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**Abstract**

**Aims:** To examine the literature on the associations between alcohol use disorders (AUD) and major depression (MD), and to evaluate the evidence for the existence of a causal relationship between the disorders.

**Methods:** PsycInfo; PubMed; Embase; Scopus; ISI Web of Science database searches for studies pertaining to AUD and MD from the 1980 to the present. Random effects models were used to derive estimates of the pooled adjusted odds ratios (AOR) for the links between AUD and MD among studies reporting an AOR.

**Results:** The analysis revealed that the presence of either disorder doubled the risks of the second disorder, with pooled AORs ranging from 2.00 to 2.09. Epidemiological data suggest that the linkages between the disorders cannot be fully accounted for by common factors that influence both AUD and MD, and that the disorders appear to be linked in a causal manner. Further evidence suggests that the most plausible causal association between AUD and MD is one in which AUD increases the risk of MD, rather than vice-versa. Potential mechanisms underlying these causal linkages include neurophysiological and metabolic changes resulting from exposure to alcohol. The need for further research examining mechanisms of linkage, gender differences in associations between AUD and MD, and classification issues was identified.

**Conclusions:** The current state of the literature suggests a causal linkage between AUD and MD, such that increasing involvement with alcohol increases risk of depression. Further research is needed in order to clarify the nature of this causal link, in order to develop effective intervention and treatment approaches.

Key words: alcohol, alcohol use disorder, major depression, literature review

In recent decades, a large number of studies have examined the comorbidities of a range of mental disorders (1-3). One issue that has been examined in detail is the association between alcohol use disorders (AUD) and major depression (MD) (4-11), with a wide range of epidemiological and clinical studies suggesting close linkages between the two disorders. The purpose of the present paper is to review the evidence concerning the links between AUD and MD, and to evaluate claims concerning possible causal relationships between the two disorders.

For the purposes of the review, the terms “alcohol use disorder” (AUD) and “major depression” (MD) will be employed to refer to the study of the association between alcohol use and depression. However, the studies described herein have used a wide variety of measures of alcohol use, misuse, and alcohol-related problems, as well as a variety of measures of depressive symptoms, which may be the source of at least some of the heterogeneity amongst the findings of various studies (12). In general, the research question addresses the issue of whether individuals who, irrespective of measurement, show *greater involvement in alcohol consumption* are also more likely to report *greater levels of depression*.

## **Methods**

### *Criteria for studies chosen for review*

The present paper examines two sets of information, chosen using differing criteria, which are detailed below. Studies were selected by author JMB and cross-checked by author DMF.

### *Criteria for meta-analysis selection*

Studies chosen for the meta-analysis of AUD-MD linkages were chosen according to the following criteria:

- i. Longitudinal or cross-sectional epidemiological studies with  $n \geq 400$ ;

- ii. Studies reporting an Adjusted Odds Ratio (AOR) for the links between AUD and MD. One important study (13) was included despite reporting an unadjusted odds ratio.

#### *Criteria for narrative review selection*

The studies included in the meta-analysis were also used in the narrative review. In addition, further studies were included and cited in the narrative review according to the following criteria:

- i. Studies that were related to the specific point in question (e.g. “alcohol induced depression”) that were found via use of the primary search terms;
- ii. Studies that have cited the studies used in the meta-analysis.

#### *Information sources*

Information sources used in searches included the following electronic bibliographic databases: PsycInfo; PubMed; Embase; Scopus; ISI Web of Science. In addition, reference lists and bibliographies from cited documents were used to handsearch for additional articles. The search terms “alcohol” and “major depression” were used, and limits were placed such that no study prior to 1980 was included.

#### *Data items*

Data taken from the studies for the purposes of meta-analyses and reporting included: number of participants; nature of the sample (e.g. NLSY data); conceptual model employed; measures of predictors and outcomes; and AORs for outcomes. In all cases, these data were taken as reported in the original articles; no AORs were calculated by the present authors.

### *Analyses and summary measures*

Estimates of the AOR pooled across studies were obtained from the use of meta-analytic methods using a random effects model (14). This procedure was undertaken twice: first, for studies predicting MD as a function of AUD; and second for studies predicting AUD as a function of MD. In these models, a pooled estimator (B1i) for the ith outcome (AUD or MD) was obtained from a weighted average of the study specific parameters ie  $B1i = \sum_j w_{ij} B1ij / \sum_j w_{ij}$  where  $w_{ij} = 1/(t_i^2 + s_{ij}^2)$  was an estimator of the inverse variance of the study specific parameter under a random effects model;  $s_{ij}^2$  was the estimated variance of the sample specific parameter; and  $t_i^2$  was an estimator of the between studies variance for outcome i derived using the method of DerSimonian and Laird (15). The standard error estimate corresponding to the pooled parameter was given by  $s.e. (B1i) = 1 / (\sum_j w_{ij})^{1/2}$ . In addition, for the pooled data, Cochran's Q tests (16) were used in all cases to test for non-homogeneity of regression parameters across studies. A p-value <.05 on Cochran's Q was taken as indicating significant heterogeneity of parameter estimates.

## **Results**

### *Evidence for the associations between AUD and MD*

Table 1 presents a summary of the longitudinal and cross-sectional studies that have reported adjusted odds ratios (AOR) for the associations between AUD and MD (13, 17-30). The criterion for choosing the studies that appear in the Table was that the studies reported an AOR, for the purposes of computing an estimate of the pooled AOR across studies. With one exception (13), the studies have controlled for a range of covariate factors, including sociodemographic background, family functioning, individual behavioural factors, and stressful life events. The Table is further subdivided into studies in which MD was used as the outcome measure and studies in which AUD was the outcome measure, with studies that were intended to simply measure an association between the two disorders noted.

The Table shows that the AORs ranged from 1.03 to 4.21 for studies using MD as the outcome measure, and from 1.19 to 4.1 for studies using AUD as the outcome. Estimates of the pooled AOR suggest that for both series of studies the pooled AOR was between 2.00 and 2.09. At the same time, the results of the Cochran's Q tests showed that there was strong evidence in both series of AORs of significant ( $p < .0001$ ) between-study homogeneity, suggesting that estimates of AOR are sensitive to variations in study design.

There may be a number of factors contributing to the heterogeneity amongst the studies chosen for the meta-analysis. First, it should be noted that there were wide variations in the measurement of AUD, with measures spanning DSM (31) alcohol abuse and alcohol dependence, and measures of frequency and volume of alcohol consumption. Second, there was also considerable variation in measures of MD, ranging from meeting DSM criteria for MD to MD symptom scores. In both cases, there were differences across studies in the instruments used to assess whether individuals met diagnostic criteria for AUD and MD. For example, some studies using CIDI (32) items to assess the disorders, whereas others used AUDADIS-IV (33). Furthermore, there was considerable variation in the time frame for the measurement of each disorder, ranging from "recent" or "current" to "lifetime disorder". Irrespective of these differences in measurement, however, the findings of this analysis were congruent with the view that after adjustment for covariate factors, the presence of either AUD or MD was associated with a doubling of risk of the other disorder, indicating a moderately strong association between AUD and MD.

INSERT TABLE 1 HERE

## **Narrative Review**

### *Addressing questions of causality*

The evidence described above clearly shows a moderately strong association between AUD and MD, which is robust to variations in both study design and measurement methods. There are two

general explanations for the observed associations between AUD and MD. First, it could be argued that both AUD and MD are caused by common underlying genetic and environmental factors that jointly increase the risk of both disorders. Second, it could be argued that AUD and MD are related in a causal manner, such that AUD increases the risk of MD, or that MD increases the risk of AUD.

These explanations can be tested using epidemiological data by controlling for a range of sources of potential confounding between the two disorders. Approaches such as this have been used in a number of studies that have found evidence of a persistent association between AUD and MD even after controlling for confounding (13, 17-30, 34-40). For example, Hasin et al (25), using data from a large US study, found that lifetime AUD and MD were significantly associated after controlling for a wide range of sociodemographic factors and other psychiatric and substance use disorders. Also, Paljarvi and colleagues (27), using longitudinal data, reported a significant association between high levels of alcohol consumption and MD symptom scores three years later after controlling for a range of socioeconomic factors, family history, negative life events, personality factors, and social support. The weight of the evidence from epidemiological studies of the links between AUD and MD suggest that confounding alone cannot explain the observed patterns of association between the disorders.

One common criticism of epidemiological studies is that they cannot control for all possible sources of confounding, thus compromising the validity of causal inferences drawn from epidemiological data (41). However, several studies that have observed residual associations between AUD and MD have used advanced methods for controlling confounding in the association between alcohol and MD, including: the use of twin data (28, 34, 35); and controlling for non-observed confounding via the fixed effects regression model (23). For example, Sihvola et al (28), using data from a longitudinal twin cohort in Finland, found that depressive disorder at age 14 was significantly associated with “frequent alcohol use” at age 17.5, after controlling for common genetic and environmental factors, and other psychiatric and substance use disorders. Also, Fergusson et al (23), using data from a longitudinal birth cohort, controlled for sources of fixed non-

observed confounding in the associations between AUD and MD via the use of conditional fixed effects regression models. The results of these analyses revealed a persistent significant association between the AUD and MD from late adolescence to early adulthood, net of both non-observed confounding and observed covariate factors. It is clear that the most parsimonious conclusion, on the basis of the present evidence, is that there is a causal relationship between AUD and MD.

### *The direction of causality*

There are three possible descriptions of the potential causal relationships that may be present in the association between AUD and MD: a) AUD causes MD; b) MD causes AUD (referred to as the “self-medication” hypothesis (42)); and c) a reciprocal causal relationship between AUD and MD, such that each disorder increases the risk of the other disorder simultaneously.

A number of epidemiological studies have provided evidence pertaining to this question using retrospective recall of disorder amongst individuals identified as either having an AUD or MD (13, 17-21, 24-26). For example, Hasin et al (25) used data from the 2001-2002 NESARC survey in the United States which asked people to retrospectively recall lifetime symptoms of both AUD and MD. The study found that individuals meeting criteria for MD were significantly more likely than those not meeting criteria for MD to also meet criteria for AUD. However, this and a number of other of these studies were intended to measure the associations between AUD and MD, rather than examine causal hypotheses (13, 20, 24, 25). An alternative approach was illustrated by Bazargan-Hejazi and colleagues (17), in a study of randomly-selected patients admitted to a hospital Emergency Department, who used retrospective recall for symptoms of AUD and a measure of “recent symptoms” of MD. They found that those reporting DSM alcohol abuse within the previous 12 months were significantly more likely to have clinical significant “current depression” scores. While this and similar studies (18, 26) have the advantage of imposing a time frame on the assessment of AUD and MD, one of the major issues in the interpretation of studies employing retrospective recall is that it is possible that the individual’s current mental state may affect his or

her recollection of symptoms and events in the past, potentially inflating estimates of association between an earlier disorder and a later disorder (43).

A further series of epidemiological studies have attempted to address the question of causality by using a natural history approach that assesses which disorder was likely to have occurred first (22, 35, 44, 45). For example, Falk et al (22) used retrospective recall data from the NESARC to determine whether individuals with co-occurring AUD and MD had experienced AUD or MD first, and used these data to derive estimates of the causal associations between AUD and MD, and the causal associations between MD and AUD. On the basis of this evidence, the researchers concluded that the causal links from AUD to MD, and from MD to AUD, were both relatively weak, but comparable in magnitude. However, as with studies noted above, one major limitation of this design is the use of retrospective recall, and the extent to which current mental states may have affected recall of past events. Prospective data from a Danish heart study were used by Flensbourg-Madsen and colleagues (45), who linked hospital register data to examine the causal relationships between AUD and MD, and between MD and AUD. On the basis of this evidence, the researchers concluded that the causal role of AUD in MD was stronger than the causal role of MD in AUD. However, one major limitation of this study, and others using a natural history approach, was that the studies were unable to control for the possibility of reverse causality, in which AUD and MD are reciprocally related to each other by a feedback loop in which alcohol increases risks of MD, while at the same time the onset of MD leads to an increased consumption of alcohol.

One way of addressing this issue, using prospectively-collected data, is through the use of structural equation models that permit reciprocal relationships between AUD and MD, and using these models to provide a guide to likely patterns of causation. This approach was used by Fergusson et al (23), who used data from a longitudinal birth cohort with three repeated measurements of AUD and MD at ages 18, 21, and 25. In the first part of their analyses, the results of analyses controlling for non-observed fixed confounding factors suggested that it was possible

that: a) AUD caused MD; b) MD caused AUD; or c) AUD and MD had a reciprocal causal relationship in which each caused the other. However, the results of the structural equation modelling used in the study showed that a structural model with causal pathways leading from AUD to MD was a better fit to the data than either of two alternative models; one in which MD led to AUD; and a further model in which there were reciprocal causal pathways between AUD and MD such that each disorder played a causal role in increasing risks of the co-occurring disorder. Fergusson et al argued that the most parsimonious conclusion was that AUD played a causal role in increasing risks of MD, but not vice-versa.

#### *Explanations for the causal links between AUD and MD*

There are several possible explanations for the factors and processes that may give rise to the causal link between AUD and MD. One possible explanation is that AUD plays a causal role in the aetiology of MD due to the effects of alcohol misuse on an individual's social, economic, and legal circumstances. Alcohol misuse can frequently lead to disruptions to family and social life, difficulties in employment, legal troubles, and compromised physical health (46), and it could be argued that these social difficulties are the source of the linkages between AUD and MD. However, studies (23, 27, 28) have addressed this issue by accounting for the possible influence of a range of life circumstances in the causal link between AUD and MD, and have found that these links persist even after controlling for social and environmental factors that may be related to both AUD and MD.

A second possible explanation for the causal linkages between AUD and MD is that the two disorders are linked by genetic factors relating to neurotransmitter functioning, increasing the risk of MD in the presence of AUD. Several studies have examined this question, finding evidence of increased risks of both AUD and MD amongst individuals with particular genotypes (47-53). For example, studies by Wang et al (53) and Luo et al (50) found that particular variants of the

muscarinic acetylcholine receptor M2 (CRHM2) gene are related to increased risks of both AUD and MD.

A third explanation for the causal linkages between alcohol and depression is that alcohol exposure may cause metabolic changes that also act to increase the risk of MD. For example, McEachin and colleagues (54), using an integrated bioinformatics approach, found evidence that exposure to ethanol led to reductions in the production of MTHFR (Methylenetetrahydrofolate Reductase), an enzyme related to folate metabolism. Reduced folate levels have in turn been linked to increased risks of MD, suggesting a possible causal link between AUD and MD via reduced MTHFR production. A further study by Sjöholm and colleagues (55) found that individuals with a particular genotype related to circadian rhythms were at greater risk of co-occurring AUD and MD. The authors argued that alcohol use alters circadian rhythms and metabolic patterns in individuals with this particular genotype, leading to an increased risk of MD.

#### *Issues arising in the study of the links between AUD and MD*

In examining the research on the associations between AUD and MD, several issues arise related to questions of causality, the extent to which findings of causality are generalizable across populations, and questions of classification. Each of these issues will be examined briefly below.

One issue related to the causal role of AUD in MD is that a number of researchers have noted that it may be possible to identify individuals who report self-medication of MD with alcohol. Several studies have identified the role of “motives for drinking” in increasing risks of AUD, and have shown that individuals who intentionally drink to reduce stress or improve mood may be treating MD via alcohol consumption (56-58), thus suggesting a causal pathway from MD to AUD for these individuals. However, it should also be noted that these studies were not able to assess possible reverse causal processes in the association between drinking motives, MD and AUD, in which the original onset of MD may have been precipitated by AUD. Furthermore, given the fact that alcohol consumption is widely viewed as having mood-enhancing properties (59), if it were the

case that alcohol expectancies were responsible for the links between MD and AUD, it is highly unlikely that analyses would have revealed evidence of a causal pathway from AUD to MD (23).

A second related issue is that a number of researchers have argued that there may be gender differences in the associations between AUD and MD. For example, Strandheim et al (60), in a study of Norwegian adolescents, found an association between alcohol and symptoms of depression for females, but not for males. Similar findings were reported by Fleming et al (61) in a study of US adolescents. Also, using a multilevel modelling technique to examine trajectories of AUD and MD over time, Marmorstein et al (62) found reciprocal linkages such that MD predicted AUD and AUD predicted MD. These linkages were stronger for adolescent girls rather than adolescent boys, but the magnitude of the gender difference decreased over time. In addition, a series of studies using data from a large Canadian sample (37-39) concluded that the link between MD and AUD applied only to females. On the other hand, Fergusson et al (23), using repeated measures of AUD and MD from late adolescence to early adulthood, found no evidence of significant gender differences in the associations between AUD and MD. One possible reason for these discrepant findings is that it has been shown that females are at significantly greater risk than males of MD during adolescence (63), and there is emerging evidence that females may progress more rapidly than males from alcohol use to AUD (64, 65). Therefore, it may be possible that gender differences are more likely appear in data obtained from adolescent or cross-sectional samples, and do not appear in older samples, or samples employing repeated measures. Such a view is supported by the research of Marmorstein et al (62), who found that the gender differences in the associations between AUD and MD decreased as age increased.

A third issue is whether there should be a classification pertaining to alcohol-induced MD, separate to that of MD that is unrelated to AUD (11, 66-68). Schuckit and colleagues (68) have argued that, on the basis of demographic differences between those individuals with alcohol-related MD and “independent MD”, a separate classification for MD unrelated to alcohol use would be of benefit in terms of diagnosis and treatment. On the other hand, it has also been argued that, since

the symptoms of MD generally do not differ according to the cause or precipitating event, there would be little benefit in abandoning the “cause neutral” approach to MD (69, 70).

A final issue concerns diagnostic difficulties in the assessment of AUD and MD, particularly amongst those with high levels of AUD and MD symptoms. For example, Hasin and Katz (71) argued that “lifetime” measurement of symptoms may be plagued by poor recall, with the result that the associations between the two disorders may be underestimated. In addition, Samet et al (72) pointed out that DSM classifications (from DSM-IV onward) differentiate between “primary” disorders and “substance-induced” disorders; failure to distinguish between these, or failure to account for “substance-induced” disorders, create difficulties in ascertaining the true magnitude of the associations between AUD and MD. More generally, however, it has been argued that the use of diagnostic classifications, rather than symptom counts or other indicators of dimensionality may result in misestimation of the true associations between disorders (73), including AUD and MD.

#### *Clinical and public health implications*

If AUD increases the risk of MD, as the evidence above suggests, then there are several clinical implications arising from these findings. The most significant of these is that, on the assumption of a causal process of AUD leading to MD, then it can be concluded that some percentage of cases of MD may in fact remit upon the treatment of AUD. Indeed, a number of studies have shown that treatment of AUD results in a reduction of MD symptoms (74-80), suggesting that treatment of MD should include assessment and treatment of AUD. An additional clinical implication is that, because individuals have reported using alcohol to self-medicate symptoms of depression (56-58), it may be the case that individuals presenting with MD may not experience complete remission of MD if treated for AUD. This suggests that a combination of treatments for AUD and MD may be a more promising approach for individuals presenting with both disorders, and who report self-medication.

The public health implications of a causal link from AUD to MD suggest that a significant portion of the burden resulting from MD in the population may be attributed to the misuse of alcohol. Indeed, rough estimates prepared for the purposes of the present article, using data from the Christchurch Health and Development study suggest that up to 10% of the overall burden of MD may be attributable to AUD.

#### *Directions for future research*

Although the preceding review of the links between AUD and MD has presented evidence of a possible causal link between the disorders in which AUD leads to MD, there remains significant scope for future research into the association between AUD and MD. First, although there is evidence of neurophysiological and metabolic links between exposure to alcohol and MD (47-55), the evidence is somewhat limited in scope. For example, while there have been studies linking AUD and MD via physiological pathways, there is as yet little evidence as to the extent of alcohol exposure required to activate these links, and whether there are age-related changes in the neurophysiological and metabolic links between these disorders. Further research is necessary to elucidate these potential pathways leading from AUD to MD.

A second avenue for further research may be to examine more fully the issue of gender differences in the associations between AUD and MD. As noted above, while some studies have found evidence for gender differences (60, 61), others have not (23), and there is at least limited evidence to suggest that gender differences in the association vary according to age (62). Given that rates and timings for AUD and MD vary according to gender (63-65), additional research is needed to understand more fully the nature of any potential gender differences in the associations between these disorders.

Finally, additional avenue for further research in the links between AUD and MD are possible cohort effects and cultural differences in the linkages between the two disorders. There is now considerable evidence that alcohol consumption patterns display considerable change over

time (81, 82), and considerable variation across cultures (83). Furthermore, there are also considerable variations across time in the conceptualization of MD (70), as well as considerable cross-cultural variation in rates of reported MD (84). Further research in this area will deepen our understanding of the links between AUD and MD, and assist in the development and implementation of treatment and intervention services that may be used to adequately address these disorders.

*Conflicts of interest statement*

The authors declare no conflicts of interest.

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Table 1. Summary of epidemiological studies used in the meta-analysis of the associations between AUD and MD

Study	Sample	AOR (95% CI) MD as outcome	AOR (95% CI) AUD as outcome	AUD Measure	MD Measure
Bazargan-Hejazi et al (17)	Random ED patients (n = 412)	2.58 (1.51-4.40)	NR	12 months DSM alcohol abuse	≥ 16 for “recent symptoms” on CES-D depression symptom scale
Brook et al (18)	Randomly selected individuals (n = 975)	2.09 (1.41-3.09)	NR	Any alcohol use at previous assessment	DSM MD 5 years later
Crum et al (19)	Sample interviewed as children in 1985/86 and as adults in 2000/01 (n = 1692)	NR	2.07 (1.31-3.26)	Lifetime DSM alcohol dependence by adult interview	High level of depressed mood (3 of 4 major symptoms)
De Graaf et al (20) <sup>2</sup>	1996 NEMESIS sample (n=7076)	NR	Males 2.6 (1.9-3.5) Females 4.1 (2.6-6.5)	Lifetime DSM alcohol dependence	Lifetime DSM MD
Epstein et al (21)	2006 California Behavioral Risk Factor Surveillance Sample (n=5692)	2.90 (1.21-6.95)	NR	Past month heavy drinking (binge on 5 or more occasions)	≥ 10 for “symptoms previous 2 weeks” on PHQ-8 depression scale
Falk et al (22)	2001-02 subsample of NESARC sample (n=19 504)	1.03 (0.77-1.39) (if AUD primary)	1.19 (0.92-1.54) (if MD primary)	Lifetime DSM AUD	Lifetime DSM MD
Fergusson et al (23)	Longitudinal birth cohort (n=1003 to 1025)	1.66 (1.08-2.55)	1.59(1.03-2.46)	DSM AUD ages 18,21,25 (pooled)	DSM MD ages 18,21,25 (pooled)
Grant & Harford (24) <sup>2</sup>	1992 NLAES sample (n=42 862)	NR	3.56 (3.29-3.86)	Lifetime DSM AUD	Lifetime DSM MD

Study	Sample	AOR (95% CI) MD as outcome	AOR (95% CI) AUD as outcome	AUD Measure	MD Measure
Hasin et al (25) <sup>2</sup>	2001-02 NESARC sample (n=43 093)	NR	1.20 (1.09-1.41)	Lifetime DSM AUD	Lifetime DSM MD
Hasin & Grant (26)	1992 “former drinkers” subsample (< 12 drinks consumed in prior 12 months) of NLAES sample (n=6050)	4.21 (2.82-6.28)	NR	Past DSM alcohol dependence	Current (12 mos) DSM MD
Kendler et al (13) <sup>2</sup>	Female twin cohort (n = 2163)	3.55 (2.48-5.08) <sup>1</sup>	NR	Lifetime DSM alcohol dependence + tolerance	Lifetime DSM MD
Paljarvi et al (27)	Finnish two-wave cohort (n=15 926)	1.14 (1.00-1.30)	NR	Highest quintile of alcohol consumption	BDI score ≥ 10
Sihvola et al (28)	Finnish twin cohort (n=1545) two waves 3 yrs. apart	NR	2.14 (1.00-4.57)	Current frequent alcohol use (≥ 2x / week) at T2 (age 17.5)	Current DSM depressive disorder age 14 (T1)
Skogen et al (29)	HUNT-2 (Norway) sample (n=38 930)	1.25 (0.99-1.57)	NR	Current highest 5% on alcohol consumption	Current HADS score ≥ 8
St John et al (30)	Randomly-selected Canadians aged 65+ (n = 1028)	1.93 (1.14-3.28)	NR	Current alcohol misuse score ≥ 1 on CAGE	CES-D score ≥ 16 current
<b>Pooled AOR estimate (95% CI)</b>		2.00 (1.19-3.35)	2.09 (1.29-3.38)		

Note: NR = not reported

<sup>1</sup> Unadjusted OR (AOR not reported)

<sup>2</sup> Study was intended to measure association, rather than examine causal hypotheses