariate models, controlling for socio-demographic factors and other mental and personality disorders.

Limitations: Long durations between follow-ups may increase risk of recall bias regarding mental health conditions.

The christ church birth cohort study (Tests of causal links

Study	Participants/ non-participants	Methods	Exposure variable	Outcome variable
Mattisson Horstmann et al. 2008 [32] Lundby Study 1947-1997	Census cohort study n: 3563 Non-participants: 1%-6% Study sample: n: 3296 Ages: 15+	Prospective study 4 waves: 1947 1957 1972 and 1997. Semi-structured interviews performed by specialists in psychiatry. Collateral information	Alcoholism according to the Lundby definition ~ DSM-IV AUD	First incidence Depression according to the Lundby definition. ~ DSM-IV MDD
Ferguson et al. 2009 [33] Christchurch Study 1977-2002	Birth cohort study n: 1265 Non-participants: 16.6% Study sample: n: 1055 Ages: 18-25	Prospective study Structured interviews by trained lay-men concerning ages 17-18 20-21 and 24-25. Collateral information	DSM-IV AUD	First incidence DSM-IV MDD
Brook et al. 2002 [34] Children of The Community Study 1975-1997	Census cohort study n: 975 Non-participants: 15.6% Study sample (1997) n: 736 Ages: 23-32	Prospective study 5 waves: 1975 1983 1986 1992 and 1997. Structured interviews by trained lay-men. Collateral information	Alcohol consumption	DSM-IV MDD
Hasin et al. 2002 [35] NLEAS 1992	Former drinkers (from NLEAS study)n: 9264 Non-participants: 2.6 %. Study sample: n: 6050 Ages: 18+	Retrospective study Structured interviews by trained lay-men	Former DSM-IV AD	Past year DSM-IV MDD
Falk et al. 2008 [36] NESARC 2001-2002	Census cohort study n: ~53200 Non-participants: 19% Study sample: n: 19504 Ages: 18+	Retrospective study Structured interviews by trained lay-men.	DSM-IV AA and/or AD	DSM-IV MDD + Depressive withdrawal syndrome + Dysthymia

Table 1: Studies where alcohol is significantly associated with later mood disorder.

Study	Participants/non-participants	Methods	Exposure variable	Outcome variable
Grant et al. 2009 [37] NESARC 2001-2002 2003-2004	wave 1 n1: 43093 wave 2 n2: 34653 Non-participants: wave 1: 29.8 % wave 2: 13.3 % Ages: 20-29 30-54 ≥ 55	Prospective study 2 wave study: Wave 1: 2001-2002 Wave 2: 2003-2004 Structured interviews by trained lay-men.	Alcohol abuse and Alcohol dependence	First incidence MDD Bipolar I Bipolar II
Wang and Patten 2001 [38] NPBS 1994-1995 1996-1997	Cohort study: Subjects without MDD at base-line: n: 12290 Non-participants: 4.4 % Study sample n : 11745 Ages: 12+	Prospective study Interviews of alcohol consumption at the 1994-1995 survey. Follow-up in 1996-97 Structured interviews acc. to CIDI-SF by trained lay men.	Any drinking Daily drinking More than 5 drinks at one occasion More than 1 drink daily	MDD A cut-point of 90% in the CIDI-SF= MDD acc. to DSM-IV

Table 2. Studies where alcohol was not significantly associated with later mood disorder.

between alcohol abuse or dependence and major depression (Ferguson et al.) [33]

Data were sampled from a birth cohort with repeated investigations since birth. The participants were interviewed at the ages 18, 21, and 25 regarding episodes of AUD and MDD acc. to DSM-IV during the past year.

Structural equation models were used to ascertain the most plausible direction of causality. Fixed-effect models controlled for confounders such as non-observed common genes and environment and time-dynamic factors including stressful life events, use of tobacco, illicit drug use, affiliation with deviant peers, unemployment, partner's substance use and engagement in criminal offending. The best fitting causal model was the one in which AUD predicts MDD; adjusted odds ratio: 1.66 (95% CI: 1.08-2.55), $P=0.02$.

Limitations: The role of the social consequences of alcohol abuse for the development of MDD might not have been fully explored.

The children of the community study (Drug use and the risk of major depressive disorder, alcohol dependence, and substance use disorders (Brook et al.) [34])

The study sample participated in the 1997 wave of a randomly selected population cohort that started in 1975 and included children aged 1 to 10 years. Interviews were performed with an updated version of the Michigan Composite International Diagnostic Interview, ensuring that MDD and AUD diagnoses met criteria of DSM-IV. Further, alcohol consumption was assessed on a five-point scale from no consumption (0) to heavy use [4]. Also, cumulative alcohol consumption was assessed.

A logistic regression analysis, controlling for parental educational level, family income, age, sex, prior episodes of MDD, Substance Use Disorders and childhood aggression, showed that those with heavy cumulative alcohol use had a higher risk of developing MDD compared to those without such consumption; odds ratio: 1.42 (95% CI:1.66-1.72).

Limitations: Earlier personality disorders were not accounted for though such disorders might have contributed to the development of later depressions.

Studies Where Alcohol Significantly Predicted Mood Disorders Retrospective Studies

The National Longitudinal Alcohol Epidemiologic Survey (NLEAS) (Major depression in 6050 former drinkers, association with past alcohol dependence (Hasin et al. 2002) [35])

The sample of former drinkers was drawn from a nationally representative sample of the US adult population (NLAES). The former drinkers were divided into those with and without past alcohol dependence (AD) acc. to DSM IV. These two groups were compared with regard to the presence of DSM IV Major Depression during the last 12 months. The former drinkers had been drinking at least 12 drinks daily for more than a year, but had been drinking less during the 12 months prior to the interview. Smokers and users of drugs during the past year were excluded.

A logistic regression analysis, controlling for sex, race, age, current marital status and education, showed that those with a history of AD had a higher risk (odds ratio: 4.2) of developing MDD during the following 12 months compared to the group without AD. When former abusers were withdrawn the odds ratio did not increase (odds

ratio: 4.12). The odds ratio did not even increase when all subjects, with any alcohol intake last 12 months (n: 3496) were removed from the analysis. Thus, a dose response relationship was not established.

Limitations: Former episodes of MDD were not accounted for.

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Age of onset and temporal sequencing of lifetime DSM-IV alcohol use disorders relative to comorbid mood and anxiety disorders (Falk et al. 2008) [36])

The NESARC study is a general community study of 43093 non-institutionalized persons aged 18 and above; the subsample used in the present study included 19504 persons with prior episodes of both mood/anxiety and substance use disorder acc. to DSM-IV. In contrast to the other studies, the outcome variable MDD included also Alcohol Depressive Withdrawal Syndrome. The ages of the first episodes of disorders were obtained by self-reports; the time span between the two types of disorders was calculated.

An alcohol primary ratio (APR) was calculated by dividing the number of primary AUD by the number of primary Mood Disorder, thus indicating the extent to which AUD or MD came first. Considering MDD the APR (2.4) differed significantly ($p<0.05$) from 1 for AA, but not significantly for AD (APR: 1.0). The ratio was larger for men than for women. Likewise, the APR for primary AA and primary dysthymia was significantly different from 1 (APR: 2.2, $p<0.05$). The corresponding figure for AD and dysthymia was 1.1, not differing significantly from 1.

The average time span from alcohol dependence to major depression was 9.9 years, for alcohol abuse the time span was 15.3 years. Compared to men, women had significantly shorter time span from onset of AUD to MDD or dysthymia.

Limitations: The data rely on memory recalls regarding onset of diagnosis. Deceased, deported, mentally or physically impaired in hospitals and those on active duty in the armed forces were excluded.

Studies with Non-Significant Results Prospective Studies

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (Socio-demographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood and anxiety disorders: Results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions (Grant et al.) [37])

The sample used in this study is based on a three-year follow-up of the NESARC study mentioned above. First incident cases of AUD and mood and personality disorders during the follow-up were registered. A hierarchical diagnostic method was used, excluding withdrawal syndromes, opposite to the study by Falk et al. [36].

AD predicted bipolar disorder I (mania) significantly when socio-demographic factors were controlled for; odds ratio: 2.4 (99% CI: 1.39-4.16). However, when other psychiatric disorders present at base-line were also controlled for, neither AA nor AD were significant predictors for any mood disorder. The odds ratios of MDD were for abuse: 1.1 (99% CI: 0.70-1.63), and for dependence: 0.9 (99% CI: 0.48 -1.83). The corresponding figures of Bipolar I were for abuse: 0.8 (99% CI: 0.40-1.77), and for dependence: 1.7 (99% CI: 0.72-4.04). The odds ratios of Bipolar II were for abuse: 0.4 (99% CI: 0.12-1.10) and for dependence: 1.3 (99% CI: 0.38-4.14).

When controlling for socio-demographic factors including income, employment status and marital status as well as psychiatric comorbidity, borderline personality disorder (BPD) at base-line

predisposed significantly for alcohol dependence and mood disorders as well. The odds ratios were for alcohol dependence: 2.4 (99% CI: 1.46-4.00), for MDD: 4.4 (99% CI: 2.74-7.10), and for Bipolar I: 4.2 (99% CI: 2.26-7.72).

Limitations: Deceased, deported, mentally or physically impaired in hospitals and those on active duty in the armed forces were excluded.

The Canadian National Population Health Survey (NPHS) (Alcohol Consumption and major depression in the Canadian general population (Wang and Patten, 2001) [38])

From a total sample of 15670 respondents, 12290 individuals above the age of twelve without depression at base-line (1994-1995 survey) were included in this study. The participants were analyzed in four different ways according to a categorization of their drinking pattern: Drinking/not drinking, drinking every day/drinking less frequently than every day, having more than 5 drinks on at least one occasion/not having more than 5 drinks on one single occasion, and having on average more than one drink daily/having less than one drink daily. At a follow-up two years later, 1996-1997, subjects with a major depressive episode during these years were identified. The incidence of MDD was estimated using bootstrap weights for the two categories in each of the four analyses that were stratified by sex, age, marital status, employment, income, medical conditions, antidepressant use, and perceived social support. The incidence of MDD in each group was calculated as the proportion of subjects who developed the condition during the follow-up period in each cohort.

In the analyses based on drinking habits with more than 5 drinks at one single occasion, both genders showed a higher incidence of MDD compared with those who reported having 5 or less drinks on one occasion in both surveys. The incidences for MDD in men were 2.9% (95% CI: 1.7%-4.2%) for those having more than 5 drinks per occasion, and 2.4% (95% CI: 1.6%-3.2%) for those having 5 drinks or less. For women, the corresponding figures were 6.4% (95% CI: 4.4%-8.3%) and 4.1% (95% CI: 3.5%-4.8%). The same trend was found when nondrinkers were excluded. For the other three analyses, there were no reported results. Women generally had higher rates than men.

In a sub-study the effect of alcohol consumption was studied separately with regard to gender, age and major depression and minor depression according to DSM-IV. Women between 19-30 years seemed to be particularly vulnerable. Those, who had more than 5 drinks at one occasion at least once a month had an incidence of major depression of 18.1% (95% CI: 6.5%-29.6%), while women in the same age-group having more than 5 drinks less frequently than once a month had an incidence of major depression of 3.0% (95% CI: 1.5%-4.5%). The same pattern, though less outspoken, was seen for men. However, no such differences were seen for minor depression [39].

Limitations: The study excluded persons who had depressions at base-line but did not account for those that eventually had depressions between baseline and follow-up. Information about drinking habits that might have changed after base-line was not obtained (Table 3) presents the evaluations of the studies according to the criteria of Hill.

Discussion of the Evaluations According to the Criteria of Hill

Consistency of the observed association

From the seven reviewed studies, five showed a significant association between alcoholism and later mood disorder [32-36].

There was little consistency with regard to gender and age. Gender did not have any effect on the risk of developing mood disorder after alcohol use in the studies including only younger people (18-32 years) [33,34], nor in the prospective NESARC study including men and women of all ages [37,38]. The Lundby study, on the other hand, found that men with alcoholism had an increased risk of developing depression. A similar increased risk could not be established for women; however, women with alcohol problems were few making conclusions uncertain [32]. The retrospective NESARC study found that women with alcohol abuse had significantly shorter time from the start of abuse to the debut of MDD or dysthymia, compared to men [36]. In the Canadian sub-study [39] women who drank more than 5 drinks at one occasion were more prone to develop MDD than men with the same habits. Women aged 19-30 seemed particularly vulnerable.

Similar results were reported from the Health Survey of England (n=5828) where intensity of drinking rather than frequency promoted self-assessed depression in both genders, but stronger in women when control was made for age, socioeconomic factors and health conditions [40].

Females are considered more vulnerable for alcohol damage than men and at higher risk of developing mood disorders [41-43]. Hence it seems reasonable to believe that females with alcoholism are more prone to develop mood disorder than men. However, although the results from the reviewed studies do not consistently confirm such a conclusion, some of the results point in that direction.

Temporal sequence of events

In order to evaluate the effect of alcohol on mood disorders studies should be designed so that it is possible to observe how alcohol and depression relate in time. To be considered a possible cause, alcohol should precede mood disorder. Ideally the outcome variable should be first incidence mood disorder. Otherwise earlier episodes of depression could have caused both the alcohol disorder and the following depressive episode.

Two studies used first incidence mood disorder as an outcome; two three of them with significant, positive associations between alcohol and later depression; The Lundby Study and The Christ Church. In the latter, follow-ups were close in time, enabling the assessment of first incidence mood disorder to be more accurate than in studies with longer time between follow-ups. First incidence outcome was also applied in the prospective NESARC study, in which the relation between alcohol and mood disorder/depression became non-significant when controlling for certain personality disorders [37].

There were four studies that used Mood Disorder, mostly MDD, as an outcome (not necessarily first incidence estimates), of which three showed positive results [34-36]. One explanation to these results could be that we are dealing with persons predisposed for depressive episodes, and that alcohol triggers periods of depressions. However, a relapse into mood disorder does not exclude that there were other causes than alcohol behind the relapse.

Strength of association

Taking into account the different methods used in the reviewed studies, the strength of the associations between alcohol and mood disorders are quite moderate. The evaluation is difficult to make because of methodological problems regarding diagnostics. The assessments of AUD according to DSM-IV rely in some studies solely on the users' own reports. These may not be accurate. Furthermore, a diagnosis of mood disorder could be missed due to concomitant alcohol use or

Studies Criteria of hill	Lundby Study [32]	Christ-church Study [33]	Children of Community Study [34]	NLEAS [35]	NESARC (Falk et al.) [36]	NESARC (Grant et al.) [37]	NPHS [38]
Consistency of the association	+	+	+	+	+	-	-
Temporal sequence of events-First incidence mood disorder as outcome	Yes	Yes	No	No	No	Yes	No
Strength of relation	OR ¹ :1.56 (95% CI:1.02-2.38) ² OR:1.67 (95% CI: 1.14-2.45) ³ (~AUD ⁵ - ~MDD ⁶)	OR:1.66 (95% CI: .08 -2.55) (AUD-MDD)	OR:1.42 (95% CI: 1.66 -1.72) (heavy cumulative alcohol use-MDD)	OR: 4.2 (95% CI: 2.82-6.28) (AD7-MDD)	APR ⁴ : 2.4 SE: 0.18 (AA6 -MDD) ##### SE: 0.33 (AA-Dysthymia)	OR : 1.1 (99% CI: .70-1.63)(AA-MDD) OR : 0.9 (99 % CI: .48-1.83)(AD-MDD)	Not reported
Dose response	Not studied	Not studied	Not studied	Studied but not found	AA led to higher risk than AD in certain Mood Disorders	AD led to higher risk than AA in Bipolar I & II	A positive trend was found in both genders
Specificity	-----	(+)-----	-----	-----	-----	-----	-----

¹Odds Ratio; ²1947-1997 cohort; ³1957-1997 cohort; ⁴APR=Alcohol Primary Ratio; ⁵AUD=Alcohol Use Disorder; ⁶AA=Alcohol Abuse; ⁷Alcohol Dependence; ⁸MDD=Major Depressive Disorder

Table 3: Reviewed longitudinal population studies of alcohol consumption/Alcohol Use Disorders and Mood Disorders acc. to DSM-IV. The results are presented according to the criteria of Hill (except for the criteria of biological evidence).

recall bias. Use of collateral information, as was the case in the Lundby Study [32], the Christ Church Study [33] and the Children of The Community Study [34], could contribute to the accuracy of diagnostics and thereby to more reliable estimations of the associations.

In addition, exclusion of participants, in particular selected groups such as prisoners, hospitalized persons, deported, and deceased, as was the case in the NESARC Study (29.8 % at wave 1 and 13.3% at wave 2) [36,37], might have influenced the strength of associations.

Dose-response relationship

The retrospective NESARC study found that abuse, but not dependence significantly associated with later mood disorder [36]. One explanation to these findings could be that alcohol dependence can lead to brain damage (dementia) disabling persons with dependence to experience depression in contrast to abusers with more preserved brain function. However, it should be taken into account that the outcome variable, in contrast to the other reviewed studies, also included alcohol depressive withdrawal syndromes.

In the retrospective NLEAS [35] men with withdrawal depressive syndrome acc. to DSM-IV were excluded. Those who had been alcohol-dependent were more prone to develop MDD than former non-dependent drinkers. When first, abusers and thereafter, all subjects, with any alcohol intake the last 12 months were withdrawn, the results became almost the same; contrary to what could be expected if a dose-response relationship existed.

The prospective NESARC study found a non-significant positive association between AA and Bipolar disorder II; an association that grew stronger but was still non-significant when it came to AD and Bipolar disorder II. No such association was found between AUD and other MD including Bipolar I [37].

Lack of a confirmed dose response relationship does not exclude that there actually exists a cause-effect relation between alcohol and mood disorder. Moreover, there are certain problems when 8909 estimating a dose-response relationship between alcohol and mood disorder. The limit between AA and AD acc. to DSM-IV might not be optimal for demonstrating a dose-response relation.

When in a subsample of the NESARC survey the dichotomous

AU and AA criteria of DSM-IV were substituted by a dimensional approach estimating alcohol disorder severity as a count of three abuse and all seven dependence criteria acc. to DSM-5, alcohol severity significantly predicted first incidence depressive disorders in a linear fashion (odds ratio 1.14, 95% CI 1.06-1.22) after 3-year follow-up. Analyses adjusted for risk factors of depression such as smoking status, general vulnerability factors (family history of depressive disorders and alcohol dependence, and childhood trauma), psychiatric co-morbidity (conduct disorder and anxiety disorder) and sub threshold depressive [44]. However, the study is based on the assumption that one criteria of abuse is as important as one criteria of dependence. Furthermore, the groups with 9 and 10 criteria had a very high risk of depression, although they represented only 18 of the total 27571 individuals, whereas those 34 individuals, who met 8 criteria, had the lowest risk of all.

A more appropriate method for showing a dose-response relationship would be to use estimates of the amount of alcohol consumed during a defined time-period [45-47]. The method was assessed in the prospective national population health survey where individuals, in particular women, who had more than 5 drinks at one single occasion, showed a trend towards higher incidence of MDD compared with those having 5 or less drinks on one occasion [38]. In a sub-study, analyzing genders separately and stratifying by age, a positive dose-response relationship was found between the amount of alcohol consumption and the incidence of MDD in both men and women, particularly in women aged 19-30 [39].

Specificity of the association

According to Flensburg-Madsen AUD is neither a necessary nor a sufficient condition for developing mood disorder [48]. However, other existing risk factors do not exclude that alcohol is another one. Psychiatric disorders probably have multiple valid explanations [49]. Alcohol problems as well as child neurosis and antisocial personality disorder significantly predicted later depression in the reviewed Lundby Study [32].

The evaluated studies adjusted to a varying degree for psychiatric comorbidity, heredity, other drug use and for social and economic factors. One of them found a residual causal association between alcohol and mood disorder, after control was made for shared heredity,

environmental factors and for the opposite pathway (that depression causes AUD), suggesting that alcohol use has a specific effect on the development of mood disorder, in particular major depression [33].

There are certain difficulties when analyzing the specific effect of alcohol. Social problems, such as loss of work, legal problems, and family conflicts including loss of the beloved one, are consequences of drinking and included in the DSM-IV criteria of AUD. However, social problems are themselves predictors of depression [50] and were not always fully accounted for in the reviewed studies, making it difficult to evaluate the specific influence of alcohol on mood disorders.

According to Boden and Fergusson there is evidence in the literature of a causal linkage between alcohol use disorders and major depression, and there is need for further research in order to clarify the nature of this causal link [51].

Biological plausibility of the observed association

Biological evidence for an etiological association between alcohol and mood disorder was not possible to study in the reviewed studies. Other ways of studying this matter would be through experimental animal studies since controlled, randomized trials are unethical to perform.

Conclusion

When reviewed according to the criteria of Hill, the majority of studies indicated that alcohol may cause or trigger mood disorders in the general population. The specific influence of alcohol on mood disorder needs to be clarified further by the amount of alcohol consumed, and by taking confounders, such as social factors and other vulnerability factors of mood disorders into account. Biological evidence could be examined by experimental animal studies.

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