Journal of Affective Disorders 126 (2010) 14–38

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review

Genetic and environmental influences on psychiatric comorbidity: A systematic review

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ARTICLE INFO

Article history:
Received 10 August 2009
Received in revised form 10 November 2009
Accepted 12 November 2009
Available online 11 December 2009

Keywords:
Comorbidity
Anxiety
Depression
Substance abuse
Conduct disorder
Epidemiology
Genetics

ABSTRACT

Background: The purpose of this review is to systematically appraise the peer-reviewed literature about the genetic and environmental determinants of psychiatric comorbidity, focusing on four of the most prevalent types of psychopathology: anxiety disorders, depression, conduct disorder and substance abuse.

Methods: We summarize existing empirical research on the relative contribution that genetic, nonshared and shared environmental factors make to the covariance between disorders, and evidence about specific genes and environmental characteristics that are associated with comorbidity.

Results: Ninety-four articles met the inclusion criteria and were assessed. Genetic factors play a particularly strong role in comorbidity between major depression and generalized anxiety disorder or posttraumatic stress disorder, while the non-shared environments make an important contribution to comorbidity in affective disorders. Genetic and non-shared environmental factors also make a moderate-to-strong contribution to the relationship between CD and SA. A range of candidate genes, such as 5HTTLPR, MAOA, and DRD1–DRD4, as well as others implicated in the central nervous system, has been implicated in psychiatric comorbidity. Pivotal social factors include childhood adversity/life events, family and peer social connections, and socioeconomic and academic difficulties.

Limitations: Methodological concerns include the use of clinical case–control samples, the focus on a restricted set of individual-level environmental risk factors, and restricted follow-up times.

Conclusions: Given the significant mental health burden associated with comorbid disorders, population-based research on modifiable risk factors for psychiatric comorbidity is vital for the design of effective preventive and clinical interventions.

Contents

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doi:10.1016/j.jad.2009.11.006

1. Introduction

Psychiatric comorbidity is the presence, simultaneously or in sequence, of two or more disorders in an individual within a certain time period (Angold et al., 1999; de Graaf et al., 2002; Stein et al., 2001). The National Comorbidity Survey Replication (NCSR) found that 27.7% of the respondents had two or more disorders during their lifetime (Kessler et al., 2005a,b). Persons with comorbid psychiatric disorders have more severe symptoms and lower social competence than those with a single disorder (Kushner et al., 2000; Latkin and Mandell, 1993; Libby et al., 2005; Schuckit, 2006). Moreover, comorbidity is associated with worse prognosis (Angold et al., 1999), so identifying persons at the greatest risk for comorbidity early becomes a public health priority.

This review synthesizes the current literature on the genetic and environmental determinants of psychiatric comorbidity. We focus our review on four of the most prevalent psychiatric disorders: depression (herein referred to as DEP), including major depression (MD)(Kessler et al., 2007) and dysthymia (Wittchen et al., 1994); anxiety (herein referred to as ANX), including generalized anxiety disorder (GAD) (Barlow and Wincze, 1998), posttraumatic stress disorder (PTSD)(Kessler et al., 1995), panic disorder (PD) (Kircanski et al., 2009), separation anxiety (SAD) (Shear et al., 2006), social phobia (Ruscio et al., 2008), agoraphobia (Curtis et al., 1998), obsessive compulsive disorder (OCD) (Grant et al., 2004), and overanxious disorder (OAD) (Manassis, 2000); conduct disorder (CD) (Petitclerc and Tremblay, 2009), antisocial personality disorder (ASPD) (Grant et al., 2004); opposition defiant disorder (ODD) (Grant et al., 2004); attention deficit hyperactivity disorder (ADHD) (Biederman, 2005); and substance use/abuse (SU/SA), including alcohol (Hasin et al., 2007), tobacco (Breslau et al., 2001) and drug abuse/dependence (Warner et al., 1995). According to the National Comorbidity Survey (NCS), 28.8% of the US population suffered from an anxiety disorder sometime in their life, while 20.8% suffered from a mood disorder, 14.6% engaged in SA and 9.5% presented symptoms of CD (Kessler et al., 2005a,b). The co-occurrence of these conditions has been consistently documented in clinical and population samples (Kendler et al., 2003a; Kessler et al., 2005a,b).Our review builds on a previous assessment of the patterns of comorbidity between these four disorders from childhood to adulthood (Cerdá et al., 2008). In our previous systematic review of prospective, population-based studies of psychiatric comorbidity published between 1970 and 2007 (Cerdá et al., 2008), we found evidence that the concurrent and sequential links between CD, substance use/abuse, ANX and DEP are neither random nor a result of bias from help-seeking clinical samples. However, a key unanswered question relates to the causes of comorbidity: the direction and mechanisms underlying causal links, as well as the potential spurious nature of such links. A review of the risk factors associated with the initiation and maintenance of comorbid conditions can help illuminate the mechanisms that underlie comorbidity in psychopathology. This is the first attempt, to the best of our knowledge, to summarize the existing literature on the genetic and environmental determinants of comorbidity across internalizing and externalizing disorders.

2. Methods

This review encompasses the peer-reviewed literature published between 1976 and 2008. We limited our review to these years in order to best characterize current thinking about psychiatric comorbidity, and to include studies that use methods that are considered standard today. The literature reviewed was identified through the Web of Science (Social Science Citation Index and Science Citation Index), and it covered both US and international studies about concurrent and sequential comorbidity between ANX, DEP, SU/SA and CD. To review studies on the relative contribution of genetic and environmental factors, we restricted the search to twin studies that tease apart the relative contribution of genetics and environmental factors (Button et al., 2006; Kendler, 1996; Kendler et al., 2007; Kendler et al., 2003b; Silberg et al., 2003). For the assessment of genetic influences, we considered clinical, twin/family, and population-based studies. For environmental influences, we only considered prospective population-based studies due to the recall, selection and temporality biases inherent to retrospective and clinical studies of environmental determinants of psychopathology. The search was limited to English-language studies in biomedical research.

Keywords included the following: 1) for SU/SA: SA, alcohol abuse, drug abuse, cannabis, cocaine, heroin, street drugs, smoking, and injection drug use; 2) for DEP: depression, dysthymia, dysthymic disorder, mood disorder, major depression, major depressive disorder, internalizing disorder; 3) for CD: CD, antisocial personality, antisocial, opposition defiant disorder, criminal behavior, externalizing behavior/disorder; 4) for ANX: anxiety, panic, phobia, GAD,

OCD, PTSD, SAD, OAD, social phobia, social anxiety disorder, agoraphobia, internalizing disorder; 5) for comorbidity: comorbidity, joint trajectories, trajectories, concurrent, co-occurrence, risk pathways, chain of risk; 6) for environmental factors: environment, social environment, residence characteristics, neighborhood, social class, income, socioeconomic factors, poverty, disadvantage, social networks, social cohesion, collective efficacy, social control, social support, discrimination, segregation, parenting, family environment, peer networks, deviant peers, school environment, exposure to violence, neighborhood stress, neighborhood outlet density, marital status, violence, metals, housing, pollution, academic achievement, isolation, stress, disasters, life events, workplace, occupation; and 7) for genetic influences: genetics, family aggregation, family studies, gene, gene–environment, twin studies, epigenetic, common genetic liability, molecular genetics, candidate genes, genotype, phenotype, DNA.

3. Results

In this paper, we review genetic and environmental influences on comorbidity between the four disorders and we present available data on the interaction between genetic and environmental determinants as they influence comorbidity. The original search started with 1559 articles, of which 190 addressed environmental or genetic contributions comorbidity. Of these, we restricted the sample to 94 that actually directly tested the relationship between environmental or genetic factors and comorbidity, rather than a single disorder. This review covers 40 studies of the relative influence of genetic and environmental factors on comorbidity, 31 studies of specific genetic influences, and 23 studies of specific environmental determinants.

The review begins with an examination of existing evidence on the relative contribution that genetic and environmental factors make to comorbidity; followed by a description of the relationship between specific candidate genes and comorbidity, and concluding with a description of evidence on environmental influences on comorbidity. Existing evidence within each category is presented by comorbid pair.

3.1. Genetic vs. environmental influences

We discuss evidence for the relative contribution that genetic and environmental factors make to comorbid disorder pairs of interest below. Studies reviewed here are summarized in Table 1.

3.1.1. Conduct disorder/problems and substance abuse

Twin studies provide some evidence of genetic and environmental contributions to covariation between CD and different forms of SA, including marijuana, illicit drug abuse and alcohol abuse and dependence (Button et al., 2006; Button et al., 2007; Krueger et al., 2002; Miles et al., 2002; Slutske et al., 1998; Young et al., 2000). All twin studies examining the genetic and environmental sources of covariation between CD and SA reported a moderate (Button et al., 2006; Miles et al., 2002; von der Pahlen et al., 2008) to strong (Button et al., 2007; Krueger et al., 2002; Legrand et al., 2008; Slutske et al., 1998; Young et al., 2000) genetic source of covariation. Variation may be partly due to the different definitions of SA—two studies focused solely on alcohol dependence (Slutske et al., 1998; von der Pahlen et al., 2008), another restricted the study to marijuana (Miles et al., 2002), and yet others combined multiple substances (Button et al., 2006; Button et al., 2007; Krueger et al., 2002; Legrand et al., 2008; Young et al., 2000).

Six of the eight studies also found a moderate contribution of nonshared environmental factors common to the two disorders (Button et al., 2006; Button et al., 2007; Krueger et al., 2002; Slutske et al., 1998; von der Pahlen et al., 2008; Young et al., 2000). Only two studies found a moderate contribution of the shared environment on comorbidity (Button et al., 2006; Legrand et al., 2008). One of the studies examined genetic and environmental contributions across the rural/urban divide, and found that while genetic influences were more important in urban settings, shared environmental influences were more important in rural settings (Legrand et al., 2008).

3.1.2. Depression and anxiety

Strong evidence also exists for shared genetic vulnerability between ANX and DEP, particularly between MD and GAD (Eaves et al., 2003; Eley and Stevenson, 1999a,b; Hettema et al., 2006b; Kendler, 1996; Kendler et al., 2007; Kendler et al., 1992, 1993; Koenen et al., 2008; Koenen et al., 2003a; Koenen et al., 2003b; Middeldorp et al., 2006; Roy et al., 1995; Silberg et al., 2001a; Skre et al., 1994; Thapar and McGuffin, 1997; Torgersen, 1990), although the extent of shared genetic sources of comorbidity that has been reported varies between studies and between subtypes of anxiety and depression. All sixteen twin studies we identified on the relationship between depression and anxiety reported that genetics contributed to the covariation between the two disorders. A particularly strong genetic link seems to exist between GAD and MD—all studies on this subject found that genetic influences were completely shared between the two disorders (Hettema et al., 2006a; Kendler, 1996; Kendler et al., 2007; Kendler et al., 1992; Roy et al., 1995) although one study found that three-fourths of genetic influences were shared among males (Kendler et al., 2007). The genetic correlation between major depression and other types of anxiety varies: Koenen et al. (2008) found a high genetic correlation between MD and PTSD (+0.77) while Hettema et al., 2006b reported a moderate correlation between MD and situational phobia (+0.43), a high correlation between MD and social phobia (+0.72) and a virtual correlation of unity between MD and PD. The proportion of the correlation between depression and anxiety accounted for by genetic factors also varies by type of anxiety and by age and sex. (Eley and Stevenson, 1999a, b; Silberg et al., 2001b).

The contribution of environmental factors to the relation between anxiety and depression varies by study and anxiety subtype. Studies investigating the covariance between anxiety subtypes and MD have found that the non-shared environment explained almost all of the covariance between MD and agoraphobia (Kendler et al., 1993) and approximately 40–43% of the covariance between GAD-MD for females (Kendler, 1996; Kendler et al., 2007) and 65% of the covariance between the same two disorders among males (Kendler et al., 2007). The shared environment did not explain any of the covariance between GAD-MD (Kendler,

Table 1
Published studies examining the relative contribution of genetic and environmental factors on psychiatric comorbidity.

Disorders	Citation	Sample	Measurement of disorders	Conclusion
SA and CD	Slutske, S et al. 1998 Journal of Abnormal Psychology; 107: 363–374.	2682 male and female twin pairs (Australia)	Semi-structured assessment for the genetics of alcoholism interview (SSAGA)	76% and 71% of association between conduct disorder and alcohol dependence, in men and women respectively, was due to genes; remaining 24% and 29% of the association in men and women was due to nonshared environmental risk factors.
SA and CD	Young et al. Neuropsychiatric Genetics 2000; 96: 684–695.	172 monozygotic (MZ) and 162 dizygotic (DZ) twins from Colorado	Diagnostic Interview Schedule For Children-IV	Heritability of latent phenotype representing CD, SUB and ADHD estimated at 0.84, with non-shared environmental factors explaining the remaining 16%.
SA and CD	Miles, DR et al., 2002. American Journal of Medical Genetics 114: 159–168.	740 adolescent twin pairs (144 MZ male, 145 MZ female, 131 DZ male, 116 DZ female, 204 DZ opposite-sex)	Number times used marijuana in life (1995) and in the past year (1996). Conduct disorder (CD) assessed using an 11 item scale based on the criteria of the DSM-IV.	CD and MU share a moderate genetic correlation ($r_g = 0.28$) and a low environmental correlation ($r_e = 0.14$).
SA and CD	Krueger, RF et al. Journal of Abnormal Psychology 2002 111(3):411–424	1048 male and female 17-year-old twins from the Minnesota Twin Family Study (MTFS)	Structured interviews developed by MTFS staff using DSM-III-R criteria; also used the Substance Abuse Module of the Composite International Diagnostic Interview (CIDI) and parent reports from the Diagnostic Interview for Children and Adolescents.	81% of variance in externalizing factor accounted for by genetic factors; nonshared environmental factors accounted for the remaining 19% of the variance.
SA and CD	Button, T. et al Twin Research and Human Genetics 2006 9(1) 38–45	880 twin pairs, age 13–18 (237 MZF, 195 MZM, 116 DZF, 118 DZM, 214 DZ opposite sex) from Colorado twin registry and sample	DSM-IV for lifetime CD; polysubstance dependence vulnerability index (DV) developed from the substance abuse module of the CIDI	Genes contributed 35% to phenotypic covariance between DV and CD symptoms (shared environment = 46%, nonshared environment = 19%).
SA and CD	Button, T.M.M. et al Drug and Alcohol Dependence 2007 87, 45–53.	645 MZ and 702 DZ twin pairs, 96 adoptive sibling pairs and 429 biological sibling pairs (Colorado samples). All aged 12–18.	DSM-IV for CD; CIDI-SAM for alcohol dependence (AD) and combined illicit drug dependence (IDD)	50% of genetic influence on AD is shared with CD. All of genetic influences on IDD also influenced AD and CD. Genetic correlation between AD and IDD is partially explained by the genetic risk they share with CD. There are also non-shared environmental influences common to all three phenotypes, a non-shared environmental vulnerability common to AD and IDD, and non-shared and shared environmental influences unique to IDD.
SA and CD	von der Pahlen, B. et al. 2008. Biological Psychiatry 78: 269–277.	3141 men (2202 twins and 939 non-twin male siblings) and 6026 women (4095 twins and 1931 non-twin female siblings). Mean age was 26 years old.	Alcohol Use Disorders Identification Test (AUDIT); Buss and Perry Aggression Questionnaire and questions on the number of cigarettes smoked per day.	Genetic correlation between aggressive behavior and alcohol dependence was 0.29 (95% CI: 0.27, 0.32) and between aggressive behavior and smoking it was 0.24 (0.22, 0.27). The level of non-shared environmental correlation was 0.22 (0.22, 0.27) between aggressive behavior and alcohol dependence and 0.08 (0.04, 0.13) between aggressive behavior and smoking.
SA and CD	Legrand, LN. 2008. Psychological Medicine 38: 1341–1350.	608 same-sex twin pairs (male: 184 MZ, 97 DZ; female: 213 MZ, 114 DZ) born in Minnesota in 1972–1979.	Diagnostic Interview for Children and Adolescents-Revised (DSM-III-R) and the Substance Abuse Module of the CIDI.	In urban environments, genetic factors accounted for 64% of the externalizing factor's variance and shared environmental influences for 25% of the variance. In rural environments, genetic influences dropped to 0% and shared environmental influences increased to 86%.
DEP and ANX	Torgersen, S. et al 1990 Am J Psychiatry 147;9:1199–1202	177 same-sex twin pairs	Present State Examination (PSE), modified for lifetime symptoms, and psychiatric records.	There is a genetic relationship between comorbid MD–anxiety disorders and MD-only; but not between comorbid disorders and anxiety-only or between pure MD and pure anxiety.

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Table 1 (*continued*)

Disorders	Citation	Sample	Measurement of disorders	Conclusion
DEP and ANX	Kendler, KS et al Archives of General Psychiatry 1992 49(9): 716–722	1033 pairs of middle-aged female twins identified from the Virginia Twin Register (590 MZ, 440 DZ)	Structured Clinical Interview using DSM-III-R criteria	Familial environment played no role in etiology of either condition; genetic factors were important for both MD and GAD and were completely shared between the two disorders.
DEP and ANX	Skre, I. 1993 Acta Psychiatrica Scandinavica 88(2):85–92.	Cases: 20 MZ and 29 DZ twin-pairs of anxiety disorder probands. Controls: 12 MZ and 20DZ twin-pairs where probands had other non-psychotic mental disorders (Norway)	Structured Clinical Interview using DSM-III-R criteria	Genetic factors are involved in the etiology of GAD with a history of mood disorder. Genes are relatively unimportant in the development of simple & social phobia.
DEP and ANX	Kendler, KS et al Psychological Medicine 1993 23(2):361–371	2163 middle-aged female twins recruited from the Virginia Twin Register.	Structured Clinical Interview using DSM-III-R criteria (MD); Diagnostic Interview Schedule Version III-A (for phobias).	Moderate genetic correlation between MD and phobias (+0.3 to +0.38). Increased comorbidity between MD and agoraphobia results almost entirely from non-shared environmental risk factors for MD.
DEP and ANX	Roy, MA 1995 Psychological Medicine 25(45):1037–1049	1002 index twin probands (Swedish Psychiatry Twin Registry for a diagnosis of unipolar or bipolar illness, excluding schizophrenics). 800 control twin probands (Swedish Twin Registry)	Structured Clinical Interview using DSM-III-R criteria	GAD and MD share the same genetic factors while their environmental determinants are mostly distinct (genetic correlation = 1).
DEP and ANX	Kendler, KS 1996 British Journal of Psychiatry Supplement 1996 30: 68–75	937 pairs of female twins recruited from the Virginia Twin Registry (547 MZ, 390 DZ)	Structured Clinical Interview using DSM-III-R criteria	Genetic correlation of unity between MD and GAD. The non-shared environmental correlation is 0.70. 57% of the covariation resulted from genes, and 43% resulted from non-shared environmental factors.
DEP and ANX	Thapar and McGuffin, 1997 J Child Psychol Psychiatr 38(6): 651–656	172 twin pairs aged 8–16 identified from the Cardiff Births Survey	Mood and Feelings Questionnaire and the Revised Children's Manifest Anxiety Scale	Most of the covariation can be explained by a common set of genes that influence anxiety and depressive symptoms.
DEP and ANX	Eley and Stevenson, 1999b J Abnormal Child Psychology 27(2):105–114	395 same-sex twin pairs 8–16 years old (Register for Child Twins — British Isles)	Children's Depression Inventory and the State-Trait Anxiety Inventory for Children	The genetic influences on depression and anxiety measures were totally shared and accounted for the 79% of the covariation between the two. Shared environmental influences accounted for 21% of the covariation.
DEP and ANX	Eley and Stevenson, 1999a J Child Psychol Psychiatr 40(8): 1273–1282	490 pairs of twins 8–16 years (Register for Child Twins — British Isles): 106 MZM, 100 DZM, 127 MZF, 87 DZF, and 109 DZMF; 252 8–11 year olds and 244 12–16 year olds	Children's Depression Inventory and the State-Trait Anxiety Inventory for Children	The proportion of correlations between anxiety and depression due to genetic, shared and nonshared environmental variance were 28%, 26%, and 46% respectively for male children, 30%, 34%, and 36% for female children, 58%, 2% and 40% for the male adolescents, and 5%, 65% and 30% for the female adolescents.
DEP and ANX	Silberg et al., 2001a Biol Psychiatry; 49: 1040–1049.	415 MZ and 194 DZ female twin pairs from the Virginia Twin Study	Child and Adolescent Psychiatric Assessment	Additive genetic factors influence earlier and later OAD and simple phobias, and middle to late adolescent depression; depression and separation anxiety in 8–13-year-olds are linked through an underlying common shared environmental factor that also influences liability to phobic symptoms later in adolescence; The shared environmental risk to depression and OAD after age 14 is reflected in earlier and later separation anxiety.

DEP and ANX	Eaves et al. J Child Psychology and Psychiatry 2003; 44(7): 1006–1014.	467 MZ and 220 DZ female twin pairs from the Virginia Twin Study	Child and Adolescent Psychiatric Assessment	1) Genetic differences in anxiety create later genetic differences in depression; 2) genes that affect early anxiety increase sensitivity (GxE) to adverse life events; 3) genes that increase risk to early anxiety increase exposure to depressogenic environmental influences (rGE).
DEP and ANX	Koenen et al., 2003b 6 (3): 218–226.	MZ and DZ cases and control twins from Vietnam Era Registry	Researchers conducted structured interviews (DIS-III-R) over the telephone to determine lifetime DSM-III-R symptomology.	Genetic factors contribute to the association between PTSD & MD and PTSD & dysthymia. MZ co-twins of PTSD probands (HR) have higher rates of MD and dysthymia than DZ co-twins of PTSD probands (DZMR).
DEP and ANX	Middeldorp et al. 2006; 90: 163–169.	4309 Dutch twins and 1008 siblings	Burnout measured with the Maslach Burnout Inventory-General Survey; depression assessed with the Young Adult Self Report	Associations between employment and anxious depression as well as between burnout and anxious depression are due to overlapping genetic and individual specific environmental factors.
DEP and ANX	Hettema et al., 2006b; Am J. of Psychiatry;163: 857–864.	9270 twins from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders. Female–female twin pairs were born in 1934–1974 and male–male pairs were born in 1940–1974.	Depression and anxiety assessed using DSM-III-R criteria by interviewers with a master's degree in mental health field or bachelor's plus 2 years of clinical experience.	A substantial proportion of the total risk variance shared between MD, GAD and panic is due to a genetic factor for neuroticism and a neuroticism-independent common genetic factor. The genetic correlation between disorders ranged from 0.98 (MD and GAD) to 0.52 (MD and animal phobia).
DEP and ANX	Kendler, KS et al Psychological Medicine 2007 37:453–462	37,296 twins from a Swedish Twin Registry (all twins born from 1926–1958) used for bivariate analyses. A subsample of 23,280 same-sex twins used for trivariate analyses.	Composite International Diagnostic Interview-Short Form (CIDI-SF) using DSM-IV criteria	Genetic factors contributed 35% of the covariance between MD and GAD in males and 60% in females, while non-shared environmental factors contributed 65% in males and 40% in females.
DEP and ANX	Koenen et al. J Affective Disorders 2008; 105: 109–115.	6744 members of the Vietnam Era Twin Registry	MD and PTSD assessed using the Diagnostic Interview Schedule (DSM-III-R criteria)	Genetic correlation between MD and PTSD was $r = 0.77$ (95% CI, 0.50–1.00); non-shared environmental correlation was $r = 0.3$ (95% CI, 0.19–0.48); common genetic liability explained 62.5% of MD–PTSD comorbidity.
SA and DEP	Prescott, CA et al 2000 Arch Gen Psychiatry 58:803–811	3755 twin pairs from the Virginia Twin Registry born 1934–1974 (FF) or 1940–1974 (MM/MF).	Standard structured interviews were used to determine DSM-III-R and DSM-IV diagnoses	Genetic influences explained 61% of the MD-alcohol dependence covariance among men and 51% among women. Non-shared environmental factors explained 39% of the covariance among men and 49% among women.
SA, ANX and DEP	Kendler, KS et al Archives of General Psychiatry 1995 52(5):374–383	1030 female–female twin pairs from the Virginia Twin Registry (590 MZ, 440 DZ).	The interview included sections of the Structure Clinical Interview for DSM-III-R and the Phobic Disorders section of the Diagnostic Interview Schedule Version III-A, based on DSM-III-criteria.	Genetic influences on these disorders are explained by two factors — one loading heavily on phobia, panic disorder (PD), and bulimia and the second loading on MD and GAD. Familial environment accounted for at most 4% of the variance for phobia, GAD, PD, MD or alcoholism, while a common non-shared environment factor accounted for a substantial proportion of variance for GAD and MD.
SA, ANX and DEP	Tambs et al. 1997; Behavior Genetics 27(3): 241–250.	2570 pairs of Norwegian MZ and like-sexed and unliked-sexed DZ twins aged 18–25	Used SCL-25 and questions on alcohol consumption frequency and intoxication.	The phenotypic correlation between alcohol and anxiety/depression in males ($r = 0.23$) could be fully explained by common genetic effects; The correlation in females ($r = 0.18$) was caused by non-shared environmental factors together with either genetic effects or shared environment.
SA, ANX and DEP	Nelson, EC et al. 2000 Psychological Medicine 30:797–804	1344 twins aged 16+ from a population based adolescent female twin sample (Missouri Adolescent Female Twin Study)	Structured diagnostic interviews adapted for telephone administration from the Diagnostic Interview for Children and Adolescents (DICA), Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), and Child's Version of the SSAGA (C-SSAGA).	The additive genetic correlation for either social phobia (SP) or MD and alcohol dependence was 0 ± 53, while that for SP and MD was 1 ± 0. Additive genetic factors accounted for 28% of the variance in SP risk. The similar respective values for MDD and ALD risk were 45% and 63%.

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Table 1 (*continued*)

Disorders	Citation	Sample	Measurement of disorders	Conclusion
CD and DEP	O'Connor et al., 1998a J Abnormal Psych 107:27–37	93 MZ, 99 DZ twin-pairs and 95 full-sibling pairs from nondivorced families; 182 full-sibling, 109 half-sibling, and 130 unrelated sibling-pairs from remarried families. All 10–18 years of age.	Self-report and parent-reports of Child Depression Inventory (CDI), Behavior Problem Index (BPI), Modified Behavior Events Inventory (BE).	43% of the observed covariation in depressive and antisocial symptoms could be explained by genetic liability, 30% by shared environmental influences and 25% by non-shared environment.
CD and DEP	O'Connor et al., 1998b J Child Pscyhol Psychiatr 39(3): 323–336	93 MZ, 99 DZ twin-pairs and 95 full-sibling pairs from nondivorced families; 182 full-sibling, 109 half-sibling, and 130 unrelated sibling-pairs from remarried families. All adolescents 10–18 years of age.	Self-report and parent-reports of Child Depression Inventory (CDI), Behavior Problem Index (BPI), Modified Behavior Events Inventory (BE).	At wave 2, 90.7% of the correlation was mediated by genetic factors, with shared and nonshared environmental factors adding minimally. Over time, the correlation was due to genetic influences (57%), shared (24%) and nonshared (19%) environmental factors. However, after controlling for depression at the prior wave, the temporal effect of antisocial behavior on depression was non-significant.
CD and DEP	Rowe, R. et al 2008 Journal of child Psychology and Psychiatry 49(5):526–534	941 twin-pairs (311 MZ, 334 opposite-sex DZ, 296 same-sex DZ) and 328 sibling-pairs aged 12–21 years from the G1219 large-scale community sample	Youth Self Report and Mood and Feelings Questionnaire short version	Among boys, the proportion of shared variance explained by genetics was 60% for oppositionality-depressed mood; 94% for physical aggression-depressed mood; and 82% for delinquency-depressed mood; the rest was contributed by non-shared environment. Among girls, the proportion of shared variance accounted for by genetics was 64% for oppositionality–depression; 91% for physical aggression–depression, and 82% for delinquency–depression; the rest was accounted for by non-shared environment.
CD, ANX and DEP	Fu et al., 2007b; 62: 1088–1094.	6744 middle-aged male–male MZ and DZ twins from the Vietnam Era Twin Registry	Diagnostic Interview Schedule for the DSM-III-R	13% of the total environmental variance in PTSD overlapped with the environmental variance in CD; no genetic covariance. The association between MD and PTSD was largely explained by common genetic influences. Of the non-shared environmental variance of PTSD, 8% of the variance in PTSD overlapped with non-shared environmental variance in MD. The association between CD and MD was explained by common genetic influences: 11% of the variance in MD overlapped with the genetic variance in CD. 2% and 3% of variance in MD overlapped with environmental variance in CD.
CD, ANX and DEP	Neuman, RJ. Et al 2001 J Child Psychiat. 42(7): 933–942.	2904 adolescent female twins (age 13–23)	SSAGA (DSM-IV criteria)	The latent class analysis found 9 classes, including 3 comorbid classes: class 6 (6.8%) with high levels of ODD, separation anxiety and depression (heritability (h2a = 51%)); class 8 (5.3%), with elevated levels of ADHD inattentive and ODD symptoms (heritability (h2a = 63%)); and class 9 (4.6%) with elevated levels of ADHD, ODD, separation anxiety and depression (heritability (h2a = 81%)).
CD, DEP and SA	Fu, Q et al. Arch Gen Psychiatry 2002 59:1125–1132	3360 twin pairs (1868 MZ 1492 DZ) from the Vietnam Era Twin Registry (population registry of male veteran twins)	DSM-III-R for antisocial personality disorder (ASPD), major depression (MD), alcohol dependence (AD), marijuana dependence (MJD) — telephone interview	Heritability was 69% for ASPD, 40% for MD, 56% for AD, and 50% for MJD. 21.6% (95% CI: 0–51.4%) of the total genetic correlation between MD and AD and 38.4% (95% CI: 0–64.5%) of the genetic correlation between MD and MJD could be explained by the MD genetic factor and the remainder (78.4%; 95% CI: 49.6–100% and 61.6%; 95% CI: 35.5–100%) by the ASPD genetic factor. The contribution of nonshared environmental influences to the total phenotypic covariance among these four disorders was small.

CD, DEP and SA	Silberg et al. 2003. Journal of Child Psychology and Psychiatry 44: 664–676.	307 monozygotic and 185 dizygotic same-sex male twin pairs, and 392 monozygotic and 187 dizygotic like-sex female pairs in Virginia	DSM-based Child and Adolescent Psychiatric Assessment (CAPA) and Olweus Aggression Scale	The covariation between depression and smoking/drug use among girls was due to genetic factors while the covariation among boys was due to a common underlying environmental factor. The covariance between depression and alcohol use among girls was due to a common environmental factor while among boys it was due to genetic factors. The covariation between CD and SU in boys and girls was accounted for by latent common genetic and shared environmental risk factors.
CD, DEP and SA	Fu et al., 2007a 10(3): 470–478	3360 middle-aged twin pairs from the Vietnam Era Twin Registry, incl. 1868 MZ and 1492 DZ	Diagnostic Interview Schedule, Version III Revised (DIS-3R) with DSM-III-R criteria	After controlling for genetic influences on CD, the partial genetic correlation between MD and ND was no longer statistically significant; 90.3% of the genetic correlation was explained by the CD genetic factor and only 9.7% by the MD genetic factor.
Internalizing and externalizing behavior	Pickens et al., 1995 Drug and Alcohol Dependence 39: 129–138	63 MZ & 67 DZ twin pairs recruited from alcohol and drug use treatment programs meeting criteria for lifetime alcohol dependence	Diagnostic Interview Schedule (DIS) with DSM-III criteria	Males: co-occurrence between alcohol dependence (AD) and antisocial personality (ASP), amphetamine abuse, cannabis abuse, or phobia was due partly to genetic factors. In females, co-occurrence between AD and major depression or ASP may be more likely due to non-shared environmental factors.
Internalizing and externalizing behavior	Gjone and Stevenson, 1997; 25(4): 277–286.	526 identical and 389 fraternal same sexed twin pairs from 5 birth cohorts in Norway	Behavior problems assessed with the Child Behavior Checklist	The covariance between internalizing and externalizing traits ($r = 0.51–0.58$) is accounted for primarily by shared environmental components. The contribution of genetic factors was higher among those aged 12–15 in contrast to those aged 5–9 years of age.
Internalizing and externalizing behavior	Kendler et al., 2003b; 60: 929–937.	5600 members of a male–male and female–female twin registry	Affective disorders and CD assessed with DSM-III-R criteria, alcohol dependence (AD) and drug abuse/dependence (DAD) with DSM-IV	The first genetic common factor had substantial loadings on all externalizing disorders while the second genetic common factor had high loadings on the internalizing disorders. The first shared environmental common factor had substantial loadings only on CD and ASPD. The second shared environmental factor had moderate loadings on phobia and CD. The first non-shared environmental common factor had substantial loadings on CD and ASPD, while the second factor had substantial loadings on MD, GAD, and AD.
Internalizing and externalizing behavior	Prescott, CA et al 2005 Am J Medical Genetics Part B (Neuropsychiatric Genetics) 134B:48–55	295 twin pairs (590 individuals) recruited prospectively from 5 psychiatric treatment facilities in St Louis, MO metro area.	Diagnostic interview schedule (DIS), the home environment and lifetime psychiatric evaluation record, and a battery of psychological tests were performed at the hospital, outpatient clinics, or in twins' homes.	The % of variance explained by genetic factors was 6% for those with both AAD and ASPD, 84% for those with alcohol abuse and dependence (AAD) and a comorbid affective disorder and 40% for those with AAD comorbid with a disorder different from ASPD or affective disorders. The contribution of the shared environment was 64% for those with ASPD + AAD, 2% for those with AAD + affective disorder, and approximately 11% for those with AAD + another comorbid disorder. The contribution of the non-shared environment was 30% for those with ASPD + AAD, approximately 14% for those with AAD + affective disorder and approximately 49% for those with AAD + another comorbid disorder.

1996; Kendler et al., 2007; Roy et al., 1995). As with genetic factors, the contribution of the shared and nonshared environment also varies by age and sex (Eley and Stevenson, 1999a; Silberg et al., 2001b).

Most studies that examine genetic and environmental determinants of comorbidity ignore the role of gene–environment interactions. Eaves et al. (2003) was the only study we were able to find that investigated the influence of genetic, environmental and gene–environment interactions on the association between depression and anxiety. They found a large genetic correlation between juvenile anxiety and later depression, and genes that increased the risk for early anxiety increased exposure to depressogenic environmental influences and sensitivity to adverse life events. Additional genetic effects, specific to depression, further increased sensitivity to adversity. When they estimated models without gene–environment interaction (GxE), the effects of genes specific to depression were less apparent, the contribution of unidentifiable non-shared environmental effects was overestimated and the direct main effect of life events on variance in depression more than doubled.

3.1.3. Substance abuse and depression/anxiety disorders

A few studies have also found shared genetic susceptibility between DEP and CD (O'Connor et al., 1998a; O'Connor et al., 1998b; Rowe et al., 2008), as well as between ANX or DEP and SA (Davids et al., 2002; Dawson and Grant, 1998; Fu et al., 2007a; Lin et al., 2007; Marques et al., 2006; Nurnberger et al., 2001; Prescott et al., 2000), although contradictory evidence has detected a lack of genetic commonality between externalizing and internalizing disorders (Kendler et al., 1997; Prescott et al., 2005; Tsuang et al., 2004).

All studies we found addressing the environmental and genetic sources of comorbidity between SA and internalizing disorders focused on alcohol abuse. Genetic and non-shared environmental factors played a strong role in disorder covariation between alcohol and MD: Prescott et al. (2000) found that genetic influences explained 61% of the covariance between MD and alcohol dependence (AD) among males and 51% among females while non-shared environmental factors explained 39% of the covariance among males and 49% among females.

Once anxiety was introduced into the analysis, studies showed a stronger genetic similarity between anxiety disorders and depression, in contrast to alcohol: Kendler et al. (1995) for example, found that genetic influences among phobia, GAD, PD, bulimia nervosa, MD and alcoholism could be disaggregated into common genetic influences for phobia, panic and bulimia, genetic influences common to MD and GAD, and genetic influences specific to alcoholism. A common non-shared environmental influence was only common to GAD and MD. Nelson et al. (2000) also found that while a common genetic component contributed significantly to AD, social phobia (SP) and MD, a genetic component specific to AD was also retained: while the additive genetic correlation between MD or SP and AD was 0.53, the genetic correlation between MD and SP was 1.0.

Only one study found that shared environmental factors could play a role in comorbidity between AD and internalizing disorders: Tambs et al. (1997) found that while the phenotypic correlation between alcohol use and symptoms of anxiety/depression could be fully explained by common genetic effects in men, the correlation in women was partly due to non-shared environmental factors.

3.1.4. Conduct disorder and depression/anxiety disorders

Genetic influences play an important role in the covariation between CD and internalizing disorder. We found three studies that focused on the relationship between CD and MD, (O'Connor et al., 1998a; O'Connor et al., 1998b; Rowe et al., 2008) while two additional studies also included anxiety in their analyses (Fu et al., 2007b; Neuman et al., 2001). O'Connor et al. conducted two studies (O'Connor et al., 1998a; O'Connor et al., 1998b) on the relationship between CD and depression, where he found that the contribution of genetic factors to comorbidity depended on the study timing. While at wave one of the study (when study respondents from the younger and older cohorts were, on average, 12.6 and 14.8 years of age), 43% of the covariation was explained by genetic liability, 30% by shared environmental influences and 25% by the non-shared environment, (O'Connor et al., 1998a) at wave 2 (3 years later), almost all of the observed covariation was mediated by genetic factors, with shared and nonshared environmental factors adding minimally to the correlation (O'Connor et al., 1998b). Rowe et al. (2008) found that while genetic effects were common to depressed mood and antisocial behavior, there were also genetic determinants specific to each disorder. Investigating the joint relationship between anxiety, depression and CD provides information about the relative contributions that genetic and environmental factors make to comorbid pairs: Fu et al. (2007b) for example, found that while common genetic influences played an important role in explaining the covariation between MD and both PTSD and CD, the shared environment, and not genetic factors, were largely responsible for explaining the relationship between PTSD and CD.

3.1.5. Depression and substance abuse/conduct disorders

Studies focusing on the relationship between depression and externalizing disorders have found that genetic factors and features of the shared familial environment play a role in generating comorbidity. Their relative contribution may vary by sex and by comorbid pair (Silberg et al., 2003). Further, genetic risk factors for CD account for part of the covariation between MD and different forms of substance use. Fu et al. (2002) examined 3360 male twin pairs from the Vietnam Era Twin Registry, and found that while 21.6% of the genetic correlation between MD and AD and 38.4% of the genetic correlation between MD and marijuana dependence was explained by genetic influences on MD, the rest depended on an antisocial personality disorder (ASPD) genetic factor. In a related study with the same sample, Fu et al. (2007a) also found that most of the genetic correlation between MD and nicotine dependence was explained by genetic risk factors for CD.

3.1.6. Externalizing and internalizing disorders

A series of studies have partitioned disorders into internalizing and externalizing spectrums, and estimated the relative contributions that the genetic, shared and nonshared environments make to each dimension (Gjone and Stevenson, 1997; Kendler et al., 2003b; Pickens et al., 1995). Kendler et al. (2003b)) found that while alcohol, CD, ASPD and drug abuse/

dependence had a common genetic source, a second genetic factor had high loadings on GAD, MD and phobia. The first shared environmental factor, as well as the first non-shared environmental factor, had substantial loadings only on CD and ASPD, while the second shared environmental factor had moderate loadings on CD and phobia, and the second non-shared environmental factor loaded substantially on MD, GAD and alcohol dependence.

3.2. Specific genetic factors: studies examining candidate genes for comorbidity

Although several genes, particularly those associated with the dopaminergic and serotonergic systems have been proposed as potential candidates, there are very few studies of the genetic variants that contribute to comorbidity and none to our knowledge use population-based samples (Hoenicka et al., 2007; Lin et al., 2007; Maron et al., 2005; Marques et al., 2006; Rowe et al., 1998; Stallings et al., 2005). We summarize the extant evidence, by comorbid pair below. Studies are presented in Table 2.

3.2.1. Conduct disorder and substance use

The bulk of studies on candidate genes for CD-SA comorbidity (Gerra et al., 2005; Hoenicka et al., 2007; Huang et al., 2004; Jain et al., 2007; Kim et al., 2006; Lee et al., 2009; Limosin et al., 2005; Lu et al., 2003; Wang et al., 2007) have focused on alcoholism and antisocial behavior, often using a case–control study design with alcoholics classified into type I (adult onset and rapid progression of dependence without criminality) and type II (teenage onset and recurrent antisocial characteristics) (Hoenicka et al., 2007; Parsian, 1999; Parsian and Cloninger, 2001; Saito et al., 2002) or using individuals with ASPD with or without a history of alcoholism (Huang et al., 2004; Lee et al., 2009; Lu et al., 2003; Wang et al., 2007). See Traber et al. (2009)) and Babor et al. (1992)) for information on how these proposed forms of alcoholism have been empirically addressed. The link between the dopamine receptor and transporter polymorphisms, such as the *TaqIA* single nucleotide polymorphism (SNP) located near the dopamine receptor D2 (DRD2) gene, and antisocial alcoholism remains equivocal (Gurling and Cook, 1999; Hoenicka et al., 2007; Munafo, 2006; Munafo et al., 2007; Wang et al., 2007). It has been suggested that the TaqIA1 allele of the TaqIA SNP and other dopaminergic gene polymorphisms might not be related specifically to alcoholism, but to a non-specific vulnerability to a wide range of impulsive and reward-inducing behaviors (Comings and Blum, 2000; Rodríguez-Jiménez et al., 2006). Homozygosity for the dopamine receptor D3 (DRD3) gene Ball polymorphism has also been associated with alcoholism and impulsiveness (Limosin et al., 2005), while polymorphisms in the dopamine transporter gene have been associated with increased risk of irritability and direct aggressiveness among heroin-dependent males (Gerra et al., 2005).

Selected genome-wide analyses have led to the identification of plausible candidate genes of SA-CD comorbidity within linked chromosomes (Corley et al., 2008; Dick et al., 2008). These include CHRNA2, the neuronal nicotinic receptor alpha 2 subunit gene, OPRM1, the mu opioid receptor gene that binds drugs such as heroin, morphine and methadone (Corley et al., 2008), and the muscarinic acetylcholine receptor MS gene (CHRM2), potentially involved in generating a disequilibrium in the central nervous system homeostatic mechanisms (Dick et al., 2008).

Finally, genes involved in the serotonergic pathway, including tryptophan hydroxylase (TPH—the rate-limiting enzyme in serotonin biosynthesis), the serotonin transporter (5-HTT), monoamine oxidase (MAOA-A), and 5-HT receptors, have been proposed as mechanisms underlying alcohol–antisocial behavior comorbidity. Numerous studies have focused on the association between the MAOA gene and antisocial alcoholism: some detected an association between low-activity alleles associated with MAOA and antisocial alcoholism (Parsian, 1999; Samochowiec et al., 1999; Schmidt et al., 2000) while others failed to find such a relationship (Parsian and Cloninger, 2001; Saito et al., 2002). One study also found a link between the serotonin transporter gene long allele, associated with higher transcriptional efficiency of the gene promoter, and antisocial alcoholism (Parsian and Cloninger, 2001).

Multiple genes are likely to contribute to psychiatric disorders in a synergistic manner. A couple of studies indicate that epistasis may contribute to comorbidity between CD and alcohol abuse. Although Wang failed to find an association between the DRD2 TaqI A polymorphism and antisocial alcoholism, they did find that among those respondents with the functional high-activity 4-repeat allele of the monoamine oxidase A (MAOA) promoter polymorphism, the A1/A2 genotype frequency of the DRD2 TaqI A polymorphism (relative to the DRD2 A1/A1 polymorphism) was higher in the antisocial non-alcoholic group than in the antisocial alcoholic group (Wang et al., 2007). Such an interaction was proposed given that MAOA metabolizes dopamine, and when metabolite pathways are influenced by the high activity of the MAOA 4-repeat allele, the rate of dopamine metabolism should increase and might decrease the dopamine level. Further, the A1 allele of the DRD2 gene has a low dopamine receptor density, which might also indicate a low level of dopamine functioning.

Lee et al. (2009) also found an interaction between MAOA and ALDH2, the major aldehyde dehydrogenase isozyme that catalyzes the oxidation of ethanol-derived acetaldehyde. ALDH2 has a functional SNP in exon 12, which results in two alleles: ALDH2*1 and ALDH2*2. The ALDH2*1/*1-encoded enzyme is an active form in the metabolism of acetaldehyde, while the enzyme encoded by the ALDH2*1/*2 or *2/*2 polymorphism is partially or completely inactive, thus leading to a reduction in enzymatic activity. An interaction between MAOA and ALDH2 is plausible, given that both isozymes are involved in the conversion of dopamine into its acid metabolites. The ALDH2*1/*2 or *2/*2 alleles were more frequent in antisocial non-alcoholics, rather than antisocial alcoholics. However, the protective effects of the ALDH2*1/*2 or *2/*2 alleles were lower among subjects that also had the MAOA–uVNTR 4-repeat polymorphism, in comparison to those that had the low-activity 3-repeat polymorphism.

3.2.2. Depression/anxiety and substance abuse

Several studies have examined the role that genes involved in the dopaminergic and serotonergic pathways play in the relationship between SA and affective disorders. The link between dopamine receptor genes and alcohol abuse

Table 2
Published studies examining the contribution of candidate genes to psychiatric comorbidity.

Disorders	Citation	Genetic factors examined	Sample	Measurement of disorders	Conclusions
Alcohol abuse (ALC) and CD	Samochowiec, J. et al. 1999. Psychiatry Research 86: 67–72	Candidate gene: functional 30-bp repeat polymorphism in the promoter region of the X-chromosomal monoamine oxidase A gene (MAOA)	488 male subjects of German descent (185 psychiatrically screened control subjects and 303 alcohol-dependent subjects)	Composite International Diagnostic Interview	The frequency of the low-activity 3-repeat allele was significantly higher in antisocial alcoholics compared to control subjects and to alcoholics without ASPD.
ALC and CD	Parsian, A. 1999. Genomics 55: 290–295.	Candidate genes: point mutation at position 941 in exon 8 and position 1460 of exon 14 of the MAO-A gene	Alcoholic group of 134 probands classified as alcoholics and 89 unrelated controls who met no DSM-III-R criteria for psychiatric disorders. All subjects are white Caucasians.	Alcoholism identified according to the Feighner criteria for alcoholism, and alcoholism subtypes identified according to the criteria of Cloninger. DSM-III-R criteria	The mutant allele frequency of exon 8 and exon 14 was significantly different in type 2 alcoholics compared to normal controls. The MAO-A activity in alcoholics was lower than that in normal controls. The frequency of the nonmutated alleles, which are associated with low activity, are higher in alcoholic groups than normal controls.
ALC and CD	Parsian, A and Cloninger, CR. 2001. Psychiatric Genetics 11: 89–94.	Candidate genes: polymorphisms in tryptophan hydroxylase (TPH), serotonin receptors (5-HT2A and 5-HT2c), serotonin transporter (5-HTT) and monoamine oxidase A (MAO-A) genes	133 alcoholics. The normal control group consisted of 88 individuals who met no DSM-III-R criteria for affective disorders, alcoholism, or psychotic or drug-use disorders. All subjects were white Caucasians.	Alcoholism identified according to the Feighner criteria and alcoholism subtypes identified according to the Cloninger criteria. DSM-III-R criteria used to evaluate presence of psychiatric disorders.	The allele frequencies of the functional polymorphism in 5-HTTLPR were different in total alcoholics and type 2 alcoholics vs. controls (higher frequencies of the long allele in alcoholics). Genotype frequencies were also different between type 2 alcoholics and controls: the former had an excess of LL homozygotes. No results were significant after correction for multiple testing.
ALC and CD	Saito, T et al. 2002. Psychiatry Research 109: 113–119	Candidate genes: functional 30-bp repeat polymorphism in the promoter region of the MAOA gene	324 male subjects of Caucasian Finnish origin, including 172 alcoholics (114 type 1 and 58 type 2) and 152 control subjects.	Clinical interview with a physician, Michigan Alcoholism Screening Test, and Johns Hopkins Symptoms Checklist 90	No difference was found in allele distribution between type 1 and type 2 alcoholics. There was also no difference in the allele distribution when each group of alcoholics was compared with controls.
ALC and CD	Lu, RB et al. 2003. Alcoholism: Clinical and Experimental Research 27(6): 889–893.	Candidate genes: number of tandem repeats located upstream (uVNTR) and *Eco*RV at exon 14 of *MAO-A*	129 Han Chinese males: 41 with antisocial personality disorder (ASPD) and alcoholism, 50 with ASPD without alcoholism and 38 with a history of antisocial behavior. Also 77 community controls.	Modified Chinese Version of the Schedule of Affective Disorder and Schizophrenia-Lifetime. Used DSM-IV criteria.	Neither antisocial personality disorder nor antisocial alcoholism was associated with the alleles of the uVNTR and the *Eco*RV polymorphisms of the *MAO-A* gene tested individually either at each site or as a haplotype.
ALC and CD	Koller, G et al. 2003. Alcohol and Alcoholism 38(1): 31–34.	MAOA–uVNTR functional polymorphism in the promoter region of the X-chromosomal monoamine oxidase (MAOA) gene	169 male alcoholic subjects and 72 controls of German descent	Brown–Goodwin Assessment for History of Lifetime Aggression, Buss Durkee Hostility Inventory, Barrat Impulsiveness Score	No significant differences were detected between the frequency of the three-repeat allele in the MAOA polymorphism and high or low scores of aggression, irritability, assault or impulsiveness in alcoholics, in comparison to controls.

ALC and CD	Hoenicka, J. et al Neurotoxicity Research 2007 11(1): 51–59	SNPs/microsatellites from four candidate genes: dopamine receptor gene (DRD2), dopamine transporter (SLC6A3), fatty acid amide hydrolase (FAAH) and the cannabinoid receptor type 1 (CNR1)	137 Spanish alcohol dependent adult males; those with childhood ADHD were excluded. 98 community controls free of psychiatric disorders.	International Personality Disorder Examination, Hare's Psychopathology Checklist Revised (PCL-R); DSM-IV ADU diagnosis verified using structured clinical interview, the Addiction Severity Index (ASI), and the Severity of Alcohol Dependence Scale (SADS)	There is a relation between the TaqIA SNP (DRD2 gene), FAAH and CNR1 genes and the PCL-R's Factor 1 (representing emotional detachment) in alcoholic patients. The relationship seems to be additive and independent and might be responsible for 11.4% of the variance in the PCL-R subscale.
ALC and CD	Wang, TJ et al. 2007. Progress in Neuro-Psychopharmacology & Biological Psychiatry 31: 108–114	Candidate genes: number of tandem repeats located upstream (uVNTR) of the monoamine oxidase A (MAOA-u VNTR) and dopamine D2 receptor (DRD2) Taq1A polymorphism	231 Han Chinese males in Taiwan: 73 antisocial alcoholics and 158 antisocial non-alcoholics.	Chinese version of the Modified Schedule of Affective Disorder and Schizophrenia-Lifetime (SADS-L)	Neither the DRD2 TaqI A polymorphism nor the MAOA gene was associated with antisocial alcoholism (rather than non-alcoholic ASPD). However, among those with the MAOA–uVNTR 4-repeat polymorphism, the DRD2 A1/A2 genotype had a protective effect against alcoholism in ASPD subjects
ALC and CD	Dick, D. et al. 2008; Archives of General Psychiatry 65(3): 310–318.	Linkage analyses using data from a genome-wide 10-cM microsatellite scan. Association analyses were conducted on 27 SNPs genotyped across the muscarinic acetylcholine receptor M2 gene (CHRM2)	Approximately 2300 individuals from 262 families	Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) interview. Lifetime alcohol dependence was assessed using DSM-IV criteria; other lifetime diagnoses assessed using DSM-III-R criteria.	Linkage analyses identified a region on chromosome 7 consistent with a gene that broadly predisposes individuals to externalizing behavior. Association analyses of CHRM2 suggest that it is involved in a general externalizing phenotype.
ALC and CD	Lee, SY et al. 2009. Alcoholism––Clinical and Experimental Research 33(6): 985–990.	Candidate genes: genotypes of ALDH2 functional polymorphisms and MAOA–uVNTR	294 Han Chinese antisocial men in Taiwan including 132 ASPD with alcoholism and 162 without alcoholism	Modified Chinese Version of the Schedule of Affective Disorder and Schizophrenia-Lifetime. Used DSM-IV criteria.	A significant difference of ALDH2 polymorphisms was found among the 2 study groups. There was a significant interaction of MAOA and ALDH2 gene in antisocial ALC (odds ratio = 2.927; $p = 0.032$). The protective effects of the ALDH2*2 allele against alcoholism might disappear in subjects with ASPD and carrying MAOA–uVNTR 4-repeat allele in the Han Chinese male population.
ALC and impulsiveness	Limosin F et al. 2005. European Psychiatry 20: 304–306.	Candidate gene frequency: Bal1 polymorphism in dopamine receptor D3 (DRD3)	108 French alcohol-dependent patients and 79 healthy controls	Interviews used the Diagnostic Interview for Genetic Studies (DIGS) and the Barratt Impulsiveness Scale (BIS-10).	Patients above the median value for cognitive impulsiveness were more frequently heterozygous for the gene coding for the DRD3 than alcohol-dependent patients without impulsiveness and healthy controls.
ALC and neuro-psychological disorder	Rodriguez-Jimenez R. 2006. European Psychiatry 21: 66–69.	Candidate gene: Taq1A polymorphism on dopamine receptor D2 (DRD2)	50 Spanish male alcoholic patients w/o other substance consumption in past-year and 98 community controls free of disorders	Structured Clinical Interview for DSM-IV (SCID), Cattell Intelligence Scales (IQ), Continuous Performance test (AX version), and the Stop task.	Alcoholics carrying the Taq1A1 allele present lower sustained attention and less inhibitory control than patients without such allele.
ALC and ADHD	Kim et al. Alcohol & Alcoholism 2006 41(4): 407–411	Candidate genes: DRD2, ALDH2, a regulatory region of the serotonin transporter (5-HTTLPR), and catechol-O-methyltransferase gene polymorphism (COMT)	85 Korean men who were diagnosed as having DSM-IV alcohol dependence (AD). Cases = comorbid ADHD and AD/controls = AD diagnosis only	Barratt impulsiveness scale, Brief anger–aggression questionnaire, Overt aggression scale, Codependence test, Obsessive compulsive drinking scale	No significant differences in gene frequencies of DRD2, ALDH2, 5-HTTLPR or COMT polymorphisms between alcoholics with and without ADHD.
SA and CD	Stallings et al., 2005 Arch Gen Psych 62:1042–1051	Quantitative train loci (QTL) that influence externalizing problem behavior — do they influence DV?	Cases: 249 adolescent sibling-pairs from 191 families. Controls: a community based sample of 4493 adolescents from Colorado	Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM), Diagnostic Interview Schedule	For both DV and CDS, there was evidence of linkage to the same region on chromosome 9q34. Composite index (DV + CDS) yielded strongest evidence for linkage at this location.

(continued on next page)

Table 2 (*continued*)

Disorders	Citation	Genetic factors examined	Sample	Measurement of disorders	Conclusions
SA and CD	Gerra, G. et al. 2005. Addiction Biology 10: 275–281	Candidate gene frequency: 3′ untranslated region of exon 15 of the SLC6A3 gene coding for dopamine transporter (DAT)	125 Italian male subjects and 104 Italian male heroin-dependent subjects (including 52 with violent behavior and criminal records).	Structured Clinical Interviews for Axis I disorders (SCID) Italian version; Buss–Durkee Hostility Inventory (BDHI); antisocial behavior evaluated by forensic psychiatric examination.	There was a difference in gene frequency between offenders and non-offenders among heroin-dependent subjects. The 9-9 genotype increases risk of irritability and direct aggressiveness more than 6–9 times compared to the 9-10 genotype. The 9-repeat allele of the DAT polymorphism confers susceptibility to antisocial-violent behavior and aggressiveness, rather than drug dependence
SA and CD	Jain, M. et al Biol Psychiatry 2007 61:1329–1339	Linkage & identification of candidate genes	18 extended and multigenerational families consisting of 616 members in Columbia (identified via proband children with ADHD diagnosis)	Structured Diagnostic Interviews and the Composite International Diagnostic Interview (CIDI) and the Disruptive Behavior Disorder module from the Diagnostic Interview for Children and Adolescents	Strong linkages among ADHD and ODD, ADHD and CD, ODD and CD, and CD and alcohol abuse/dependence — major genes underlie a broad behavioral phenotype that manifest as ADHD, disruptive behaviors (CD and ODD) and alcohol abuse or dependence. Evidence of linkage for comorbid ADHD phenotypes to loci: 8q24, 2p21–22.3, 5p13.1–p13.3, 12p11.23–13.3, 8q15, 14q21.1–22.2.
SA and CD	Corley, RP et al. 2008. Drug and Alcohol Dependence 96: 90–98.	Single nucleotide polymorphism (SNP) association from a targeted gene SNP assay (SNP chip)—designed to assay 1500 SNPs across 50 candidate genes	231 primarily Caucasian male probands in treatment with antisocial drug dependence and matched controls	CIDI-SAM and DISC-IV or DIS	Two genes, CHRNA2 and OPRM1, each probed with multiple SNPs, emerged as plausible candidates for a genetic role in antisocial drug dependence after gene-based permutation testing.
ALC and DEP	Nurnberger, JI et al 2001 Am J Psychiatry 158:718–724	Linkage analyses & identification of candidate genes	Cases: families with 2 additional alcoholic members. Control families: population-based. Initial = 987 individuals (105 families); Replication = 1295 individuals (157 families)	Probands and all available first-degree relatives were interviewed using SSAGA for DSM-III-R.	Peak lod scores for alcoholism OR depression on chromosome 1, 2, 6, and 16. Peak Lod score for comorbid alcoholism and depression was located on chromosome 2 for the replication and combined data sets (score 4.12 and 2.16 respectively).
ALC and DEP	Terayama et al., 2003 Acta Neuropsychiatrica 15:129–132	Candidate gene frequency: human serotonin 2A receptor (5-HTR2A) polymorphism	80 patients with mood disorders, 50 patients with schizophrenia, 41 patients with alcohol dependence. 112 healthy controls from medical staff. All subjects were Japanese.	A psychiatrist and a psychologist conducted clinical interviews and rated participants using the Positive and Negative Syndrome Scale (PANSS) for schizophrenia.	5-HTR2A polymorphism does not seem be associated with susceptibility to schizophrenia, mood disorders, or alcohol dependency.
ALC and DEP	Marques, FZC et al 2006 Psychiatric Genetics 16(3):125–131	Candidate gene: serotonin transporter 5-HTTLPR	114 male Brazilian patients of European descent with alcohol dependence and 218 controls from a European Brazilian blood donor bank	DSM-III-R Criteria for alcohol dependence determined using the SSAGA.	ALC patients with comorbid MDD, drug abuse, and nicotine dependence presented higher frequency of the S allele than pure ALC patients. ALC patients with comorbid MDD and drug abuse also had higher frequencies of the S-allele than controls.
ALC and DEP	Szczepankiewicz A et al. 2007. Alcohol & Alcoholism 42(2): 70–74.	Candidate genes: one SNP for each dopamine receptor gene 1–4	317 patients with bipolar disorder, including 42 with alcohol abuse. 350 control subjects.	Interviews with at least two psychiatrists, using the structured clinical interview for DSM-IV Axis 1 disorders (SCID)	Found no association of any of the analyzed dopamine gene polymorphisms with comorbid alcohol abuse in bipolar patients, compared to controls.

ALC and ANX	Young, RM et al. 2002. Alcohol & Alcoholism 37: 451–456.	Candidate genes: Taq I A alleles (A1 and A2) of the D2 dopamine receptor (DRD2) gene	91 Caucasian veterans in the Australian armed forces, hospitalized for PTSD and 51 controls, recruited from Brisbane hospitals	Mississippi Scale for Combat-Related Posttraumatic Stress Disorder. Patients also had a psychiatric history taken or were assessed by a clinical nurse.	DRD2 A1 allelic frequency was significantly higher among the harmful drinkers with PTSD (27.6%) than in the non-harmful drinkers with PTSD (14.2%) and among the controls (6.9%).
ALC, DEP and ANX	Huang, SY et al. 2004. Alcoholism—−Clinical and Experimental Research 28(3): 374–384.	Candidate genes: dopamine D2 receptor (DRD2) gene, alcohol dehydrogenase 1B (ADH1B), and aldehyde dehydrogenase (ALDH2) genes	Han Chinese subjects: 71 had pure alcohol dependence, 113 had alcohol dependence and anxiety–depression and 129 only had anxiety–depression. 152 were normal controls.	Chinese version of the modified Schedule of Affective Disorders and Schizophrenia-Lifetime	The DRD2 gene was not associated with pure alcohol dependence or ANX/DEP, but was associated with ANX/DEP ALC. Furthermore, the association between the DRD2 gene and ANX/DEP ALC was shown to be under the stratification of the ALDH2*1/*1 and ADH1B*1/*2 genotypes.
ALC, DEP and ANX	Lin, S. et al Progress in Neuro-Psychopharmacology & Biological Psychiatry 2007 31:1526–1534.	Candidate genes: dopamine D2 receptor (DRD2), serotonin transporter promoter region (5-HTTLPR) gene	46 alcohol dependents and 87 ANX/DEP ALC recruited from two hospitals in Taipei, Taiwan. 57 individuals without history or diagnosis of ALC recruited from the community.	Modified Schedule of Affective Disorder. The Tridimensional Personality Questionnaire (TPQ) measured personality traits (novelty-seeking (NS) and harm-avoidance (HA))	ANX/DEP ALC are characterized by higher NS and HA scores; NS was elevated only in ANX/DEP ALC patients with the DRD2 Taq1 A1 allele and in those with the 5-HTTLPR S/S genotype, while HA was elevated only in ANX/DEP ALC samples carrying 5-HTTLPR S/L or L/L genotype.
ALC, DEP and ANX	Huang, SY et al. 2007. Journal of Psychiatry & Neuroscience 32(3): 185–192.	Candidate genes: MAOA polymorphisms and dopamine DRD2 receptor gene	427 Han Chinese men (201 control subjects and 226 with alcoholism—108 with pure alcohol dependence (ALC) and 118 with alcohol dependence and anxiety, depression or both (ANX/DEP ALC).	Chinese version of the Modified Schedule of Affective Disorders and Schizophrenia-Lifetime.	The genetic variant of the DRD2 gene was only associated with the ANX/DEP ALC phenotype, and the genetic variant of the MAOA gene was associated with pure ALC. Subjects carrying the MAOA 3-repeat allele and genotype A1/A1 of the DRD2 were 3.48 times (95% confidence interval = 1.47–8.25) more likely to be ANX/DEP ALC than the subjects carrying the MAOA 3-repeat allele and DRD2 A2/A2 genotype.
DEP and ANX	Rowe, DC et al 1998 Behavior Genetics 28(3):218–225	Candidate gene frequencies (transmission disequilibrium): dopamine transporter (DAT1)	Clinic-referred cases comprise 125 families and controls 53 families, mostly male (83%). From Tucson.	Parents children's behavioral problems using the Emory Diagnostic Rating Scale (EDRS).	Symptoms of all eight disorders increased with a greater number of 10-repeat DAT1 alleles. Three disorders show association between- and within-families: (GAD), social phobia, and Tourette's disorder. This suggests that DAT1 makes a contribution to GAD and social phobia that is independent of its contribution to ADHD.
DEP and ANX	Camp, NJ et al. 2005. American Journal of Medical Genetics Part B 135B, 85–93 (115)	Genome-wide linkage analyses	87 large, extended Utah pedigrees. Prospective participants needed to have a family history consisting of ≥3 family members with MDD	The brief screen for psychopathology (BSP) was developed by study staff, as an adaptation to the CIDI.	Evidence for linkage on chromosomes: 3centr (dominant, MDD-recurrent or anxiety), 7p (dominant, MDD-RE or anxiety), and 18q (dominant, MDD-RE and anxiety). Best evidence for 3p12.3-q12.3 (accepted locus for panic disorder, agoraphobia, neuroticism) and 18q21.33–q22.2 (accepted locus for bipolar disorder).

(*continued on next page*)

Table 2 (*continued*)

Disorders	Citation	Genetic factors examined	Sample	Measurement of disorders	Conclusions
DEP and ANX	Maron et al., 2005 Psychiatric Genetics 15(1):17–24	Haplotype analyses of 21 candidate genes: serotonin, cholecystokinin, dopamine, and opioid neurotransmitter systems	127 patients with PD (60 PD-comorbid, 42 PD-pure) and 146 healthy control subjects from Tartu, Estonia.	Mini International Neuropsychiatric Interview (MINI), substantiated by medical records.	Several polymorphisms in the cholecystokinin, serotonin, and dopamine systems were associated with PD-all (HTRC2C Cys23Ser, HTR1A, CCK2, CCK1 1270C-G polymorphism, DRD4-1217del-G polymorphism) and/or PD-comorbid (HTR1A, CCK1 receptor 246G-A and 1270C-G polymorphisms, CCK gene haplotype-45 T/1270G) phenotypes, while pure PD was associated only with the HTR2A receptor and DRD1 receptor polymorphisms.
DEP and ANX	Lawford, BR. et al 2006. European Psychiatry 21: 180–185.	Candidate gene frequency: A1 allele of the D2 Dopamine receptor (DRD2)	57 untreated Caucasian Vietnam veterans with PTSD in Australia.	PTSD diagnosed by psychiatrist according to DSM-IV. For other psychopathologies, participants were Interviewed using the General Health Questionnaire-28 (GHQ).	Participants with the DRD2 A1 allele had higher scores for anxiety/insomnia, social dysfunction, and depression. Cluster analysis identified 2 groups: high-psychopathology (comorbid somatic, anxiety/insomnia, social dysfunction, depression) and a low-psychopathology cluster. DRD2 A1 allele veterans compared to those without this allele were more likely to be found in the high than in the low psychopathology cluster group.
DEP and ANX	Wray, NR. et al 2007 Arch Gen Psychiatry 64:318–326	6 SNPS from the PLXNA2 gene	Study twins selected according to extreme concordant or discordant neuroticism scores from an Australian population cohort of 18,742 twins and their siblings. Total $n = 624$ individuals.	Composite International Diagnostic Interview (CIDI), the 23-item Neuroticism scale of the revised Eysenck Personality Questionnaire, and the Kessler Psychological Distress Scale.	There was evidence of an allelic association between one SNP (rs2478813) of PLXNA2 and ANX, DEP, neuroticism and psychological distress. Individuals who are comorbid for anxiety may drive the association of rs2478813 with depression, neuroticism, and psychological distress.
ALC, CD, DEP and ANX	Schmidt, LG et al. 2000. Journal of Neural Transmission 107: 681–689.	Candidate genes: functional 30-bp repeat polymorphism in the promoter region of the MAOA gene [variation in the number of repeats (3–5) of the MAOA gene-linked polymorphic region (MAOA-LPR)]	298 male alcohol-dependent patients of German descent, of whom 59 also exhibited an antisocial disorder and 31 had an anxious-depressive personality disorder, plus 182 male and 180 female controls, derived from a sample of healthy volunteers.	Substance Abuse Section of the Composite International Diagnostic Interview, while psychiatric comorbidity was diagnosed according to DSM IV criteria——final diagnoses were made based on information from a clinical i nterview by trained clinicians	Among males, the frequency of the low-activity 3-repeat MAOA genotype was significantly higher in antisocial alcoholics than in controls. Among male alcoholics, a significantly lower frequency of the 3-repeat allele was found in anxious-depressive patients compared to antisocial subjects. In females, no significant differences in genotype frequencies of alcoholic subtypes and controls, but there was a trend of fewer genotypes with a 3-repeat allele in the anxious-depressive subgroup compared to female alcoholics with no other diagnoses.

comorbid with affective disorders, for example, remains controversial and may depend on the specific type of affective disorder under study (Huang et al., 2004; Huang et al., 2007; Lin et al., 2007; Szczepankiewicz et al., 2007; Young et al., 2002).

Selected studies have also found an association between polymorphisms that result in low serotonin levels and comorbidity. A high frequency of the S allele in the serotonin transporter has been associated with comorbid major depressive disorder, nicotine dependence and drug abuse among alcohol dependent male Brazilian patients (Marques et al., 2006), as well as with a novelty-seeking personality in Taiwanese ANX/depressive comorbids (Lin et al., 2007). We found one study that examined the relationship between the serotonin 2A receptor polymorphism and mood disorders and alcohol dependence, but failed to find an association between the two (Terayama et al., 2003).

3.2.3. Depression and anxiety

Comorbidity between depression and anxiety has been linked to a range of different candidate genes. A specific variable number tandem polymorphism repeat in the dopamine transporter gene, for example, was associated with attention deficit hyperactivity disorder (ADHD), generalized ANX and social phobia in a clinic-referred United States sample (Rowe et al., 1998). In a sample of Caucasian Vietnam veterans in Australia, the TaqI A allele of the dopamine receptor gene was associated with comorbid anxiety and depression (Lawford et al., 2006). Maron et al. (2005) screened 90 SNPS in genes associated with the neurobiology of anxiety. They found that in a case–control study of patients with PD in Estonia, polymorphisms in cholecystokinin (CCK)-related genes and the serotonin 1A receptor (HTR1A) were associated with PD comorbid with affective disorders. Finally, PLXNA2 gene, which encodes for plexin 2A, has been implicated in comorbidity between depression and anxiety (Wray et al., 2007). Plexin 2A acts as a receptor for class 3 semaphorins, which are expressed in the adult nervous system—they are plausible candidates for common etiology of a range of psychiatric disorders because of their role in the development, maintenance and apoptosis of the nervous system.

3.3. Specific environmental determinants of comorbidity

Studies summarizing existing evidence on environmental determinants of comorbidity are presented in Table 3. Much of the research assessing the influence of social factors on comorbidity has studied the quality of the family and peer environments as common factors that underlie the association between disorders (Aseltine et al., 1998; Fergusson et al., 2003; Goodwin et al., 2004; Ingoldsby et al., 2006; Kim et al., 2003; Kirisci et al., 2009; McGee et al., 2000; Rowe et al., 2004; Wanner et al., 2009; Windle and Davies, 1999; Wu et al., 2006). Silberg et al. (2003), for example, found that a common shared environmental factor lay behind the correlation behind substance use, CD, and two risk factors: family disturbance and selection of deviant peer groups. From this, we may conclude that family dysfunction and deviant peers constitute key components of the shared adverse environment. Parenting and family support have been linked with comorbidity between SA and either depression or CD, as well as between CD and depression. Peer deviance has been associated with comorbidity between SA and either anxiety, depression or CD. In a three-year follow-up of 1208 adolescents who were 14–17 years old at baseline, low family support and high peer pressure differentiated youths with co-occurring depression and SA from those with depressed mood only, while low levels of family and friend support and conflict with friends differentiated the comorbids from those with SA only (Aseltine et al., 1998). Depressive symptoms and conduct problems were also significant predictors of involvement with antisocial peers, according to a study of school-age children in four sites across the US (Ingoldsby et al., 2006). In contrast, a study of 206 boys followed from ages 9 to 24 did not find that parenting practices, operationalized as parental warmth/support, lack of aversive behavior and disciplinary skills, mediated the impact of boys' antisocial behavior on levels of depressive symptoms at ages 14–15 (Kim et al., 2003).

Stressful life events, such as parental death, as well as traumatic events, such as exposure to violence, also played an important role in generating comorbidity between externalizing and internalizing disorders, and between ANX and DEP (Copeland et al., 2007; de Graaf et al., 2004a,b; Fergusson et al., 2003; Hayatbakhsh et al., 2007; Hettema et al., 2006a; Murray and Farrington, 2008; Windle and Davies, 1999; Wu et al., 2006). Traumatic exposures have been associated with an increased for comorbid mood and SA among individuals with ANX. In the Great Smoky Mountains Study, children ages 9–13 were followed annually until age 16; those who had experienced traumatic events and had a history of ANX had a higher likelihood of exhibiting PTSD (Copeland et al., 2007).

Longitudinal studies of adults also found that the risk of comorbidity between ANX and mood and SA increased for those who experienced a traumatic event (de Graaf et al., 2004a,b), (Hettema et al., 2006a; Moffitt et al., 2007). In a study of 7065 adults aged 18–65, transitions from pure ANX to comorbidity with mood or SA were associated with childhood traumas and recent stressful life events (de Graaf et al., 2004a) while a study of adult twins found that GAD was associated with a higher risk of onset of MD in the presence of stressful life events (Hettema et al., 2006a).

Traumatic events have also been linked with a higher risk for comorbidity among individuals who suffered from DEP. In a study of 975 high school students followed for 2 years, adolescents who were heavy drinkers and were classified as depressed had the highest levels of stressful life events (such as death of a parent, failing an academic subject, going to a new school, or breaking up with a boyfriend), in comparison to the DEP-only, heavy-drinking-only and no problems groups (Windle and Davies, 1999). Longitudinal studies from infancy to adulthood and during adolescence indicate that the link between DEP and smoking (Fergusson et al., 2003) and DEP and heavy alcohol use (Windle and Davies, 1999; Wu et al., 2006) may be due to shared risk factors, including adverse life events. Finally, one study indicates that parent–child separation due to parental imprisonment, a potentially traumatic event for a child, increased the likelihood of co-occurrence of internalizing problems and CD (Murray and Farrington, 2008).

Academic difficulties also emerged in three studies as an important factor that differentiated comorbid groups from groups with single disorders (Ingoldsby et al., 2006; Repetto et

Table 3
Published studies examining environmental factors associated with psychiatric comorbidity.

Citation	Environment factors	Sample	Follow-up time	Measurement of disorders	Conclusions
Young, R et al. 2008. Alcohol & Alcoholism; 43(2): 204–214.	Social class; receiving alcohol from parents	2586 pupils (1335 males and 1251 females) from a school-based cohort in Scotland	Followed from age 11 to 15	Diagnostic Interview Schedule for Children (Voice-DISC).	Short-term simultaneous models support a reciprocal relationship between antisocial behavior and alcohol misuse for females, regardless of social class, and for males from manual (lower social class) backgrounds; among males from non-manual social class, the susceptibility hypothesis is supported (antisocial behavior leads to alcohol misuse, but not the other way around).
Wanner, B et al. Psychology of Addictive Behaviors 2009; 23(1): 91–104.	Socioeconomic status, parental supervision, deviant peers	1) Francophone boys from schools in disadvantaged areas in Montreal ($n=502$); 2) participants in a longitudinal study from Quebec, Canada ($n=663$).	Followed from age 5 to age 23	Diagnostic Interview Schedule for Children-Child Version and SRDQ	After controlling for disinhibition, deviant peers and parental supervision, the links between adolescent substance use and adult violence and theft were no longer significant. For sample 2, the link of adolescent theft to adult substance use remained significant.
Kirisci, L et al. 2009. The American Journal of Drug and Alcohol Dependence 35: 145–150.	Deviance of peers	Sample of boys ($n=380$) and girls ($n=127$) whose fathers were initially recruited for a study due to their substance dependence diagnosis.	Followed from age 10–12 to age 16	Neurobehavioral disinhibition (ND) measured with indicators of affect regulation, behavior control and executive cognitive capacity	Peer social deviance mediated the association between ND and number and frequency of illegal drugs used. In boys, peer deviance mediated the association between ND at age 10–12 and number of illegal drugs ever used/frequency of illegal drug use. Also in boys only, ND at age 16 mediated the association of peer deviance at age 10–12 with number of illegal drugs used at age 16.
Crum and Pratt, 2001; 158: 1693–1700.	Education level, marital status	1161 individuals from five metropolitan US areas (ECA)	4 years	Diagnostic Interview Schedule	The crude relative risks for heavy drinking in people with social phobia did not change with the inclusion of socio-demographic characteristics (sex, age, race), marital status, age at first intoxication, and history of other psychiatric or illicit drug use disorders
Goodwin et al. J Psychiatric Research 2004; 38: 295–304.	Childhood abuse, adverse family life events, parental history of depression, parental criminal offending, and illicit drug use	1265 children born in Christchurch, New Zealand	Birth to 21 years	Composite International Diagnostic Interview	Associations between anxiety disorder and substance dependence are largely or wholly non causal and reflect the presence of confounding factors (fixed childhood factors, substance dependence, comorbid depression, concurrent affiliations with deviant peers) that are associated with increased susceptibility to anxiety disorder
Hayatbakhsh et al. 2007. Journal of the	Socio-demographic factors, parental psychopathology,	3239 Australian young adults	Birth to 21 years	Young Adult Self-Report (YASR); cannabis use	The association between cannabis and AD (anxiety and depression)

American Academy of Child and Adolescent Psychiatry 46(3): 408–417.	familial conflict, childhood physical and sexual abuse, personality factors during youth			retrospectively assessed	is not explained by measured individual and social factors at baseline.
Aseltine et al. 1998. Development and Psychopathology 10: 549–70.	Stress, social support, family support, peer pressure	900 adolescent (9th, 10th and 11th graders) in Boston, MA	3 years	Center for Epidemiological Studies Depression Scale (CES-D); measures of alcohol and drug use adapted from Monitoring the Future studies	The comorbid group (both depressed problems and substance use problems) had significantly higher levels of stress and lower levels of support than those with neither problem; Peer pressure is strongly related to co-occurring problems but not to depression, and the comorbid subgroup also evidences significantly lower levels of family support
Windle and Davies, 1999; 11: 823–844.	Perceived social support–family, close-friend characteristics, and stressful life events.	1195 high school sophomores and juniors from western New York	1 year (between time 2 and time 4)	Center for Epidemiological Studies Depression Scale(CES-D); alcohol consumption measured with a Standard Quantity Frequency Index	Compared to the no-problem, depression only and alcohol use only subgroups, the mixed subgroup reported the most pervasive, low levels of functioning, with the highest levels of stressful life events, lowest levels of family social support, and high levels of delinquency
Fergusson et al. Psychological Medicine 2003; 33: 1357–1367.	Confounding factors: childhood adversity, novelty-seeking, neuroticism, parental smoking, parental attachment, deviant peer affiliations.	Birth cohort of 1265 children (635 males, 630 females) born in Christchurch, New Zealand in mid 1977.	Assessed at birth, 4 months, 1 year, annually to age 16 and at 18 and 21.	Diagnostic Interview Schedule for Children (DISC) and Composite International Diagnostic Interview (CIDI)	The association between smoking and depression is potentially due to confounders that affected the development of both outcomes, including childhood adversity, novelty-seeking, neuroticism, childhood conduct problems, parental smoking, parental attachment, alcohol abuse dependence, deviant peer affiliations, and adverse life events.
Wu et al. Pediatrics 2006; 118(5): 1907–1915.	Parental psychopathology, monitoring, discipline, maternal warmth and support, physical abuse; stressful life events, exposure to violence, antisocial behavior.	1119 Puerto Rican children and early adolescents in New York City and in San Juan, PR	4 years	Child alcohol use measured with questions regarding lifetime and past-year alcohol use and questions from the alcohol abuse section of the DISC-IV; Depressive symptoms were assessed.	Depressive symptoms and alcohol shared some significant risk and protective factors such as parental psychopathology, parenting, child exposure to violence, and antisocial behaviors.
de Graaf et al., 2004a. Journal of Affective Disorders; 82: 461–467.	Gender, age, education, living with partner, employment, somatic disorder; neuroticism, social support, childhood trauma, parental psychiatric history, negative life events.	7065 adults aged 18–65 in the Netherlands	Baseline, 1 year, 3 years	Composite International Diagnostic Interview (CIDI)	Comorbid transition from pure mood disorder was associated with higher age, external mastery and severity of the disorder; comorbidity developing from pure anxiety disorder was associated with past and recent stressful life circumstances and physical functional disability. Predictors of comorbid transition from pure substance use disorder were personal and social vulnerability variables only (high neuroticism, low social support).

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Table 3 (*continued*)

Citation	Environment factors	Sample	Follow-up time	Measurement of disorders	Conclusions
de Graaf et al., 2004b. Acta Psychiatrica Scandinavica; 109: 55–63.	Education, living with partner, paid employment, social support, childhood trauma, life events: negative life events, ongoing difficulties.	4796 adults in the Netherlands	Baseline, 1 year, 3 years	Composite International Diagnostic Interview (CIDI)	Comorbidity was predicted by negative life events and ongoing difficulties. Paid employment was the only factor predicting a greater likelihood of comorbidity than a pure mood disorder; negative life events and ongoing difficulties signaled a greater likelihood of comorbidity than of pure anxiety disorder; low self-esteem, childhood trauma, negative life events and ongoing difficulties indicated greater odds of comorbidity than a pure substance use disorder.
Repetto et al. J Adolescent Health 2004; 35: 468–477.	Stressful life events	579 African American students from a Midwestern city	4 years	Brief Symptom Inventory	Adolescents who presented consistently high levels of depressive symptoms were more likely to be female, reported more anxiety symptoms, lower self-esteem, higher stress, and lower GPA that adolescents in other trajectories.
Hettema et al., 2006a Psychological Medicine; 36: 789–795.	Stressful life events (SLEs)	8068 adult twins from the Mid-Atlantic Twin Registry	3 interviews: completed every year to four years.	Interviewers assessed MDD according to DSM-III-R "A Criteria," GAD using DSM-III-R criteria.	Prior GAD is associated with greater risk of depressive onset due to the impact of SLEs. Gender differences: Males and females with GAD are at similarly high risks of developing MDD after experiencing SLEs, however without prior GAD, females are at a consistently higher risk for developing MDD at every level of threat.
Copeland et al. Arch Gen Psychiatry 2007; 64: 577–584.	Traumatic events	1420 children aged 9,11 and 13 from western North Carolina	Until 16 years of age (7, 5 and 3 years)	Child and Adolescent Psychiatric Assessment (CAPA)	Children exposed to trauma had almost double the rates of psychiatric disorders of those not exposed. Depression, anxiety disorders and ADHD were associated with subclinical PTSD symptoms. Although past depression best predicted first trauma, a history of anxiety disorders best predicted PTS symptoms in response to trauma exposure.
Moffitt et al. 2007. Psychological Medicine 37(3): 441–452.	Family psychiatric history, low childhood socioeconomic status, parental harsh discipline, maltreatment, parental loss, Inhibited temperament.	1037 member of a birth cohort (972 were assessed by the last measurement) in New Zealand.	21 years (studied at 11,13,15,18,21,26, and 32 years)	Diagnostic Interview Schedule for Children-Child Version, and with the Diagnostic Interview Schedule	The co-morbid MDD + GAD group scored worse than the GAD-only on 3 of 13 risk factors, and the MDD-only group on 9 of 13 risk factors. Adults diagnosed with both MDD and GAD had the most pronounced risk histories as indicated by family psychiatric history, childhood adversity, and behavior; GAD, whether comorbid or pure, was associated with maternal internalizing symptoms, low SES, maltreatment, inhibited temperament.

Bjelland et al. Social Science & Medicine 2008; 66: 1334–1345.	Education level	33,774 adults in Nord-Trondelag County, Norway	11 years	Expanded Hospital Anxiety and Depression Scale (EHADS)	Higher educational level, or the factors reflected by higher educational level may protect against anxiety and depression, and the protective effect seems to accumulate throughout life. Effect sizes with >4 years college as reference were Primary School: 0.26(0.23–0.29), High School <3 years: 0.16(0.13–0.19), High School: 0.12(0.08–0.17), College <4 years: 0.04(0.00–0.08).
Kim et al. 2003; Journal of Family Psychology 17(4); 571–583.	Parent's mental health history; parental transitions; parental Income; parenting practices	206 boys recruited through 4th grade classes (depression studied from ages 14–15 to 23–24) in Oregon	10 years	Center for Epidemiologic Studies Depression Scale (CES-D); Antisocial Construct from items from the Teacher Child Behavior Checklist	Parenting effects (warmth/support, lack of aversive behavior and disciplinary skills) did not mediate the impact of young men's antisocial behavior on level of depressive symptoms at ages 14–15.
Ingoldsby et al., 2006. Journal of Abnormal Child Psychology 34: 603–621.	Academic adjustment and social competence; antisocial peer relations;	431 school-age children from Durham, NC; Nashville, TN; Seattle, WA; central Pennsylvania	5th grade to 7th grade	Conduct problems: Things You Have Done survey, Self-Report Delinquency Scale, Child Behavior Checklist, Teacher's Report Form; Depressive Symptoms: Reynolds Child Depression Scale and the Child Behavior Checklist	Youth with co-occurring problems in the fifth grade were demonstrating significantly lower academic adjustment and social competence 2 years later and more antisocial peers and substance use than youth with depressive symptoms only or low problems overall.
Murray and Farrington, 2008 Development and Psychopathology; 20: 273–290.	Parental imprisonment	411 males from a working class area of Southern London	Followed from age 8 to 48	Antisocial personality assessed from interviews, anxiety and depression were measured using the General Health Questionnaire	Parent–child separation due to parental imprisonment predicted the co-occurrence of internalizing and antisocial problems
Dierker and Merikangas, 2001 J Am Acad Child Adolesc Psychiatry; 40(10: 1159–1167.	Socioeconomic status	173 participants aged 7 to 17 years	Mean of 2.5 years in wave 1, mean of 3.5 years in wave 2	Child diagnoses based on a version of the Schedule for Affective Disorders and Schizophrenia for School-age Children	Socioeconomic status — when entered as a main effect in the full multivariate model, the reported associations between psychiatric disorders and nicotine dependence remained unchanged (see Notes).
McGee et al. Addiction 2000; 95(4): 491–503.	Socioeconomic status	A large sample of New Zealand children being followed from birth across the life span.	26 years	Cannabis use first assessed by self-report, then using the Diagnostic Interview Schedule for DSM-III-R criteria; Mental assessed with Diagnostic Interview Schedule for Children	At least part of the early association between cannabis use and mental disorder reflected shared pathways from socio-economic disadvantage and behavior problems in childhood, coupled with low attachment to parents at adolescence.
Rowe et al. 2004. Journal of Substance Abuse Treatment 26(6): 129–140.	Family factors: parent psychopathology, family cohesion, family conflict, family drug problems, mental health problems and legal problems.	182 adolescents in Philadelphia referred to drug treatment. Average age 15 years old; all subjects met criteria for a substance use disorder.	Baseline, discharge, and 6 and 12 months post-discharge	Diagnostic Interview Schedule for Children, 2nd edition (DISC-2.3) and the Child Behavior Checklist.	According to parent reports, families of Exclusive Substance Abusers had higher levels of cohesion than families of Mixed teens, and lower levels of conflict than both Mixed Substance Abusers and Externalizers. Family drug problems, mental health problems and legal problems were significantly higher in the Mixed group than among the Exclusive Substance Abusers.

al., 2004; Windle and Davies, 1999). In a study of children from four sites across the US who were followed from fifth to seventh grade, children who had both CD and depressive symptoms had lower academic competence (Ingoldsby et al., 2006). Similarly, Windle and Davies, (1999) followed 975 high school students aged 15.5 at baseline, and found that adolescents who were involved in heavy drinking and were depressed had a lower academic grade point average (GPA) than those who either had a single disorder or no disorder. Repetto et al. (2004) focused on African American students from a Midwestern city, and found that individuals with consistently high levels of depressive symptoms not only also had high levels of anxiety, but they also had a lower GPA than respondents who followed other trajectories.

Economic circumstances have also been associated with comorbidity in selected studies, although the scarce evidence is mixed (Bjelland et al., 2008; Crum and Pratt, 2001; de Graaf et al., 2004b; Dierker and Merikangas, 2001; McGee et al., 2000; Moffitt et al., 2007; Young et al., 2008). A birth cohort of 1037 persons followed over 21 years found that the comorbid GAD–MD group had significantly lower childhood socioeconomic status than the MD-only group (Moffitt et al., 2007). Among a sample of 4796 adults followed for 3 years, unemployment was the only risk factor that differentiated comorbids with SA, anxiety and depression, from adults with a pure mood disorder (de Graaf et al., 2004b).

4. Discussion

To date, a number of studies have shown that anxiety, depression, substance abuse and CD cluster in individuals across the lifecourse. One of the key questions that remain, however, relates to the causes of comorbidity: the direction and mechanisms underlying causal links, as well as the potential spurious nature of such links. This is the first review, to our knowledge, that summarizes the existing evidence on genetic and environmental determinants of comorbidity between CD, DEP, ANX and SA. Such information is critical if we are to develop an effective research agenda on psychiatric comorbidity.

Considerable variation exists across studies in terms of the contribution that genetic and environmental factors make to psychiatric comorbidity. Despite such heterogeneity however, a few consistent findings can be highlighted. Genetic factors play a particularly strong role in comorbidity between MD and GAD or PTSD, while both the shared and non-shared environments make an important contribution to comorbidity between mood and anxiety disorders. Genetic and non-shared environmental factors also make a moderate to strong contribution to the relationship between CD and SA.

Twin studies indicate that disorders within the internalizing and externalizing spectrums seem to share more common genetic and environmental influences than disorders across the internalizing/externalizing divide. Preliminary evidence also highlights the importance of conducting developmental and sex-stratified studies of comorbidity. Heterogeneity of findings by age indicate that the expression of genetic and environmental effects may change during development, leading to different genes or environmental factors affecting the same phenotype at different ages, while variation by sex indicates that the same genetic and environmental factors may contribute to different phenotypes in males and females. Finally, studies with multiple disorders indicate that some of the phenotypic correlations among disorders may be due to genes that act on just one disorder, as was the case with the covariation between MD and drug dependence, which was primarily explained by genetic influences on CD.

A range of candidate genes involved in dopaminergic and serotonergic processes and in the central nervous system has been implicated in psychiatric comorbidity. Two types of studies predominate in the literature: candidate gene association studies and genome-wide analyses, which sometimes also involve a gene association sub-analysis of candidate genes. Candidate gene studies have begun to shift from examining the isolated contribution of specific genes on comorbidity, to consider epistasis: the joint action of multiple genes.

Current molecular studies on comorbidity suffer from a range of important limitations. The bulk of candidate gene studies use a case–control study design with clinical samples and different types of control groups, which makes comparison across studies difficult. Such studies often do not have the full range of comparison groups necessary to assess the relationship between specific candidate genes and comorbidity in case–control studies: that is, a group with one of the comorbid disorders, one with the other comorbid disorder, a group with no disorders, and one with both disorders. Further, little consideration is often given to the actual comparability of comparison groups in factors such as age, sex, ethnic and social background. Second, sample sizes are often too small to detect real variation in genetic polymorphisms in different groups–reproducible associations for SNPs have small effect sizes that are only detectable with sample sizes in the thousands–the bulk of studies reviewed have sample sizes in the low hundreds, which means they are drastically underpowered to detect true associations. Underpowered studies, with less stringent *p*-value thresholds, have a higher risk of detecting false-positive findings. Third, genetic association studies using large numbers of SNP markers, many of which have linkage disequilibrium, are often subject to problems of multiple testing. Failure to adjust for multiple testing appropriately may produce excessive false positives or overlook true positive signals. Given such limitations, the findings reported in the reviewed studies need to be taken as strictly preliminary and hypothesis-generating. Genome-wide association studies (GWAS) with careful adjustment for multiple testing will, in the future, hopefully help us find biologically-plausible candidate genes for comorbidity, that we may then test in adequately-powered samples.

One of the key elements to discern the causal links between comorbid disorders involves understanding the modifiable environmental factors that are associated with comorbidity. The main social factors that come across as pivotal include childhood adversity/life events, family and peer social connections, and socioeconomic and academic difficulties. Research on the social epidemiology of comorbidity is still in its infancy however, and the scarce research that exists does not allow us to make conclusive statements about the particular types of factors associated with each combination of disorders. Moreover, prior investigation has been restricted to characteristics of the individual and the family that may influence comorbidity, but has not begun to examine the potential role that an individual's residential context could play in generating comorbid patterns. Finally, we cannot draw any conclusions about the influence

that social factors have on specific types of comorbid patterns—concurrent comorbidity vs. sequential comorbidity, for example. The existing studies do point, however, to the potential importance that environmental factors may have in generating comorbidity. Importantly, traumatic event and environmental stressor exposure is potentially modifiable, hence making the study of these factors particularly important from a public health and prevention point of view.

In conclusion, a large number of twin studies have established that genetic and environmental factors contribute to the longitudinal and concurrent relationships between disorders. The current challenge lies in identifying the specific genetic and environmental factors that explain, modify or mediate comorbid relationships. GWAS linkage studies are needed to identify plausible candidate genes for psychiatric comorbidity. Prospective population-based studies that investigate the developmental trajectories of comorbid disorders and examine the influence of genetic and environmental factors at multiple levels of influence as potential confounders, moderators and mediators of comorbid relationship provide a promising avenue to understand the underlying etiology of psychiatric comorbidity.

Role of the funding source

This manuscript was funded by support from the Robert Wood Johnson Foundation Health and Society Scholars Program (RWJF) and through federal funding from the National Institutes of Health, including grants DA 022720, MH 082729 and MH 078152. The RWJF, NIDA and NIMH had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Conflict of interest

The authors report no competing interests.

Acknowledgements

We would like to thank the staff at the University of Michigan Library for assistance in the literature search.

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