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Can a rapid measure of self-exposure to drugs of abuse provide dimensional information on depression comorbidity?

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Abstract

Background and Objectives—Addictions to heroin or to cocaine are associated with substantial psychiatric comorbidity, including depression. Poly-drug self-exposure (e.g., to heroin, cocaine, cannabis or alcohol) is also common, and may further affect depression comorbidity.

Methods—This **case-control study** examined the relationship of exposure to the above drugs and depression comorbidity. Participants were recruited from methadone maintenance clinics, and from the community. Adult male and female participants (n=1,201) were ascertained consecutively by experienced licensed clinicians. The instruments used were the SCID-I, and Kreek-McHugh-Schluger-Kellogg (KMSK) scales, which provide a rapid dimensional measure of maximal lifetime self-exposure to each of the above drugs. This measure ranges from no exposure to high unit dose, high frequency, and long duration of exposure.

Results—A multiple logistic regression with stepwise variable selection revealed that increasing exposure to heroin or to cocaine was associated greater odds of depression, with all cases and controls combined. In cases with an opioid dependence diagnosis, increasing cocaine exposure was associated with a further increase in odds of depression. However, in cases with a cocaine dependence diagnosis, increasing exposure to either cannabis or alcohol, as well as heroin, was associated with a further increase in odds of depression.

Discussion and Conclusions—This dimensional analysis of exposure to specific drugs provides insights on depression comorbidity with addictive diseases, and the impact of poly-drug exposure.

Scientific Significance—A rapid analysis of exposure to drugs of abuse reveals how specific patterns of drug and poly-drug exposure are associated with increasing odds of depression.

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Introduction

Addictions to heroin or cocaine are associated with psychiatric comorbidity, especially depression, based primarily on the study of categorical diagnoses (1, 2). This comorbidity affects the course and severity of individual patients' conditions (1). Preclinical literature shows that the pattern, duration and amount of exposure to specific drugs of abuse can affect behavioral and depressant-like effects, and underlying neurobiological changes (3–7). The underlying variables which affect comorbidity of addictive diseases and depression are not well understood, and may include genetic, epigenetic and environmental factors, as well as neurobiological changes that occur due to exposure to specific types of drugs of abuse (8, 9).

Poly-drug exposure in persons with heroin or cocaine addiction diagnoses is common, and can include exposure to other substances, principally cannabis and alcohol. The impact of specific types of poly-drug exposure on depression-like effects has been studied in a limited number of preclinical studies (10, 11), therefore our understanding of the neurobiology of this phenomenon is limited.

Recent research in psychiatry and addiction has placed emphasis on "dimensional" analysis of bio-behavioral phenomena, in addition to categorical diagnoses (12–14). A validated set of scales, the Kreek-McHugh-Schluger-Kellogg (KMSK) scales, provide a rapid dimensional measure of maximal lifetime self-exposure to specific drugs in humans, ranging from no exposure to heavy exposure (15, 16). Some studies have examined dimensionally how drug exposure and poly-drug exposure are associated with depression, in diagnosed participants (17–19). Some of the instruments used in these studies could not be easily applied in the field, due primarily to their length. The KMSK scales thus potentially provide the opportunity to rapidly examine the relationship of drug exposure and depression comorbidity, in a dimensional manner. The main hypothesis of this study was that maximal exposure to specific drugs of abuse, as well as specific patterns of poly-drug exposure, will have characteristic association with major depression comorbidity.

Methods

This was a **case-control study**, with two consecutive cohorts of sequentially ascertained participants, examined as outpatients in a research hospital. **"Cases"** herein are participants with an addictive disease diagnosis (DSM IV criteria), and **"controls"** are participants without an addictive disease diagnosis. We further stratified all participants (cases or controls) by the presence of depression diagnosis. This is a secondary analysis of participants systematically ascertained for genetic association studies (20).

In this secondary base study, cases and controls were ascertained sequentially (cumulatively sampled) from several methadone maintenance clinics, and also from the community, within a large urban area (21) (Table 1).

Recruitment, inclusion and exclusion criteria

Participants were recruited through Institutional Review Board (IRB)-approved posted notices and newspaper advertisements in the area. **Study Inclusion criteria:** Participants

were required to be ≥18 years of age, competent to understand study procedures, and to understand and sign the informed consent in English. **Study Exclusion criteria:** Participants with uncontrolled schizophrenia or other psychotic mental illnesses which prevented them from understanding study procedures or informed consent, were excluded (22).

Participants were excluded from the control category if they had any of the following: **a)** current or continuing abuse of alcohol, or at least one instance of drinking to intoxication during the previous 30 days, **b)** any use of illicit drugs including opiates, cocaine, and amphetamines (but excluding cannabis) during the 30 days prior to ascertainment, **c)** if they had used illicit drugs (with the exception of cannabis) for at least three times a week for a period of at least 1 month, in their lifetime, and **d)** if they had used cannabis on more than 12 days in the 30 days prior to ascertainment. The latter criterion (i.e., **d)** was originally adopted based on the approximate frequency of cannabis use in controls in this urban area (22). **Cohorts and ascertainment:** ***Cohort 1*** was composed of 617 consecutive participants (4/4/02–5/27/05). ***Cohort 2*** was composed of 579 consecutive participants (6/9/05–8/1/13).

As mentioned above, participants were also recruited through postings at several methadone maintenance clinics in New York City. Current or prior abuse of other drugs in addition to heroin or opioids was not an exclusion criterion for these participants. Participants with addictive diseases were also ascertained as part of community recruitment in the area, therefore the present cases are not only representative of participants in current or previous methadone maintenance treatment. All ascertainments were completed during a standardized face-to-face interview with a trained licensed clinician (e.g., Ph.D. Psychologist, M.D., D.O., Nurse Practitioner or Registered Nurse).

Questionnaires and diagnostic categories

Participants were ascertained with the SCID I/P (Version 2.0) (23), and with KMSK questionnaires for lifetime exposure to each of heroin, cocaine, cannabis or alcohol, during a standardized face-to-face interview (15). KMSK scores provide a rapid dimensional measure of maximal lifetime self-exposure to each substance of interest, and can be obtained within an interview in ≈15 minutes. The scale for each drug ranges in integers from “0” (no exposure/never used), to a maximal score (i.e., 13 for heroin and alcohol, 14 for cannabis and 16 for cocaine). The exposure score is a composite of estimated unit doses, frequency (e.g., times/day) and duration (e.g., in years), at the time in a participant’s life when use was the heaviest (15). Prior studies show that KMSK scores at or above a specific “cutpoint” for each drug have high concurrent validity with the respective DSM IV dependence diagnosis (15, 16).

The KMSK questionnaires also collect data on basic age trajectory of exposure, as age of first use and of heaviest use for each drug (in whole years). If a participant entered a range of ages for heaviest use, the first year in the range is taken as the onset of heaviest use, and analyzed herein. The KMSK scales are freely available at http://lab.rockefeller.edu/kreek/kmsk (13, 24, 25).

Statistical analyses

Univariate analyses—Univariate analyses, including Mann-Whitney t-tests and contingency analyses were completed with the GraphPad Prism program. The $p<0.05$ α level was set for rejection of null hypotheses.

Multiple logistic regressions—Three multiple logistic regressions were performed using Akaike Information Criterion (AIC) stepwise selection, and were performed in: **a)** all participants combined (i.e., all cases and controls), **b)** all cases with an opioid dependence diagnosis, **c)** all cases with a cocaine dependence diagnosis. The dependent variable for all regressions was presence or absence of depression diagnosis (binary). The "*glm"* function and "MASS" and "LogisticDx" packages in "R" software were used for parameter estimation, selection of variables based on the AIC, and goodness of fit evaluation. Additionally, a Monte Carlo experiment with 1,000 balanced re-samples (with equal numbers of depressed and "non-depressed" participants) was performed, with two goals: 1) to evaluate the fitted models' performance in hold-out samples; 2) to obtain more robust confidence interval estimates for the Odds Ratios of the stepwise-selected variables.

Independent variables for demographics were: gender [females as reference group], ethnicity [Caucasian as reference group], cohort [cohort 1 as reference group]) and age of ascertainment [in whole years]. In the regression which included all participants, a further binary variable was added for controls, versus cases as the reference group. **Independent variables for dimensional analysis of drug exposure were**: KMSK lifetime exposure scores for heroin, cocaine, alcohol and cannabis. As mentioned above, KMSK scores have high concurrent validity with the respective dependence diagnosis (e.g., heroin KMSK scores ≥"cutpoint" are highly predictive of the opioid dependence diagnosis) (15, 16). Thus, heroin KMSK scores were not entered as an independent variable for the regression in cases with opioid dependence diagnosis, and cocaine KMSK scores were not entered as an independent variable for the regression in cases with cocaine dependence diagnosis. This design therefore allowed a dimensional examination of the phenomenon of poly-drug exposure in participants with a specific dependence diagnosis.

Results

Sample Demographics

Age: Sample demographics are in Table 1. For both cohorts, mean age at the time of ascertainment was greater for participants with a substance abuse or dependence diagnosis (cases), versus controls (Mann-Whitney t-tests). **Gender:** For both cohorts, males with a substance abuse or dependence diagnosis (cases) were more frequent than females. **Ethnicity:** A χ^2 analysis of ethnicity across cases and controls was not significant in cohort 1, but was significant in cohort 2. These demographic variables are examined further in multiple logistic regression analyses (below).

Drug dependence diagnoses—The main DSM IV dependence diagnoses in the cases were opioid, cocaine, cannabis and alcohol dependence, and cases with multiple dependence

diagnoses to these drugs were common. Other dependence diagnoses were relatively uncommon.

Depression and other comorbid diagnoses—Other than drug abuse or dependence diagnoses, the most common DSM IV Axis I diagnosis was depression (Major Depressive Disorder), followed by anxiety. Other Axis I diagnoses were relatively uncommon. Our analysis therefore focuses on depression, the most common comorbid diagnosis. Total numbers of participants with depression diagnoses are shown in Table 1, stratified by gender (26). Due to the low numbers of controls with depression diagnoses, a basic analysis of depression diagnoses was carried out with cohorts combined. A contingency analysis for the presence of depression diagnosis with cohorts combined was significant (χ^2 =7.04; p=0.008).

Depression comorbidity and age trajectory of exposure (age of first use and age of heaviest use)—The presence or absence of depression diagnosis did not affect age of heroin first use or of heaviest use, in cases with opioid dependence diagnosis (Mann-Whitney tests, not shown). Also, the presence or absence of depression diagnosis did not affect age of cocaine first use or of heaviest use, in cases with cocaine dependence diagnosis (Mann-Whitney tests, not shown).

Multiple logistic regressions for depression diagnosis as dependent variable

Three multiple logistic regressions with stepwise selection were performed: **a)** in all cases and controls combined, **b)** in cases with opioid dependence diagnosis, and **c)** in cases with cocaine dependence diagnosis.

Independent variables for demographics

Cases versus controls: As expected based on Table 1, controls had lower odds of depression, compared to cases (participants with an abuse or dependence diagnosis), in the overall regression. **Gender:** Females had greater odds of depression than males in all regressions. **Ethnic/Cultural Groups:** African-Americans (AA) had lower odds of depression than Caucasians (Cau) in the overall regression, and in cases with opioid dependence diagnosis, but not in cases with cocaine dependence diagnosis. **Cohort effect:** Participants in cohort 2 had greater odds of depression than those in cohort 1, in all regressions. **Age of ascertainment:** Older age of ascertainment was associated with greater odds of depression only in the regression for cases with cocaine dependence.

Independent variables for dimensional analysis of drug exposure (KMSK exposure scores)—We report below data for drugs that were retained in each multiple regression model. Odds ratios for exposure were calculated per 1-unit score in KMSK scales for each drug.

Overall regression—In the overall regression with all cases and controls combined, exposure to either heroin or cocaine were each associated with greater odds of depression (see Fig. 1.

Cases with opioid dependence diagnoses—In cases with opioid dependence diagnosis, greater cocaine exposure was associated with increased odds of depression comorbidity (Fig. 1).

Cases with cocaine dependence diagnoses—In cases with cocaine dependence diagnoses, greater exposure to cannabis or alcohol, as well as heroin, were each associated with increased odds of depression (Fig. 1).

Discussion

This study provided a dimensional analysis of the relationship of exposure to specific drugs of abuse with depression comorbidity, in participants diagnosed with specific addictive diseases. Of practical relevance, KMSK scales used herein provided a rapid measure of drug exposure to several major drugs of abuse, obtained within clinical interviews.

Gender differences

Females had higher odds of depression compared to males, in the overall multiple logistic regression analysis (with all cases and controls combined). This gender difference was also observed in regressions limited to cases with opioid or cocaine dependence. The increased odds of depression in females with specific addictive disease diagnoses is consistent with previous studies (1, 27). The specific bio-behavioral factors which underlie this difference are unclear. However, gender differences have been reported in both MOPr and dopaminergic receptor populations in human PET studies (28, 29). It is also known that major neurobiological effects of drugs of abuse, including MOPr agonists, cocaine, alcohol and cannabis can be sexually dimorphic (30–33). Some preclinical studies have also reported that exposure to specific drugs of abuse has sexually dimorphic depressant-like effects (34–36). Overall, this analysis confirms that women with either opioid or cocaine dependence diagnoses have greater odds of depression comorbidity than men.

Ethnic/Cultural group differences

Participants of African-American background had lower odds of depression in the overall regression analysis, compared to Caucasians. These reduced odds of depression were also observed in African-American cases with opioid dependence diagnosis, but not those with cocaine dependence diagnosis. A lower prevalence of depression diagnoses in African-Americans has been previously reported in persons with opioid addiction (1, 37), but not necessarily in other clinical conditions (38). Such variations may be due to genetic (19), environmental, or cross-cultural differences in both reporting of symptoms and in their diagnosis (39), as well as other social and cultural factors (40, 41). Since African-Americans with cocaine dependence diagnoses did not have decreased odds of depression in this study, it may be postulated that factors in addition to environment and cross-cultural presentation or diagnosing, are involved in the differential risk of depression comorbidity.

Age trajectory of drug exposure

Ages of first use and of heaviest use of each drug are collected in KMSK questionnaires. In cases with opioid dependence diagnosis, ages of first use or heaviest use of heroin did not

differ, when stratified by presence or absence of depression. A similar finding was obtained for cocaine, in cases with cocaine dependence diagnosis. This suggests that the age trajectory of exposure to heroin or cocaine was not significantly affected by the presence of depression herein, in cases with the respective dependence diagnosis. As a limitation, we were unable to collate systematic data on the age of onset of depression, based on the instruments used herein. Therefore we cannot examine further whether the age trajectory of exposure was associated with different onset of depression. Other studies have examined the relative onset of specific addictive diseases and comorbid depression (42, 43). These prior studies showed different temporal patterns in subsets of patients (e.g., onset of addictive disease preceding onset of depression or *vice versa)*. The underlying mechanisms in these different groups are not understood. It is possible that further dimensional analyses of drug exposure may enhance these efforts in the future.

Dimensional examination of drug exposure and depression comorbidity

In all cases and controls combined, greater exposure to either heroin or cocaine exposure was associated with increased odds of depression diagnoses. Some prior studies have reported that heroin, cocaine, alcohol, cannabis exposure were a risk factor for depression comorbidity, using primarily categorical diagnoses (19, 43, 44). In the analysis with all cases and controls combined, exposure to either alcohol or cannabis were not detected as significant. However alcohol or cannabis exposure were detected as significant when the analysis was limited to cases with cocaine dependence diagnoses (see below). Practical dimensional measures such as KMSK scales may be used further to determine how exposure to specific drugs, even at “sub-diagnostic” levels, can affect odds of depression (45). Future studies with larger numbers of participants without addictive disease diagnoses may therefore utilize such an approach.

Patterns of poly-drug exposure and depression comorbidity

Poly-drug exposure is relatively common in clinical populations with addictive diseases, and may also differ depending on the stage of exposure (e.g., early vs late stages) (46). Poly-drug abuse is a challenge, both for clinical prognosis and disease nosology (47, 48). The present study provides new insight into how specific patterns of poly-drug exposure affect depression comorbidity, in persons with specific dependence diagnoses.

Thus, we found here that in cases with opioid dependence, cocaine exposure increased the odds of depression comorbidity. Dual use of heroin and cocaine is commonly reported, and is associated with greater depression comorbidity than single-drug use, based on studies using primarily categorical diagnoses (48–50). In preclinical studies, cocaine and MOPr agonists such as heroin share qualitatively similar effects with each other, for example on striatal dopamine dialysate levels, acutely or chronically (51–53). Dopaminergic systems are known to affect hedonic states, therefore it could be postulated that a shared downstream mechanism can underlie the increase in depression comorbidity in cocaine/heroin poly drug-users users.

By contrast, the regression in cases with cocaine dependence diagnosis revealed that increasing exposure to either cannabis or alcohol, as well as heroin, resulted in greater odds

of depression comorbidity. Prior clinical studies, using more complex clinical instruments, found that poly-drug exposure to cocaine or cannabis was associated with increased risk of depression, in persons with alcohol dependence (54). One intriguing conclusion from this analysis is that even a relatively small increase in exposure to cannabis or alcohol (as detected dimensionally with KMSK scales) results in further increased odds of depression, in cases with cocaine dependence. It is known that CB1 receptor systems interact with the effects of cocaine, from preclinical and clinical studies (55, 56). Alcohol and cocaine also share some downstream neurobiological effects (51).

Taken together, these findings suggest that specific types of poly-drug exposure are associated with differential depression comorbidity, likely based on the neurobiological mechanisms which are affected by specific drug combinations. Therefore, the mechanisms underlying depression comorbidity in cocaine/heroin poly-drug users are not necessarily the same as those in cocaine/cannabis poly-drug users (as an example). Recent fMRI neuroimaging studies also show that persons with a categorical depression diagnosis could be further sub-divided into several “biotypes”, based on specific neurophysiological characteristics (57).

Few preclinical studies have focused on how poly-drug exposure affects the emergence of depression-like behaviors or neurobiological changes (10, 11). Therefore knowledge on the neurobiological mechanisms of poly-drug exposure and depression is limited. Of translational value, this study indicates specific patterns of poly-drug exposure associated with increased odds in depression comorbidity, and these could be potentially modeled in future preclinical studies.

Design considerations and limitations

Only a relatively small number of controls (i.e., participants without an addictive disease diagnosis) were diagnosed with depression (1). The relatively small number of controls with depression in these cohorts may have limited our capacity to detect how “sub-diagnostic” exposure to specific drugs would affect odds of depression. This limitation may be remedied by future studies of drug exposure and depression, with a larger number of participants without addictive disease diagnoses.

Age of ascertainment was older in cases versus controls. One possible reason for this is the recruitment in long-standing methadone treatment programs, where participants may be older than volunteers from the general community. However, older age was only associated with greater odds of depression in cases with cocaine dependence diagnoses, and therefore was not likely to be a general confounder herein.

As is the case with many case-control studies, recall bias cannot be excluded herein (58). Other study designs and sampling strategies could be used to confirm and extend these studies, to address this possible concern. Likely due to the chronological aspects of these cohorts (with participants of at least 18 years of age in 2002–2013), illicit prescription opioid exposure was low, with heroin being the principally reported MOPr agonist. KMSK questionnaires also include separate forms for illicit use of prescription opioids, which may

also be associated with substantial depression comorbidity (59). Future studies may examine dimensionally how exposure to illicit prescription opioids impacts depression comorbidity.

Further dimensional studies of cannabis exposure and depression comorbidity would also be of value, for cohorts reaching adulthood at later times, given evolving trends in the legal availability of cannabis. Of interest, increasing cannabis exposure was associated with greater odds of depression in cases with cocaine dependence diagnosis. Exposure to cannabinoid CB1-receptor agonists such as Δ9-tetrahydrocannabinol (especially in adolescence) is known to cause depressant-like effects in preclinical models (30, 34). Some, but not all, studies report an increase in depression comorbidity in cannabis users (18, 60), and it is possible that differential cannabis exposure across studies is a major reason for these apparent discrepancies.

Summary and conclusions

This study provided a rapid dimensional analyses of how exposure to major drugs of abuse is associated with depression comorbidity, in clinically diagnosed participants. The study also provided valuable dimensional data on the association of specific patterns of poly-drug exposure and depression comorbidity.

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Abbreviations

95%CL	95% confidence limits
AA	African-American
AIC	Akaike information criterion
Cau	Caucasian
CB1	Cannabinoid receptor-1
KMSK scale	Kreek-McHugh-Schluger-Kellogg scale for exposure to drugs of abuse
N.S	non-significant

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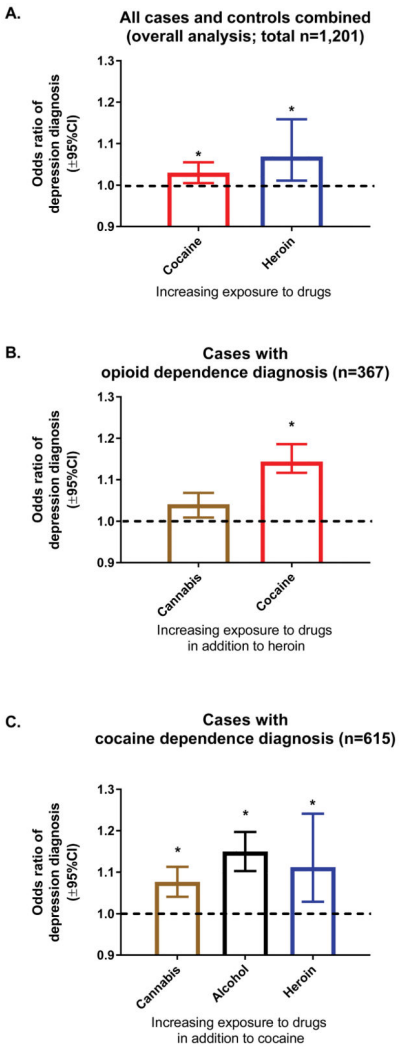

Figure 1.

Impact of drug exposure on depression, in all participants combined (all cases and controls), in cases with opioid dependence diagnosis, and in cases with cocaine dependence diagnosis (panels A–C, respectively). Bars represent odds ratios **(±95%CL)** of depression diagnosis with increasing exposure for drugs that were retained in the multiple regression models. Odds ratios are presented for a 1-score increment in each KMSK exposure scale. *Indicates significant independent variables.

Table 1

Study Demographics

Cohort 1. ***Ascertained 4/4/02–5/27/05***			
	Controls (n=140):	**Cases (n=477):**	**t or χ^2 [df]; p value**
Mean Age (SEM)	33.7 (SD= 11.1)	40.6 (SD=10.6)	t [465]=6; p<0.001
Gender: N **(% of total)**			
Male	61 (43.6%)	324 (67.9%)	χ^2=27; p<0.001
Female	79 (56.4%)	152 (32.1%)	
Depression Diagnosis: N **(% of total within gender)**			
Male	4 (1.0%)	60 (15.6%)	*N/A (one cell had low "N")*[a]
Female	11 (4.8%)	48 (20.8%)	
Ethnic/Cultural Group: N **(% of total)**			
African-American	69 (49.3%)	209 (43.8%)	χ^2=6.7; n.s.
Caucasian	41 (29.3%)	126 (26.4%)	
Hispanic	17 (12.1%)	105 (22.0%)	
Remaining/Mixed	13 (9.3%)	37 (7.8%)	
Cohort 2. ***Ascertained 6/9/05–8/1/13***			
	Controls (n=163)	**Cases (n=421)**	t or χ^2 [df]; p value
Mean Age (SEM)	33.0 (SD=11.2)	44.6 (SD=8.6)	t=[581]11.8; p<0.001
Gender: N **(% of total)**			
Male	76 (46.6%)	257 (61.0%)	χ^2=9.97; p<0.002
Female	87 (53.4%)	164 (39.0%); *n=1 M to F transgender*	
Depression Diagnosis: N **(% of total within gender)**			
Male	3 (1.0%)	74 (22.2%)	*N/A (one cell had low "N")*[a]
Female	8 (3.1%)	65 (24.9%)	
Ethnic/Cultural Group: N **(% of total)**			
African-American	60 (36.8%)	241 (57.2%)	χ^2=24.2; p<0.0001
Caucasian	41 (25.2%)	70 (16.6%)	
Hispanic	31 (19.0%)	72 (17.1%)	
Remaining/Mixed	31 (19.0%)	38 (9.1%)	

[a] χ^2 analysis on the data from both cohorts combined was significant (χ^2=7.04; p=0.008).