

10-Year Research Update Review: The Epidemiology of Child and Adolescent Psychiatric Disorders: II. Developmental Epidemiology

E. JANE COSTELLO, PH.D., DEBRA L. FOLEY, PH.D., AND ADRIAN ANGOLD, M.R.C.PSYCH.

ABSTRACT

Objective: To describe the growth of developmental epidemiology in the past decade and to illustrate it with examples of recent studies. **Method:** A review of publications on developmental epidemiology in the past 10 years and a discussion of some key examples. **Results:** The authors describe how the interaction between developmental psychopathology and psychiatric epidemiology has produced developmental epidemiology, the study of patterns of distribution of psychiatric disorders in time as well as in space. They give two examples of the kinds of questions that developmental epidemiology can help to answer: (1) Is the prevalence of autism increasing? Does the use of vaccines explain the increase? (2) Is there an epidemic of child and adolescent depression? Finally, they describe two areas of science that are beginning to inform developmental epidemiology: molecular genetics and the use of biological measures of stress. **Conclusions:** While child and adolescent psychiatric epidemiology continues, as described in the first of these reviews, to address questions of prevalence and burden, it has also expanded into new areas of research in the past decade. In the next decade, longitudinal epidemiological data sets with their rich descriptive data on psychopathology and environmental risk over time and the potential to add biological measures will provide valuable resources for research into gene–environment correlations and interactions. *J. Am. Acad. Child Adolesc. Psychiatry*, 2006;45(1):8–25. **Key Words:** epidemiology, development, review.

As we discussed in the first of these two reviews (see the October 2005 issue of the journal), epidemiology wears two hats: it supports public health by identifying the extent of mental illness and service needs and it aids in the scientific search for causes of mental disorders (Earls, 1979). The first of these reviews discussed the contributions of epidemiology to knowledge about the public health burden of child and adolescent psychiatric

disorders. This review deals with epidemiology as a scientific tool for understanding how psychiatric disorders develop.

In this article, we first describe the process by which child psychiatric epidemiology has morphed into developmental epidemiology by incorporating ideas from developmental psychopathology, which in turn used developmental science to change our thinking about psychopathology. Next, we review what has been learned about the development of psychiatric disorders from an epidemiological point of view in the past decade: what we have learned about changes in disease prevalence over recent decades, about age at onset, comorbidity, and the order in which disorders first appear. Third, from the wealth of new knowledge, we highlight two “hot” topics in psychiatric epidemiology: (1) Is autism caused by vaccines? and (2) Is there an epidemic of child or adolescent depression? Finally, we look to the future in two areas that are likely to produce huge dividends in the next decade: the development of biomarkers for stress, and the integration of molecular genetics and environmental risk studies.

Accepted August 5, 2005.

Drs. Costello and Angold are with the Center for Developmental Epidemiology, Duke University Medical School, Durham, NC; and Dr. Foley is with the Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond.

Work on this article was supported in part by grants 06937, 01002, and 01167 from the National Institute of Mental Health, and grants 011301 and 016977 from the National Institute on Drug Abuse.

Correspondence to Dr. E. Jane Costello, Box 3454, Duke University Health Systems, Durham NC 27710; e-mail: elizabeth.costello@duke.edu.

0890-8567/05/4501-0008©2005 by the American Academy of Child and Adolescent Psychiatry.

DOI: 10.1097/01.chi.0000184929.41423.c0

FROM DEVELOPMENTAL PSYCHOPATHOLOGY TO DEVELOPMENTAL EPIDEMIOLOGY

To understand how the epidemiological study of child and adolescent psychiatric disorders has changed in the past decade, we need to go back in history to the 1980s and examine the integration of child psychiatric and normative developmental research that created a new discipline: developmental psychopathology.

The relationship between child and adolescent psychiatry and developmental psychology has waxed and waned during the past century. In its earliest decades, child and adolescent psychiatry tended to equate "development" with psychodynamic concepts. In the 1980s, this situation changed radically, with landmark papers by Cicchetti (1984), Garber (1984), Rutter and Garmezy (1983), Sroufe and Rutter (1984) and others, introducing *developmental psychopathology* as an integrative discipline seeking to unify, within a developmental, lifespan framework, contributions from multiple fields of inquiry including biology and developmental science. Sroufe and Rutter (1984) defined developmental psychopathology as "the study of the origins and course of individual patterns of behavioral maladaptation, whatever the age of onset, whatever the causes, whatever the transformations in behavioral manifestation, and however complex the course of the developmental pattern may be." Developmental psychopathology strives to understand psychopathology in relationship to normative adaptation, integrating knowledge across scientific disciplines at multiple levels of analysis and multiple domains, rather than espousing a single theory that would account for all developmental phenomena (Rutter and Sroufe, 2000).

The unifying developmental orientation of the discipline posed new types of questions in new ways. The developmental psychopathologist is concerned not simply with differences in symptom presentation at different developmental periods but rather with the degree of convergence or divergence in the organization of biological, psychological, and social-contextual systems as they relate to symptom manifestation and disorder (Boyce et al., 1998; Cicchetti and Toth, 1998, 1995). This means that rather than being satisfied with a static comparison between children with a given psychiatric disorder and a "control group," for example, a developmental psychopathologist will use a research design that illuminates ways in which the evolution of symptoms

over development leads to the creation of a group that could be defined as having a disorder (Cicchetti and Sroufe, 2000).

Developmental Epidemiology

This view of developmental psychopathology has several implications for epidemiological research: (1) it presupposes change and novelty, (2) it underscores the importance of timing in the establishment and organization of behavior, (3) it expects that a causal factor may have many outcomes, whereas several causal factors may have the same outcome (Cicchetti and Cohen, 1995), and (4) therefore leads us not to expect invariant relationships between causes and outcomes across the span of development (Costello and Angold, 1995). These characteristics have been woven into several epidemiological studies in recent years, under the label *developmental epidemiology*.

The term was first coined in the 1970s to describe a longitudinal community study in Woodlawn, IL (Kellam and Werthamer-Larsson, 1986). It has been revived in the past decade to describe an approach to child and adolescent psychiatric epidemiology that incorporates principles of developmental psychopathology into epidemiological research. The task is to understand the mechanisms by which developmental processes affect risk of specific psychiatric disorders and to propose preventive strategies appropriate to the various stages of risk. Such strategies must be appropriate to the developmental stage of both the individual at risk and the development of the disorder. An example of this approach is the work of Tremblay and colleagues in Montreal, showing that physical aggression in the population has a "normal" developmental trajectory; it "increases during the first 3 years after birth and then decreases steadily until adulthood" (Tremblay, 2004). Children who will grow up to be unusually aggressive have their own dysfunctional, developmental trajectory. In one study, for instance, children who were consistently highly aggressive as preschoolers were already significantly more likely to have a difficult temperament by 5 months of age (Tremblay et al., 2004).

A second theme of developmental epidemiology is the need to disentangle how the trajectories of symptoms, environment, and individual development intertwine to produce psychopathology. For example, the "difficult" children of Tremblay et al. (2004) were also

more likely to be born into stressed and dysfunctional families.

In another example, Jaffee et al. (2004) sought to clarify whether physical maltreatment leads to the development of antisocial behavior via an environmental causal pathway or via a genetic pathway. Associations between children's physical maltreatment and their antisocial behavior may reflect genetic transmission because parents provide both their child's genotype and their rearing environment. A child's genotype may be correlated with his or her rearing environment (passive genotype-environment correlation). Parental physical maltreatment of a child may also be correlated with other antisocial acts, and adult antisocial behavior is partly heritable. A childhood history of maltreatment may therefore be associated with future antisocial behavior because the genes that parents transmit to their children are the same genes that influence adult antisocial behavior, because childhood maltreatment is causally related to antisocial outcomes, or for both reasons. Developmental, genetically informative epidemiological data are required to tease out these pathways. Parental antisocial behavior may not perfectly capture all genetic risk factors for juvenile antisocial behavior if there are age-specific genetic effects that vary across the life span. Genetically informative designs that control for age-specific effects, such as juvenile twin data in which twins are perfectly correlated for age, permit such effects to be controlled for. Jaffee et al. (2004) used a longitudinal-epidemiological study of twins and their parents to show that physical maltreatment plays a causal role in the development of children's antisocial behavior.

RECENT RESEARCH ON PREVALENCE, ONSET, AND COMORBIDITY

There are two important measures of disorder in the population: prevalence, the proportion of the population with a disorder, and incidence, the rate at which new cases arise. Changes in the prevalence of a disorder over time can provide clues about etiology. We briefly review some recent findings from studies of both children and adults and then discuss two cases in which the possibility of recent increases in prevalence has caused a public furor: autism and early-onset depression. Then we review recent information about the age at incidence of major psychiatric disorders in the population and developmental effects on comorbidity.

Is the Prevalence of Psychiatric Disorders Changing?

Recent national surveys of adults have made it clear that many cases of psychiatric disorder have their origins well before adulthood. For example, Kessler et al. (1993) used data from the first National Comorbidity Survey to demonstrate that in half of the cases of major depression, the first episode had occurred by the mid-20s. The mean age at onset of bipolar disorder was 21 in both sexes (Kessler et al., 1997). In another article, Kessler et al. (1999) found that the reported onset of suicidal ideation, plans, and attempts rose to its highest point in the late teens and early 20s, with the median in the mid-20s. In the case of social phobia and simple phobia, about two thirds of cases had their onset by age 18 (Magee et al., 1996). When respondents had both addictive and other mental disorders in their lifetime, the median age at onset of the mental disorder was 11 years (Kessler et al., 1999) as compared with 21 years for the addictive disorders (Kessler et al., 1996a). Publications from other studies of adults confirmed these findings; for example, in a comparison of seven population samples, Vega et al. (2002) found that hazard rates for first use of alcohol, cannabis, and other drugs peaked in the late teens.

Several researchers have used these and other kinds of prevalence data to argue that there have been secular changes in the proportion of the population of a given age with a lifetime history of a psychiatric disorder; that is, controlling for age, prevalence is higher in more recent cohorts. Here, we discuss three examples in which different methods have been used to test this belief: conduct disorder (CD), depression, and autism.

CD Example. Robins (1999) recently updated the evidence first presented by Rutter et al. in 1984 (see Rutter et al., 1998) that the prevalence of CD has increased in recent decades. Both, however, pointed out the difficulties of drawing conclusions across time, particularly for CD, in which the changes from *DSM-III* to *DSM-III-R*, for example, resulted in a dramatic "masculinization" of the criteria and a shift in the sex ratio (Robins, 1999).

Collishaw and colleagues (2004) recently made ingenious use of three British birth cohort studies to circumvent this problem. Each birth cohort contained subjects 15 to 16 years old, and each measured conduct problems. A calibration study was carried out to ensure that the measures used in the three cohorts were comparable.

(However, they did not map directly on to *DSM-IV* CD.) The authors found a significant increase in mean scores between the cohorts born in 1958 and 1970, and the cohorts born in 1970 and 1983 to 1984. Also, the proportion scoring above a predetermined cut point identifying severe conduct problems rose from 6.8% to 10.4% to 14.9% across the three cohorts, so that by 1999 (when the latest-born cohort was 15 to 16 years old), more than twice as many children fell into the "severe" range as in 1974, when the earliest-born cohort was assessed at the same age. Trends were the same for boys and girls. It really looks as though there has been a significant increase in the proportion of young people with conduct problems and perhaps of CD.

Depression Example. A disturbing conclusion from many adult surveys is the suggestion that recent cohorts of adults (i.e., those born later than the oldest participants in the studies) had higher rates of psychiatric disorders, particularly depression, than did older cohorts when they were the same age (Lewinsohn et al., 1993; Wickramaratne et al., 1989). For example, Kessler et al. (1996b) used the National Comorbidity Survey (NCS) data to argue that depression is a growing public health problem because about 20% of respondents born before 1965 had their onset of pure or primary major depressive disorder by age 18, whereas in the youngest cohort, born between 1965 and 1974, 50% had their first episode by age 18. They make the same case in a recent analysis of the NCS replication study (Kessler et al., 2003).

As several investigative teams have pointed out (Giuffra and Risch, 1994; Patten, 2003; Paykel, 2000; Simon et al., 1995; Wittchen et al., 1994), these studies have a major methodological weakness: they asked adults anywhere up to 54 years old (in the NCS) or even in their 90s (for the Epidemiologic Catchment Area [ECA] and NCS replication) to date the earliest episode of a given psychiatric disorder. Dating of symptoms is unreliable even over short periods of time and varies with the age of the respondent and the time elapsed since the occurrence (Angold et al., 1996; Sanford et al., 1999). Therefore, it is possible that the oldest cohorts have simply forgotten how young they were at their first episode. The result of this would be the appearance that in earlier-born cohorts, fewer children and adolescents had psychiatric disorders than do today's youths (Foley et al., 1998; Pickles et al., 1998).

We recently reviewed this question using a different methodology. Rather than asking adults to recall the

onset of their illness, we reviewed the 30 years of studies of children and adolescents (Costello et al., submitted), asking the question: "Do successive birth cohorts of young people report increasing rates of depression?" Data are available for cohorts born in the 1960s to cohorts born in the 1990s. A meta-analysis of 26 studies with close to 60,000 observations showed absolutely no evidence for an "epidemic" of child or adolescent depression, controlling for subjects' age at interview, sex, diagnostic taxonomy, psychiatric interview used, or time frame of the interview (3 months, 6 months, etc.). This was true of major depressive disorder and also of any depressive diagnosis. This sort of study may provide more valid evidence about whether rates of depression are increasing because subjects are being asked about something that occurred or did not occur in the past few months rather than decades ago. Analysis of this type is only possible with cohorts born since the 1960s because before that there were neither epidemiological methods to diagnose depression in children nor studies of representative epidemiological samples. There may have been an increase in the past 30 years compared with earlier decades.

Autism Example. An impassioned argument in recent epidemiological publications concerns the possibility that the prevalence of autism and other pervasive developmental disorders is increasing. Fombonne (2003a) provided a masterly review of the literature up to 2001, which serves as a fine primer on the methodological problems presented by the study of rare disorders in service-poor situations, particularly when our understanding of the clinical phenomenology of those disorders leads to the use of varying diagnostic criteria over time. More recent studies have suggested that autism is far more common than we thought 20 years ago, when a published prevalence rate of about 4 to 6/10,000 was the norm (Lotter, 1980). Summarizing the results from 32 studies published since 1966, Fombonne concluded that at least 10 children per 10,000 suffer from core autism, whereas twice that number have other pervasive developmental disorders (PDDs), including estimates of 2.5 and 0.2/10,000 for Asperger syndrome and childhood disintegrative (Heller) syndrome, respectively. The more recent of the studies reviewed, and others published since 2001 (Fombonne, 2003b; Fombonne et al., 2003; Jick and Kaye, 2003; Yeargin-Allsopp et al., 2003) suggest that the true rates are probably even higher, with a total prevalence of PDD of about

60/10,000, of whom 15/10,000 meet full *DSM-IV* or *ICD-10* criteria for autism. Rett syndrome probably occurs in at least one girl per 10,000, about three fourths of typical cases having a mutation at the MECP2 locus on the X chromosome, which is usually lethal in males (Chakrabarti and Fombonne, 2001; Fombonne et al., 2003; Leonard et al., 1997; Van den Veyver and Zoghbi, 2002), but we can expect this figure to be revised as we learn more about the phenotypes associated with MECP2 dysfunction (Kerr and Ravine, 2003). In this case, unlike the CD example discussed earlier, the most likely explanations for the apparent increase in the prevalence of autism are methodological: (1) changes in the definition of PDDs and (2) increased sophistication of case finding approaches (Fombonne, 2003b; Jick and Kaye, 2003).

These three cases illustrate the pitfalls on the road to the truth about changing rates of child psychiatric disorders. One day we will have regular nationally representative studies that will enable us to monitor the rise and (perhaps) fall in rates of psychiatric disorders in the same way that we now monitor changes in drug use and abuse through regular surveys by the Centers for Disease Control and Prevention.

Age at Onset of Psychiatric Disorders

The first data on age at onset of various psychiatric disorders came from single-wave, cross-sectional studies of adults, who were asked to recall the onset of their first episode. The ECA studies, five community surveys of adults 18 years old and older conducted in the 1980s, first demonstrated that the onset age of several psychiatric disorders was much earlier than had been thought from clinical research (Burke et al., 1990; Christie et al., 1988). In the ECA, close to 80% of respondents with a history of major depressive disorder, an anxiety disorder, or a drug use disorder dated its onset to before age 20 (Christie et al., 1988), and the peak hazard rate for major depression, mania, obsessive-compulsive disorder, phobias, and drug and alcohol disorders was in childhood or adolescence (Burke et al., 1990).

Recent studies, both clinical and epidemiological, show a group of disorders in which the majority of cases begin in childhood (attention-deficit/hyperactivity disorder [ADHD], autism and nonautistic PDD, separation anxiety, specific phobia, oppositional defiant disorder) and a different group that usually begin

in adolescence (social phobia, panic disorder, substance abuse, depression, anorexia nervosa, bulimia nervosa). Most of the childhood-onset disorders have more male than female cases, whereas most adolescent disorders have more female than male cases (Rutter et al., 2003). Conduct disorder is a special case; it has been argued (Moffitt, 1993; Moffitt et al., 2002) that, for boys at least, antisocial behavior beginning in childhood has antecedents and a course different from those of adolescent-onset deviance. The seriousness of early-onset deviant behaviors, long emphasized by Moffitt (1993) as a predictor of life-course criminal offending, has been confirmed in several studies (Tolan and Thomas, 1995), although many have also pointed out that environmental characteristics may account for the early onset (Stouthamer-Loeber et al., 1999; Tolan and Thomas, 1995). Studies that report the onset of CD show that in the majority of cases, the onset of the first symptoms is early in life. Lahey et al. (2000), using the Methodology for Epidemiology in Children and Adolescents data on subjects 9 to 17 years old, found that 72% of those meeting criteria for CD by age 17 had their first symptom before age 10. This finding was replicated in the Great Smoky Mountains Study (GSMS), a longitudinal community study beginning at age 9, where unpublished analyses show that of youths who had CD by age 16, 75% had their first symptom before age 10 and 89% before age 13. This would imply that the vast majority of cases of child and adolescent CD are in fact early-onset cases. Future research will need to be careful to specify whether it is concerned with *DSM-IV* CD, which includes a range of symptoms that do not necessarily involve delinquent behavior, or the more extreme forms of behavioral deviance. It makes sense that children who actually break the law at an early age may be different from adolescent law breakers and have different antecedents (Kim-Cohen et al., 2005; National Research Council and Institute of Medicine, 2001; Raine et al., 2005). The *DSM-IV* criteria for CD, which include fighting, lying, bullying, and committing acts of cruelty to animals are less likely to produce markedly different groups as a function of sex or age at onset than are "official" categories resulting from arrest or conviction (National Research Council and Institute of Medicine, 2001).

Data from the past decade of research show that depression is one of the later developing disorders of childhood and adolescence. Lewinsohn et al. (1994), using

the Oregon Adolescent Depression Project, found that in cases occurring by age 18, the mean onset age for major depressive disorder was 14.7 years for girls and 15.4 years for boys. Other adolescent-onset disorders are panic disorder (13.9 in GSMS), anorexia nervosa and bulimia nervosa (peak onset ages 16 to 17; Lewinsohn et al., 2000), and drug abuse (Costello et al., 1999). It is important to distinguish between age at onset of the full *DSM* disorder and onset of the first symptom in children who will go on to develop the full disorder. The GSMS and Oregon studies found similar age at onset of the full *DSM-IV* diagnosis through age 16, but in GSMS, the mean age at first symptom in those who developed depression by age 16 was 10.7 (SE = 3.9). This was 2 years earlier than the mean onset of the first depressive symptom in those who did not develop the full syndrome (12.4, SE = 3.3).

“Follow-back” analyses that track the onset of psychiatric disorders in adults are just beginning to appear. An important report from the Dunedin study in New Zealand, which has followed a birth cohort since the 1970s, found that of individuals with a psychiatric diagnosis at age 26, three fourths had a diagnosis at age 18, and 50% had one by age 15 (Kim-Cohen et al., 2003). In most cases, a childhood disorder predicted the same diagnosis later on, but there were exceptions. Early CD and/or oppositional disorders predicted a wide range of adult diagnoses, and conversely adult anxiety and schizophreniform disorders were predicted by a wide range of diagnoses. Of course, the prospective studies reviewed here cannot tell us what proportion of all cases have their onset in childhood or adolescence because they do not cover the entire period of risk for most disorders, but they do show that a large proportion of adults with psychiatric disorders had an early onset and that the cumulative prevalence of many disorders is similar in pre-adult studies to that seen in adult studies. This implies that onset before adulthood may be a characteristic of the majority of adult psychiatric disorders.

Developmental Comorbidity

In the past decade, we have learned a great deal more about comorbidity among child and adolescent psychiatric disorders. A review (Angold et al., 1999) presents data from approximately 20 studies in a form that enables readers to see for themselves the numbers of cases of each disorder and their co-occurrence in each

study. The report also presents, for the first time, a meta-analysis of co-occurring disorders that takes into account other forms of comorbidity; for example, comorbidity between depression and ADHD controlling for comorbidity between ADHD and other disorders. A similar meta-analysis of comorbidity with substance abuse/dependence has also been carried out (Armstrong and Costello, 2002). A summary of the findings of both studies can be seen in Figure 1. The highest levels of comorbidity were between disruptive behavior disorders and ADHD, and anxiety disorders and depression. The lowest were between anxiety and disruptive behavior disorders; however, these were still statistically significant.

In other analyses of comorbidity among anxiety disorders in GSMS (Costello et al., 2004), much of the comorbidity between anxiety disorders and depression was confined to overanxious disorder and generalized anxiety disorders, what have been called the worry disorders as opposed to fear disorders such as separation anxiety and the phobias (Costello et al., 2004), and to panic disorder and posttraumatic stress disorder. Lewinsohn et al. (1997) found significant lifetime comorbidity between depression and all of the anxiety

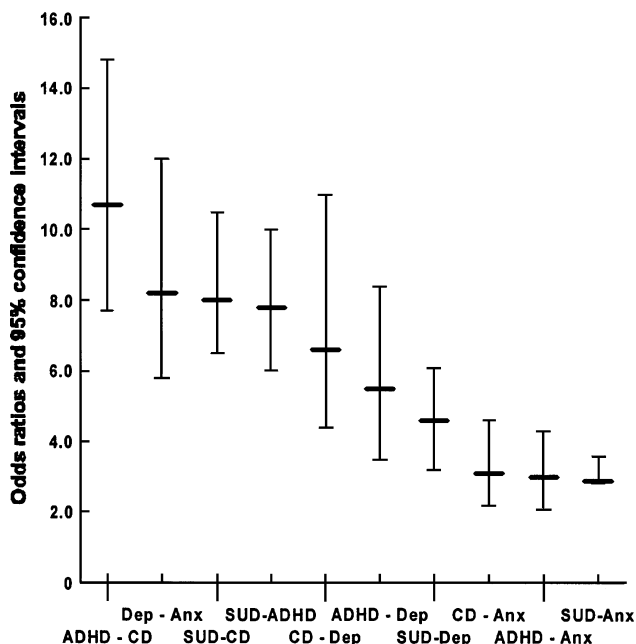


Fig. 1 Comorbidity among psychiatric disorder: the results of meta-analysis. ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder or oppositional defiant disorder; Dep = depression; Anx = anxiety; SUD = substance use disorder (substance abuse and/or dependence).

disorders except obsessive-compulsive disorder, controlling for comorbidity.

An important caveat in interpreting these data is that many of the studies took a broad view of the time frame for defining comorbidity. Comorbidity refers to co-occurrence in the same time interval, but that interval may be defined narrowly (at the same moment), or more broadly (within the same 6 months or year) or even to refer to the whole lifetime. Further work has been done recently to examine differences between concurrent comorbidity and successive comorbidity (Angold et al., 1999). Using longitudinal data from the GSMS on youths 9 through 16 years old (Costello et al., 2003), although there was a high degree of concurrent comorbidity among almost all of the disorders assessed (25 of 30 tests of association), a different picture appeared when the question asked is which diagnoses predict which over time. Table 1 shows the results of these lagged analyses. In every case, there was significant homotypic continuity, that is, each disorder increased the risk of the same disorder in the future. In contrast, there was relatively little heterotypic continuity, that is, an increased likelihood of a disorder following a different disorder. Heterotypic continuity was significant, controlling for other comorbidities, only for anxiety–depression and depression–anxiety, anxiety–substance abuse/dependence (substance use disorder), and ADHD–oppositional defiant disorder. Furthermore, heterotypic continuity was significantly more likely in girls than in boys.

In our current state of knowledge, comorbidity can be expected in almost every child seen in a mental health setting. An important task for future research is to distinguish between “real” comorbidity and comorbidity

caused by a faulty taxonomy or other artifacts of our diagnostic process.

Developmental Ordering of Psychiatric and Substance Abuse Disorders

Related questions for developmental epidemiology deal with the order in which psychiatric disorders appear and the extent to which one disorder increases the risk or accelerates the onset of other disorders.

Lewinsohn et al. (1997) used three waves of data from the Oregon Adolescent Depression Project to examine age at onset of other disorders relative to depressive disorders in adolescents. They found that the mean age at onset of affective disorder in both males and females who developed bipolar disorder during adolescence was 11.75 years, significantly younger than the onset age of youths with major depression but no bipolar disorder (14.95). Simple phobia, separation anxiety, overanxious disorder, and social phobia typically preceded the onset of major depressive disorder, whereas panic disorder and obsessive-compulsive disorder tended to have later onsets. This temporal ordering is consistent with genetic studies (Silberg et al., 2001) suggesting that early symptoms of anxiety influence liability to depressive symptoms expressed in middle to late adolescence.

Both the Oregon Adolescent Depression Project and the GSMS have shown that childhood psychiatric disorders affect both the likelihood and the age at onset of substance use disorders (Costello et al., 1999; Orvaschel et al., 1995; Sung et al., 2004). For example, Sung et al. (Sung et al., 2004) found that CD by age 13 greatly increased the risk of substance use disorder in early adolescence, whereas CD occurring later in adolescence had much less effect as a predictor of substance use

TABLE 1
Homotypic and Heterotypic Continuity, With and Without Controls for Comorbidity

	Past Depression	Past Anxiety	Past Conduct Disorder	Past ODD	Past ADHD	Past Substance Abuse
Predicting for depression	7.0 (3.1, 15.9)***	3.0 (1.7, 5.4)***				
Controlling for comorbidity	4.2 (2.1, 8.3)***	2.7 (1.8, 5.2)**				
Anxiety	5.7 (2.2, 14.5)***	2.4 (1.6, 3.7)***				
Controlling for comorbidity	2.8 (1.2, 6.5)*	2.0 (1.2, 3.4)*				
Conduct disorder			11.2 (5.9, 21.1)***			
Controlling for comorbidity			10.3 (4.3, 24.7)***			
ODD				3.7 (2.2, 6.2)***	2.0 (1.1, 3.8)*	

Note: ODD = oppositional defiant disorder; ADHD = attention-deficit/hyperactivity disorder.
p* < .05; *p* < .01; ****p* < .001.

disorder. This may be because substance use disorder was much less common in younger adolescents, and the cases needed a more toxic risk environment before they developed (see Flavell et al., 2005, for an example with diabetes). Kaplow et al. (2001), using the same data set, found that an apparent lack of association between anxiety disorders and alcohol use was in fact the result of two contradictory processes: children with generalized anxiety disorder were more likely to use alcohol and did so at an earlier age than other children, whereas children with separation anxiety disorder were less likely to use alcohol and began later.

Among the anxiety disorders, there has been a clinical tradition that separation anxiety disorder in childhood is a developmental precursor of panic disorder in adolescence and adulthood (Klein, 1995; Silove et al., 1996). This has been challenged in three epidemiological studies (Hayward et al., 2000; Pine et al., 1998; A. Bittner, unpublished). Using large samples and prospective data, none found any association between separation anxiety disorder and later panic attacks or panic disorder. Future longitudinal studies will, we hope, clarify the developmental course of the anxiety disorders.

New studies are not always needed, however. There is a wealth of information about the developmental organization of psychopathology hiding within existing longitudinal data sets. Recent developments in design and statistics (Cairns et al., 1998; Muthen and Muthen, 2000; Nagin and Tremblay, 2001; Sullivan, 1998) will help with this task. One important conclusion to be drawn from recent studies (Angold et al., 1999; Ford et al., 2003) is that some examples of comorbidity may turn out to be “epiphenomenal” (Angold et al., 1999); for example, what appears in bivariate analyses to be comorbidity between anxiety and CD turns out, when all possible comorbidities are considered in the model, to be the result of comorbidity between (1) anxiety and oppositional defiant disorder, and (2) oppositional defiant disorder and CD.

EARLY RISK FOR PSYCHIATRIC DISORDERS

Developmental science has expanded our understanding of risk and protective factors so dramatically in the past decade that it is beyond the scope of this review to cover the whole area. Instead, we focus on two topics of particular interest for child and adolescent psychiatry: the interrelationship between medical and

psychiatric risk factors and outcomes and the causal role of vaccines in autism and PDD.

Interrelationship Between Medical and Psychiatric Risk Factors and Outcomes

The birth cohort studies of the 1960s and 1970s, which have been so important in demonstrating the early onset and widespread prevalence of psychiatric disorders, are now increasingly being used to illuminate both the psychosocial origins of the “medical” chronic diseases of middle age (Barker, 2003) and the role of early physiological problems in the development of psychiatric disorders (e.g., Brown and Susser, 2002; Opler et al., 2004). Here, we look at one example: effects of low birth weight on later psychopathology. Evidence is emerging linking undernutrition of the fetus, indexed by low birth weight, with depression in adolescence (Saigal et al., 2003), adulthood (Bellingham-Young and Adamson-Macedo, 2003; Gale and Martyn, 2004), and old age (Thompson et al., 2001). Attention deficit problems have long been reported to be more prevalent in children who were preterm or of low birth weight (Breslau et al., 1996; Pharoah et al., 1994; Whitaker et al., 1997), although other studies question the association (Sommerfelt et al., 1996) or suggest that this may have more to do with socioeconomic deprivation or mental retardation than low birth weight itself (Kreppner et al., 2001; Levy et al., 1996). The link between other kinds of conduct problems and low birth weight is unclear (Breslau et al., 1996; Sommerfelt et al., 1993). Few differences have been found in anxiety disorders (Breslau et al., 1996; Saigal et al., 2003), although Whitaker and colleagues noted increased separation anxiety in a subgroup (Whitaker et al., 1997).

There are several mechanisms by which low birth weight may mark permanent changes that increase later vulnerability to depression and other psychiatric disorders. Thompson et al. (2001) suggest three. Programming of the hypothalamus-pituitary-adrenal axis could lead to raised plasma cortisol level, which is a consistently demonstrated biological abnormality in primary depressive disorder (Lopez et al., 1998; Murphy, 1991; Nemeroff et al., 1984). Second, median 24-hour plasma growth hormone concentrations are related to weight at 1 year (Fall et al., 1998), and in depression, the control of growth hormone secretion is known to be disturbed in both children and adults (Birmaher et al., 2000;

Checkley, 1996; Sakkas et al., 1998). Third, reduced plasma thyrotropin levels coupled with impaired response to thyrotropin-releasing hormone are associated with depression (Oomen et al., 1996), and thyroid function may be set during fetal growth and infant feeding (Phillips et al., 1993).

Low birth weight is just one example of a “biological” developmental risk factor that seems to serve as a risk marker for both medical and psychiatric disorders later in life. There is also growing evidence of a common core group of socioeconomic and developmental risk and protective factors that influence the course of both sets of conditions. Poverty, lack of attachment to primary caregivers, poor family relationships, maternal depression, poor school achievement, and disrupted family structure certainly predict child psychiatric disorders, but they also predict chronic medical conditions (Mantymaa et al., 2003; Steptoe et al., 2000; Wright et al., 1998), including cancer (via their link to tobacco use; see Swan et al., 2003).

Vaccines, Autism, and PDD

The suspicion that the true rates of autism and other PDDs are rising has fueled research on what could cause such an increase. The prime suspect has been measles-mumps-rubella (MMR) vaccine (specifically its live, attenuated measles virus component). The putative MMR-autism link story began to attract international attention with case reports of 12 children with PDD presenting with a chronic enterocolitis characterized by nongranulomatous ileocolonic lymphonodular hyperplasia (Wakefield et al., 1998b), although this was not the first clinical suggestion that there may be a link (Gupta, 1996). That initial study gave some prominence to reports of eight of the children’s parents or physicians that their first behavioral symptoms had begun shortly (1 to 14 days) after receiving MMR immunizations. This, and a subsequent report on an extended sample of 60 children with histories of normal development followed by developmental regression, was followed by a storm of contentious debate that resulted in a significant fall in the uptake of MMR vaccination (and a subsequent rise in outbreaks of measles) in more than one country (Horton, 2004a,b; Noble and Miyasaka, 2004; Wakefield, 1999; Wakefield et al., 2000). Several years later, 10 of the 13 authors of the 1998 paper (Wakefield et al., 1998b) retracted the interpretation that autism may be causally linked to MMR

(Murch et al., 2004). This confusing story needs to be broken into several components if we are to make sense of it.

PDDs and Gut Disorders. First is the question of whether there is an association between PDDs and a novel (and probably immunopathological) gut disorder distinct from both Crohn’s disease and ulcerative colitis. There is clinical evidence in support of this idea, and it certainly deserves further investigation (Ashwood et al., 2003; Furlano et al., 2001; Horvath et al., 1999; Wakefield et al., 2000). The second question concerns whether such a bowel disease may itself be a cause of PDDs, with some cases of the latter constituting what Wakefield et al. (2002) have called enterocolonic encephalopathies. This argument is based on various clinical analogies and is, at present, entirely speculative, but already faces some disconfirmatory epidemiological evidence (Black et al., 2002).

PDDs and Measles. Is bowel disease an aberrant response to exposure to measlesvirus? There is again clinical evidence of the presence of measles antigen in the affected bowel (Kawashima et al., 2000; Martin et al., 2002; Uhlmann et al., 2002; Wakefield et al., 1998a), but similar findings have also been reported in Crohn’s disease and ulcerative colitis in the absence of PDD (Hendrickson and Turner, 2002; Wakefield and Montgomery, 2000), so it is unlikely to be related to a specific PDD gut disorder. None of the measles findings in any of these diseases is securely associated with measles antigens rather than cross-reacting host antigens (Ghosh et al., 2001; Hendrickson and Turner, 2002; Iizuka et al., 2000; Morris et al., 2000). We must also bear in mind that the presence of apparent viral antigens could be a result of gut immunological disorder rather than its cause (Hendrickson and Turner, 2002).

PDD and MMR. Is MMR immunization directly (perhaps an aberrant long-term outcome analogous to subacute sclerosing panencephalitis following wild-type measles) or indirectly associated with PDDs? A number of relatively large-scale studies have now reported on this question, using several different strategies. The least satisfactory are demonstrations of a lack of correlation between apparent increases in records of the number of individuals with autism and rates of MMR immunization uptake in the United States and the United Kingdom (Dales et al., 2001; Kaye et al., 2001). More convincing are studies showing that there was no clustering of PDD onsets around the time of

immunization, no correlation between the timing of immunization and the timing of onsets of PDDs, and no difference between the age of PDD onset in the unimmunized versus the immunized (DeStefano et al., 2004; Madsen et al., 2002; Taylor et al., 1999). Most convincing of all are studies with a sufficient representation of unimmunized participants to permit a reasonably powered straightforward test of the association between immunization (yes/no) and PDDs (Madsen et al., 2002; Smeeth et al., 2004). Again, the results provided absolutely no support for the existence of an MMR-PDD link. A recent study from Japan showed that the incidence of autism increased in the decade following the withdrawal of MMR (Honda et al., 2005). Although none of these studies was by any means perfect, the concordance of their negative results across several countries and data collection and analysis approaches is impressive. It may be theoretically impossible to prove the null, but it is difficult in the face of all this accumulated evidence to believe that there is a PDD risk from MMR immunization that outweighs the risks of remaining unimmunized.

Thimerosal and PDDs. A second vaccine-autism link concerns vaccines containing thimerosal (sodium ethyl mercury thiosalicylate, 49% mercury by weight, also known as thimerosal in some countries), which has been used to prevent bacterial and fungal contamination since the 1930s (Verstraeten et al., 2003). The situation with respect to thimerosal is conceptually straightforward: Methyl mercury poisoning involves prominent neurological symptoms, characteristically ataxia, dysarthria, constricted visual fields, and peripheral neuropathy, so perhaps autism, despite its different clinical presentation (Nelson and Bauman, 2003), results from thimerosal (although ethyl mercury crosses the blood-brain barrier much less easily than the methylated form). It has also now been found that blood hemoglobin concentrations in infants following vaccination are low and that ethyl mercury is rapidly eliminated via the stool (Pichichero et al., 2002). A recent study found, however, that an autoimmune disease-susceptible strain of mice, but not nonsusceptible mice, showed behavioral and neural morphological and histochemical responses to thimerosal in doses meant to mimic those used in human vaccination schedules (Hornig et al., 2004). This compound is also not a good candidate for explaining any supposed recent increases in autism incidence because it has been absent from vaccines in the

United Kingdom and Denmark during periods in which higher rates of autism and other PDDs have been reported (e.g., Madsen, 2004). Nelson and Bauman (2003) provided a helpful summary of a range of earlier work, but only since then has a small flurry of general population studies of the question appeared. One has reported positive associations (Geier and Geier, 2003)—a study of reports to the Vaccine Adverse Events Reporting System of the U.S. Centers for Disease Control and Prevention related to diphtheria, tetanus, acellular pertussis (DTP) vaccine, which contained thimerosal (administered in years 1992–2000) versus those relating to non-thimerosal-containing DTP (1997–2000). The relative risks for reports of autism and mental retardation were 6, whereas that for speech disorders was 2.2 (with mean postvaccination onset times of 8–22 days). The authors claim that the fact that the thimerosal-containing vaccines were administered over a longer period (1992–2000) would help to preclude the possibility of reporting biases based on popular media publicity. In Denmark, for instance, thimerosal had already been eliminated from vaccines by 1992. Those concerned with this issue could surely have influenced reporting to the Centers for Disease Control and Prevention during this period. It would be helpful to know whether the incidence of adverse reports in those who received thimerosal-containing vaccines increased during the period of the study. Such an increase would not be expected under the hypothesis that thiomersal caused autism and mental retardation but probably would have occurred if reporting bias were responsible for the apparent differences. Nor is it true that biased reporting would have been reflected in an increased incidence rate of acute adverse reaction (Geier and Geier, 2003) because the expectation of activists in this area would relate specifically to neurodevelopmental disorders, not to vasculitis or death.

Much more reliable evidence comes from Hviid and colleagues (2003) and from Madsen et al. (2003), large, representative Danish studies that found no evidence that thimerosal was associated with PDDs, but that rates of official record diagnoses of autism continued to rise after the removal of thimerosal from all vaccines. Similarly negative results have been reported from an HMO database study (Verstraeten et al., 2003), the U.K. General Practice Research Database (Jick and Kaye, 2004), and a United States-Sweden-Denmark comparison of average thimerosal exposures and rates of PDDs

(Stehr-Green et al., 2003). In summary, then, there is little evidence that thimerosal has been a substantial cause of autism or other PDDs.

AREAS OF FUTURE GROWTH IN DEVELOPMENTAL EPIDEMIOLOGY

It would be agreeable to think that the tasks involved in monitoring the prevalence and burden of child and adolescent psychiatric disorders—the “public health” duties of epidemiology—would in the next decade be taken over by the agencies tasked to carry out surveillance studies of disease, above all the Centers for Disease Control and Prevention. Then the research funding available from the National Institutes of Health could be used, as intended, for scientific, etiological research rather than for “counting noses.” Even if epidemiology has to divide its resources between its two functions, it will nevertheless make progress in two important and interesting areas: genetics and biomarkers.

Genetically Informed Psychiatric Epidemiology

The idea that genes “cause” psychiatric disorders has a long history. What has changed recently is the relationship between genetics and mainstream epidemiology (Rutter et al., 1999a). Both disciplines have altered their attitudes and approach. In 1999, Rutter and colleagues published two comprehensive papers summarizing advances in quantitative and molecular genetics (Rutter et al., 1999b) and reviewing empirical findings related to child and adolescent psychiatric disorders (Rutter et al., 1999a). These remain essential background reading on the genetics of child and adolescent psychiatric disorders. In the past few years there have been several advances that deserve comment here.

First, the behavioral genetic studies of the past decade that focus on children and adolescents have paid much more attention to issues of sampling and generalizability to the population (an obsession of epidemiologists) than used to be the case. Researchers have become much more sensitive to the problems inherent in trying to generalize from adoption or family-based high-risk studies. Twin studies have increasingly used representative sampling frames rather than relying on volunteers or members of twin parents’ groups, and sample sizes have also increased. For example, the Virginia Twin Study of Adolescent Behavioral Development (Eaves et al., 1997; Hewitt et al., 1997; Simonoff et al., 1997) used school

records to identify all of the twin pairs in Virginia 9 to 17 years old and recruited 1,400 of them, and a nationwide birth registry was used to identify 1,200 infant twin pairs for the Environmental Risk (E-risk) Longitudinal Twin Study currently under way in the United Kingdom (Caspi et al., 1995). Representative sampling, always a major concern to epidemiologists, is particularly important in genetic studies in which there is a possibility that the genes involved in a disorder may vary in different subpopulation groups (Risch et al., 2002).

Second, recognizing the genome as, in a sense, a blueprint for development, recent behavioral genetics studies have moved toward developmentally informative designs. This has yielded important insights. For example, analyses from Virginia Twin Study of Adolescent Behavioral Development (Silberg et al., 2001) suggest that self-reported depression before and after puberty may be etiologically distinct syndromes, with genetic risk for postpubertal depression expressed as overanxious disorder and specific phobias before puberty. In the behavioral problem area, the E-risk study has shown that although genetic factors did not account for significant variation in children’s experience of physical maltreatment, maltreatment assessed at age 5 predicted antisocial behavior 2 years later, even after controlling for any genetic transmission of antisocial behavior (Jaffee et al., 2004).

The third and most dramatic development in the genetic epidemiology of child and adolescent psychopathology is the result of recent technological developments in molecular genetics, which have made the collection of biodata for DNA feasible in large field studies using cheek scrapes or small blood samples from finger sticks, and have made testing for candidate genes economically feasible for large samples. In two landmark studies, Caspi et al. (2002, 2003) used data from the Dunedin, New Zealand, longitudinal study to demonstrate that gene-environment interactions predicted psychiatric problems more powerfully than either genes or environmental risk on their own. In the first study (Caspi et al., 2002), the group genotyped the variable number tandem repeat polymorphism at the promoter of the monoamine oxidase A (MAOA) gene, which is known to affect its expression. (Because the MAOA gene is located on the X chromosome, only boys were used in this analysis.) Using data from the early waves of this study, whose participants are now young adults, they created a measure of maltreatment between the ages of 3 and 11.

Maltreatment groups did not differ on MAOA activity, suggesting (as in the E-risk twin study discussed earlier [Jaffee et al., 2004]) that genotype did not influence exposure to maltreatment. Four measures of adolescent and adult antisocial behavior were derived from later waves of the Dunedin data. In each case, the effect of early maltreatment on later antisocial behavior was significant for those with low MAOA activity, but not for those with high MAOA activity.

The interaction of low MAOA activity with early adversity was replicated recently in a study using different measures of both CD and early stressors (Foley et al., 2004). This is important in showing that the gene-environment interaction is robust to measurement methods.

In a second study (Caspi et al., 2003), the group examined the interaction of life stress in young adulthood and human serotonin transporter (5-HTT) genotype on depression at age 26. Both males and females with one or two copies of the short allele of the 5-HTT promoter polymorphism showed more depressive symptoms, diagnosable depression, and suicidality after stressful life events than did participants who were homozygous for the long allele. Three replications of this finding, two positive and one negative, are under review.

These studies are particularly important for child and adolescent psychiatric epidemiology in that they use a regular population sample rather than requiring a special "genetically informative" subgroup of the population such as twins, adoptees, or children of affected parents. This means that existing epidemiological samples, provided that they are large enough and can obtain biodata for DNA extraction, can be used to examine both candidate genes and the role of environmental factors as a function of genetic vulnerabilities.

Another implication of these important studies is that they demonstrate the value of genetic and environmental data collected prospectively from early in life (Foley et al., 2004) as well as accurate assessments of psychopathology over time. Epidemiological studies that meet these criteria (and there are several) have the potential to contribute importantly to developments in psychiatric genetics in the next decade (Jaffee et al., 2004).

Biological Markers of Stress and Psychiatric Disorder

A new and exciting phase in epidemiological research is opening with the development of methods, previously available only in the laboratory, for exploring biological

processes that mediate environmental stressors in children's lives. So far, in psychiatric epidemiology as in much clinical work, we have been dependent on verbal descriptions of symptoms and stressors. We have had to assume a causal connection between stressors and symptoms via an unmeasured construct "stress." Now we are beginning to be able to look at possible markers of stressor exposure, such as cortisol reactivity (Granger et al., 1998; Strickland et al., 2002) at baseline or in response to a challenge, using saliva or small amounts of blood collected using the kind of finger-stick technique familiar from diabetes testing.

The use of autonomic tone as a measure of response to stressors has a long history in laboratory studies; for example, Snidman et al. (1995) have demonstrated that shy and inhibited children also show a shift in autonomic balance favoring sympathetic over parasympathetic tone. Portable electrocardiographic monitors now make this kind of research possible in field studies.

A third approach to stress measurement is to use immunocompetence as a marker for response to stressors. Antibodies to resident viruses reflect immunocompetence in keeping the virus in check, which capacity is eroded by stress. On the one hand, in individuals infected with the Epstein-Barr virus, circulating levels of viral antibody have been consistently linked to daily stress levels (Kiecolt-Glaser, 1999; Sarid et al., 2001) and negative affective states (Esterling et al., 1993). On the other hand, social integration and support and stress management interventions are paralleled by lower Epstein-Barr virus antibodies (Esterling et al., 1992; Lutgendorf et al., 1994). The relationship of immunocompetence to stress means that Epstein-Barr virus antibodies represent an ongoing bioassay of chronic stress and immunocompetence: the higher the titer, the greater the level of ongoing stress-related immunocompromise (Glaser et al., 2005). Simply put, more antibody indicates more stress. Preliminary results (McDade, 2002) show promise for this as an ecologically valid measure of medium- to long-term stress.

Fourth, research on adults is beginning to explore the use of C-reactive protein (CRP) and other proteins that mediate inflammatory response as useful biomarkers of risk for leading causes of adult morbidity and mortality, including cardiovascular disease, diabetes, and, most recently, depression. The dominant acute phase protein mediating innate immunity, CRP was the first discovered component of inflammatory response and as such

had long been exclusively related to systemic infection (Du Clos and Mold, 2001; Gabay and Kushner, 1999; Mold et al., 1999). Recently, CRP has been identified as perhaps the most powerful predictor of cardiovascular disease (Danesh et al., 2000; Koenig et al., 1999; Kuller et al., 1996; Ridker et al., 2003). CRP both indexes the degree of systemic wear and tear and plays an atherogenic role in plaque formation from childhood onward (Mold et al., 1999). Mildly and moderately increased levels have been linked to all of the components of the metabolic syndrome (upper body obesity, abnormal glucose, hypertension, low high-density lipoprotein, and elevated triglycerides [Festa et al., 2000; Han et al., 2002; Ridker et al., 2003; Tamakoshi et al., 2003]). Increased CRP has also been associated with reduced activity and physical fitness among children and adolescents (Cook et al., 2000; Isasi et al., 2003). Ongoing psychological distress and disorder may reinforce the systemic burden indexed by CRP (Miller et al., 2001, 2002; Roose et al., 2001). Depression is prospectively linked to coronary artery disease (Glassman and Shapiro, 1998) and has been associated with increased CRP and other inflammatory risk markers (Danner et al., 2003; Dentino et al., 1999; Ford and Erlinger, 2004; Maes, 1999). Similar associations have been found with posttraumatic stress disorder (Miller et al., 2001). So far, this work has been carried out on adult samples, but longitudinal epidemiological studies that collect blood routinely will be able to explore the value of CRP as a marker of the extent to which children experience stressors, such as maltreatment and trauma, as stress, that is, the “allostatic load” (McEwen, 2002) or cost of coping, and the implications for the development of psychiatric disorder.

CONCLUSIONS AND IMPLICATIONS FOR TREATMENT AND PREVENTION

In summary, developmental epidemiology has made considerable progress in the past decade as both a descriptive and an analytic science. Descriptively, it has shown that there are clear timing patterns in the onset of different psychiatric disorders, that the onset of one disorder affects the timing of others, and that individual development intertwines with the development of the disease process. Analytically, it has begun to make use of new techniques to move beyond what epidemiologists Mervin and Ezra Susser (Susser and Susser,

1996) have criticized as “the identification rather than the explanation of causal factors” and begun to search for “mediation and causal chains” (Schwartz, 1998).

In the past decade, developmental epidemiology has come to see itself as part of a more general activity called life course epidemiology (Ben-Shlomo and Kuh, 2002; Elder, 1996, 1998; Singer and Ryff, 1999). A life course approach to epidemiology has been defined as “the study of long-term effects on chronic disease risk of physical and social exposures during gestation, childhood, adolescence, young adulthood and later adult life. It includes studies of the biological, behavioral and psychosocial pathways that operate across an individual’s life course, as well as across generations” (Ben-Shlomo and Kuh, 2002). A major reason for the absorption of psychiatric epidemiology into life course epidemiology is the growing tendency to think of psychiatric disorders as chronic diseases, amenable to the same epidemiological research methods as diabetes or cardiovascular disease. A single risk marker, such as low birth weight, can lead to many different outcomes via different pathways.

Role of Developmental Epidemiology in Treatment and Prevention

Treatment interventions attempt to reduce the prevalence of disease in the community by reducing the duration of illness and the likelihood of relapse, whereas preventive interventions try to reduce the incidence of new cases (Rothman and Greenland, 1998). The goal of prevention science is to create an environment in which children (even genetically vulnerable children) are not exposed to risk factors for disease or are protected from their effects. This may be achieved by reducing the spread or strength of risk factors for a disease (“primary” or “universal” prevention) or by breaking the link between risk factors and disease (“secondary” or “targeted” prevention). The main role of epidemiology has been to provide basic information, measurement tools, and research designs for preventive interventions (although clinical epidemiologists play an important role in treatment interventions, too, especially in the conduct of complex, multisite clinical trials).

It follows, then, that developmental epidemiologists will have a strong interest in identifying the risk factors that predict incidence and that are amenable to preventive interventions, and a great deal of work has been done in this area in the past decade. It has often been

the older studies, with birth cohorts from the 1960s and 1970s, that have begun to yield the most valuable information about risk. The reason for this is that their participants are now adults, some even middle aged. They have passed through the highest period of risk for the onset of childhood disorders and even, as discussed earlier, for many adult psychiatric disorders. So prevention scientists can look back and identify not only key risk factors but also key critical periods when exposure was most dangerous, and therefore when prevention programs may be most effective. An interesting example discussed earlier is low birth weight, an eminently preventable condition that is only now emerging as a key risk factor for both medical (Barker, 2003) and psychiatric (Gunnell et al., 2003) disorders of adulthood. Here, the critical period of risk lies years, even decades, before the disease outcome. It is also an example of a risk factor probably best attacked through universal prevention programs rather than by targeting small high-risk groups such as pregnant women with a family history of schizophrenia.

The literature on risk for child and adolescent psychiatric disorders was summarized recently in a series of papers from the National Institute of Mental Health. The link between developmental epidemiology and current progress in prevention science is laid out in several recent papers (Anonymous, 2002; Dodge, 2001; Hawkins et al., 2002; Kellam et al., 1999; Spoth et al., 2002) and is too big an issue to be adequately covered here. For the future, developmental epidemiology can contribute to its goal of working even more closely with prevention scientists and clinicians to develop the range of interventions needed to reduce the burden of child and adolescent mental illness.

Disclosure: The authors have no financial relationships to disclose.

REFERENCES

- Angold A, Costello EJ, Erkanli A (1999), Comorbidity. *J Child Psychol Psychiatry* 40:57–87
- Angold A, Erkanli A, Costello EJ, Rutter M (1996), Precision, reliability and accuracy in the dating of symptom onsets in child and adolescent psychopathology. *J Child Psychol Psychiatry* 37:657–664
- Anonymous (2002), The implementation of the Fast Track program: an example of a large-scale prevention science efficacy trial. *J Abnorm Child Psychol* 30:1–17
- Armstrong TD, Costello EJ (2002), Community studies on adolescent substance use, abuse, or dependence and psychiatric comorbidity. *J Consult Clin Psychol* 70:1224–1239
- Ashwood P, Anthony A, Pellicer AA, Torrente F, Walker-Smith JA, Wakefield AJ (2003), Intestinal lymphocyte populations in children with regressive autism: evidence for extensive mucosal immunopathology. *J Clin Immunol* 23:504–517
- Barker D (2003), The developmental origins of adult disease. *Eur J Epidemiol* 18:733–736
- Bellingham-Young DA, Adamson-Macedo EN (2003), Foetal origins theory: links with adult depression and general self-efficacy. *Neuroendocrinol Lett* 24:412–416
- Ben-Shlomo Y, Kuh D (2002), A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol* 31:285–293
- Birmaher B, Dahl RE, Williamson DE et al. (2000), Growth hormone secretion in children and adolescents at high risk for major depressive disorder. *Arch Gen Psychiatry* 57:867–872
- Black C, Kaye JA, Jick H (2002), Relation of childhood gastrointestinal disorders to autism: nested case-control study using data from the UK General Practice Research Database. *BMJ* 325:419–421
- Boyce WT, Frank E, Jensen PS, Kessler RC, Nelson CA, Steinberg L; MacArthur Foundation Research Network on Psychopathology and Development (1998), Social context in developmental psychopathology: recommendations for future research from the MacArthur Network on Psychopathology and Development. *Dev Psychopathol* 10:143–164
- Breslau N, Chilcoat H, DelDotto J, Andreski P, Brown G (1996), Low birth weight and neurocognitive status at six years of age. *Soc Biol Psychiatry* 40:389–397
- Brown AS, Susser ES (2002), In utero infection and adult schizophrenia. *Ment Retard Dev Disabil Res Rev* 8:51–57
- Burke KC, Burke JD, Regier DA, Rae DS (1990), Age at onset of selected mental disorders in five community populations. *Arch Gen Psychiatry* 47:511–518
- Cairns RB, Cairns BD, Rodkin P, Xie H (1998), New directions in developmental research: models and methods. In: *New Perspectives on Adolescent Risk Behavior*, Jessor R, ed. London: Cambridge University Press, pp 13–40
- Caspi A, Henry B, McGee RO, Moffitt TE, Silva PA (1995), Temperamental origins of child and adolescent behavior problems: from age three to fifteen. *Child Dev* 66:55–68
- Caspi A, McClay J, Moffitt TE et al. (2002), Role of genotype in the cycle of violence in maltreated children. *Science* 297:851–854
- Caspi A, Sugden K, Moffitt T et al. (2003), Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 301:386–389
- Chakrabarti S, Fombonne E (2001), Pervasive developmental disorders in preschool children. *JAMA* 285:3093–3099
- Checkley S (1996), The neuroendocrinology of depression and chronic stress. *Br Med Bull* 52:597–617
- Christie KA, Burke JD, Regier DA, Rae DS, Boyd JH, Locke BZ (1988), Epidemiologic evidence for early onset of mental disorders and higher risk of drug abuse in young adults. *Am J Psychiatry* 145:971–975
- Cicchetti D (1984), The emergence of developmental psychopathology. *Child Dev* 55:1–7
- Cicchetti D, Cohen DJ (1995), Perspectives on developmental psychopathology. In: *Developmental Psychopathology, Volume 1: Theory and Methods*, Cicchetti D, Cohen DJ, eds. New York: John Wiley & Sons, pp 3–20
- Cicchetti D, Sroufe LA (2000), The past as prologue to the future: the times, they've been a-changin'. *Dev Psychopathol* 12:255–264
- Cicchetti D, Toth S (1998), The development of depression in children and adolescents. *Am Psychol* 53:221–241
- Cicchetti D, Toth SL (1995), A developmental psychopathology perspective on child abuse and neglect. *J Am Acad Child Adolesc Psychiatry* 34:541–565
- Collishaw S, Maughan B, Goodman R, Pickles A (2004), Time trends in adolescent mental health. *J Child Psychol Psychiatry* 45:1350–1362
- Cook DG, Mendall MA, Whincup P, Isasi CR (2000), C-reactive protein concentration in children: relationship to adiposity and other cardiovascular risk factors. *Atherosclerosis* 149:139–150

- Costello EJ, Angold A (1995), Developmental epidemiology. In: *Developmental Psychopathology, Volume 1*, Cicchetti D, Cohen D, eds. New York: John Wiley & Sons, pp 23–56
- Costello EJ, Egger HL, Angold A (2004), The developmental epidemiology of anxiety disorders. In: *Phobic and Anxiety Disorders in Children and Adolescents: A Clinician's Guide to Effective Psychosocial and Pharmacological Interventions*, Ollendick T, March J, eds. New York: Oxford University Press, pp 61–91
- Costello EJ, Erkanli A, Federman E, Angold A (1999), Development of psychiatric comorbidity with substance abuse in adolescents: effects of timing and sex. *J Clin Child Psychol* 28:298–311
- Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A (2003), Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch Gen Psychiatry* 60:837–844
- Dales L, Hammer S, Smith N (2001), Time trends in autism and in MMR immunization coverage in California. *JAMA* 285:1183–1185
- Danesh J, Whincup P, Walker M et al. (2000), Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ* 321:199–204
- Danner M, Kasl SV, Abramson JL, Vaccarino V (2003), Association between depression and elevated C-reactive protein. *Psychosom Med* 65:347–356
- Dentino AN, Pieper CF, Rao KM et al. (1999), Association of interleukin-6 and other biologic variables with depression in older people living in the community. *J Am Geriatr Soc* 47:6–11
- DeStefano F, Bhasin TK, Thompson WW, Yeargin-Allsopp M, Boyle C (2004), Age at first measles-mumps-rubella vaccination in children with autism and school-matched control subjects: a population-based study in metropolitan Atlanta. *Pediatrics* 113:259–266
- Dodge K (2001), The science of youth violence prevention: progressing from developmental epidemiology to efficacy to effectiveness to public policy. *Am J Prev Med* 20:63–70
- Du Clos TW, Mold C (2001), The role of C-reactive protein in the resolution of bacterial infection. *Curr Opin Infect Dis* 14:289–293
- Earls F (1979), Epidemiology and child psychiatry: historical and conceptual development. *Compr Psychiatry* 20:256–269
- Eaves LJ, Silberg JL, Maes HH et al. (1997), Genetics and developmental psychopathology: 2. The main effects of genes and environment on behavioral problems in the Virginia Twin Study of adolescent behavior development. *J Child Psychol Psychiatry* 38:965–980
- Elder GH (1996), Human lives in changing societies: life course and developmental insights. In: *Developmental Science*, Cairns R, Elder GH Jr, Costello EJ, eds. London: Cambridge University Press, pp 31–62
- Elder GH Jr. (1998), The life course as developmental theory. *Child Dev* 69:1–12
- Esterling BA, Antoni MH, Kumar M, Schneiderman N (1993), Defensiveness, trait anxiety, and Epstein-Barr viral capsid antigen antibody titers in healthy college students. *Health Psychol* 12:132–139
- Esterling BA, Antoni MH, Schneiderman N et al. (1992), Psychosocial modulation of antibody to Epstein-Barr viral capsid antigen and human herpesvirus type-6 in HIV-1-infected and at-risk gay men. *Psychosom Med* 54:354–371
- Fall C, Hindmarsh P, Dennison E, Kellingray S, Barker D, Cooper C (1998), Programming of growth hormone secretion and bone mineral density in elderly men: a hypothesis. *J Clin Endocrinol Metab* 83:135–139
- Festa A, D'Agostino RB, Howard G, Mykkanen L, Tracy RP, Haffner SM (2000), Chronic subclinical inflammation as part of the insulin resistance syndrome: the insulin resistance atherosclerosis study (IRAS). *Circulation* 102:42–47
- Flavell DM, Ireland H, Stephens JW et al. (2005), Peroxisome proliferator-activated receptor alpha gene variation influences age of onset and progression of type 2 diabetes. *Diabetes* 54
- Foley DL, Eaves LJ, Wormley B et al. (2004), Childhood adversity, monoamine oxidase A genotype, and risk for conduct disorder. *Arch Gen Psychiatry* 61:738–744
- Foley DL, Neale MC, Kendler KS (1998), Reliability of a lifetime history of major depression: implications for heritability and comorbidity. *Psychol Med* 28:857–870
- Fombonne E (2003a), Epidemiological surveys of autism and other pervasive developmental disorders: an update. *J Autism Dev Disord* 33:365–382
- Fombonne E (2003b), The prevalence of autism. *JAMA* 289:87–89
- Fombonne E, Simmons H, Ford T, Meltzer H, Goodman R (2003), Prevalence of pervasive developmental disorders in the British nationwide survey of child mental health. *Int Rev Psychiatry* 15:158–165
- Ford DE, Erlinger TP (2004), Depression and C-reactive protein in US adults: data from the Third National Health and Nutrition Examination Survey. *Arch Intern Med* 164:1010–1014
- Ford T, Goodman R, Meltzer H (2003), The British child and adolescent mental health survey 1999: The prevalence of DSM-IV disorders. *J Am Acad Child Adolesc Psychiatry* 42:1203–1211
- Furlano RI, Anthony A, Day R et al. (2001), Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism. *J Pediatr* 138:366–372
- Gabay C, Kushner I (1999), Mechanisms of disease: acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 340:448–454
- Gale CR, Martyn CN (2004), Birth weight and later risk of depression in a national birth cohort. *Br J Psychiatry* 184:28–33
- Garber J (1984), Classification of childhood psychopathology: a developmental perspective. *Child Dev* 55:30–48
- Geier MR, Geier DA (2003), Neurodevelopmental disorders after thimerosal-containing vaccines: a brief communication. *Exp Biol Med* 228:660–664
- Ghosh S, Armitage E, Wilson D, Minor PD, Afzal MA (2001), Detection of persistent measles virus infection in Crohn's disease: current status of experimental work. *Gut* 48:748–752
- Giuffra LA, Risch N (1994), Diminished recall and the cohort effect of major depression: a simulation study. *Psychol Med* 24:375–383
- Glaser R, Padgett DA, Litsky ML et al. (2005), Stress-associated changes in the steady-state expression of latent Epstein-Barr virus: implications for chronic fatigue syndrome and cancer. *Brain Behav Immun* 19:91–103
- Glassman AH, Shapiro PA (1998), Depression and the course of coronary artery disease. *Am J Psychiatry* 155:4–11
- Granger DA, Serbin LA, Schwartzman A, Lehoux P, Cooperman J, Ikeda S (1998), Children's salivary cortisol, internalising behaviour problems, and family environment: results from the Concordia Longitudinal Risk Project. *Int J Behav Dev* 22:707–728
- Gunnell D, Rasmussen F, Fouskakis D, Tynelius P, Harrison G (2003), Patterns of fetal and childhood growth and the development of psychosis in young males: a cohort study. *Am J Epidemiol* 158:291–300
- Gupta S (1996), Immunology and immunologic treatment of autism. *Proc Natl Autism Assoc* 1996:455–460
- Han TS, Sattar N, Williams K, Gonzalez-Villalpano C, Lean ME, Haffner SM (2002), Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City Diabetes Study. *Diabetes Care* 25:2016–2021
- Hawkins JD, Catalano RF, Arthur MW (2002), Promoting science-based prevention in communities. *Addict Behav* 27:951–976
- Hayward C, Killen J, Kraemer H, Taylor CB (2000), Predictors of panic attacks in adolescents. *J Am Acad Child Adolesc Psychiatry* 39:207–214
- Hendrickson BA, Turner JR (2002), MMR vaccination, ileal lymphoid nodular hyperplasia, and pervasive developmental disorder. *Lancet* 359:2051–2052
- Hewitt JK, Silberg JL, Rutter M et al. (1997), Genetics and developmental psychopathology: I. Phenotypic assessment in the Virginia Twin Study of Adolescent Behavioral Development. *J Child Psychol Psychiatry* 38:943–963
- Honda H, Shimizu Y, Rutter M (2005), No effect of MMR withdrawal on the incidence of autism: a total population study. *J Child Psychol Psychiatry* 46:572–579
- Hornig M, Chian D, Lipkin WL (2004), Neurotoxic effects of postnatal thimerosal are mouse strain dependent. *Mol Psychiatry* 9:833–845
- Horton R (2004a), The lessons of MMR. *Lancet* 363:747–749
- Horton R (2004b), A statement by the editors of *The Lancet*. *Lancet* 363:820–821
- Horvath K, Papadimitriou JC, Rabsztyan A, Drachenberg C, Tildon JT (1999), Gastrointestinal abnormalities in children with autistic disorder. *J Pediatr* 135:559–563
- Hviid A, Stellfeld M, Wohlfahrt J, Melbye M (2003), Association between thimerosal-containing vaccine and autism. *JAMA* 290:1763–1766

- Iizuka M, Chiba M, Yukawa M et al. (2000), Immunohistochemical analysis of the distribution of measles related antigen in the intestinal mucosa in inflammatory bowel disease. *Gut* 46:163–169
- Isasi CR, Deckelbaum RJ, Tracy RP, Starc TJ, Berglund L, Shea S (2003), Physical fitness and C-reactive protein level in children and young adults: The Columbia University Biomarkers Study. *Pediatrics* 111:332–338
- Jaffee S, Caspi A, Moffitt T, Taylor A (2004), Physical maltreatment victim to antisocial child: evidence of an environmentally mediated process. *J Abnorm Psychol* 113:44–55
- Jick H, Kaye JA (2003), Epidemiology and possible causes of autism. *Pharmacotherapy* 23:1524–1530
- Jick H, Kaye JA (2004), Autism and DPT vaccination in the United Kingdom. *N Engl J Med* 350:2722–2723
- Kaplow JB, Curran PJ, Angold A, Costello EJ (2001), The prospective relation between dimensions of anxiety and the initiation of adolescent alcohol use. *J Clin Child Psychol* 30:316–326
- Kawashima H, Mori T, Kashiwagi Y, Takekuma K, Hoshika A, Wakefield A (2000), Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism. *Dig Dis Sci* 45:723–729
- Kaye J, Melero-Montes del Mar M, Hershel J (2001), Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. *BMJ* 322:460–463
- Kellam SG, Koretz D, Moscicki E (1999), Core elements of developmental epidemiologically based prevention research. *Am J Community Psychol* 27:463–482
- Kellam SG, Werthamer-Larsson L (1986), Developmental epidemiology: a basis for prevention. In: *A Decade of Progress in Primary Prevention*, Kessler M, Goldston SE, eds. Hanover, NH: University Press of New England, pp 154–180
- Kerr AM, Ravine D (2003), Review article: breaking new ground with Rett syndrome. *J Intellect Disabil Res* 47:580–587
- Kessler RC, Berglund P, Demler O et al. (2003), The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 289:3095–3105
- Kessler RC, Borges G, Walters EE (1999), Prevalence of and risk factors for lifetime suicide attempts in the National Comorbidity Survey. *Arch Gen Psychiatry* 56:617–626
- Kessler RC, McGonagle KA, Swartz MS, Blazer DG, Nelson CB (1993), Sex and depression in the National Comorbidity Survey: I. Lifetime prevalence, chronicity and recurrence. *J Affect Disord* 29:85–96
- Kessler RC, Nelson CB, McGonagle KA, Edlund MJ, Frank RG, Leaf PJ (1996a), The epidemiology of co-occurring addictive and mental disorders: implications for prevention and service utilization. *Am J Orthopsychiatry* 66:17–31
- Kessler RC, Nelson CB, McGonagle KA, Liu J, Swartz M, Blazer DG (1996b), Comorbidity of DSM-III-R major depressive disorder in the general population: results from the US National Comorbidity Survey. *Br J Psychiatry* 168:17–30
- Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S (1997), The epidemiology of DSM-III-R bipolar I disorder in a general population survey. *Psychol Med* 27:1079–1089
- Kiecolt-Glaser JK (1999), Norman Cousins Memorial Lecture 1998. Stress, personal relationships, and immune function: health implications. *Brain Behav Immun* 13:61–72
- Kim-Cohen J, Arseneault L, Caspi A, Tomas MP, Taylor A, Moffitt TE (2005), Validity of DSM-IV conduct disorder in 41/2–5-year-old children: a longitudinal epidemiological study. *Am J Psychiatry* 162:1108–1117
- Kim-Cohen J, Caspi A, Moffitt T, Harrington H, Milne B, Poulton R (2003), Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Arch Gen Psychiatry* 60:709–717
- Klein RG (1995), Is panic disorder associated with childhood separation anxiety disorder? *Clin Neuropsychol* 18:S7–S14
- Koenig W, Sund M, Froelich M et al. (1999), C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (monitoring trends and determinants in cardiovascular disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 99:237–242
- Kreppner JM, O'Connor TG, Rutter M, English Romanian Adoptees Study Team (2001), Can inattention/overactivity be an institutional deprivation syndrome? *J Abnorm Child Psychol* 29:513–528
- Kuller LH, Tracy RP, Shaten J, Meilahn EN (1996), Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. *Am J Epidemiol* 144:537–547
- Lahey B, Miller T, Schwab-Stone M et al. (2000), Age and gender differences in oppositional behavior and conduct problems: a cross-sectional household study of middle childhood and adolescence. *J Abnorm Psychol* 109:488–503
- Leonard H, Bower C, English D (1997), The prevalence and incidence of Rett syndrome in Australia. *Eur Child Adolesc Psychiatry* 6(suppl 1): 8–10
- Levy F, Hay D, McLaughlin M, Wood C, Waldman I (1996), Twin-sibling differences in parental reports of ADHD, speech, reading and behaviour problems. *J Child Psychol Psychiatry* 37:569–578
- Lewinsohn P, Zinbarg J, Lewinsohn M, Sack W (1997), Lifetime comorbidity among anxiety disorders and between anxiety disorders and other mental disorders in adolescents. *J Anxiety Disord* 11:377–394
- Lewinsohn PM, Clarke GN, Seeley JR, Rohde P (1994), Major depression in community adolescents: age of onset, episode duration, and time to recurrence. *J Am Acad Child Adolesc Psychiatry* 33:809–818
- Lewinsohn PM, Rohde P, Seeley JR, Fischer SA (1993), Age-cohort changes in the lifetime occurrence of depression and other mental disorders. *J Abnorm Psychol* 102:110–120
- Lewinsohn PM, Striegel-Moore RH, Seeley JR (2000), Epidemiology and natural course of eating disorders in young women from adolescence to young adulthood. *J Am Acad Child Adolesc Psychiatry* 39:1284–1292
- Lopez JF, Chalmers DT, Little KY, Watson SJ, AE Bennett Research Award (1998), Regulation of serotonin1A, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: implications for the neurobiology of depression. *Biol Psychiatry* 43:547–573
- Lotter V (1980), Methodological problems in cross-cultural epidemiologic research: illustrations from a survey of childhood autism in Africa. In: *Studies of Children*, Earls F, ed. New York: Neale Watson, pp 126–144
- Lutgendorf SK, Antoni MH, Kumar M, Schneiderman N (1994), Changes in cognitive coping strategies predict EBV-antibody titre change following a stressor disclosure induction. *J Psychosom Res* 38:63–78
- Madsen K, Hviid A, Vestergaard M et al. (2002), A population-based study of measles, mumps and rubella vaccination and autism. *N Engl J Med* 347:1477–1482
- Madsen KM (2004), Response. *N Engl J Med* 348:953
- Madsen KM, Lauritsen MB, Pedersen CB et al. (2003), Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. *Pediatrics* 112:604–606
- Maes M (1999), Major depression and activation of the inflammatory response system. *Adv Exp Med Biol* 461:25–46
- Magee W, Eaton W, Wittchen H, McGonagle K, Kessler R (1996), Agoraphobia, simple phobia, and social phobia in the National Comorbidity Survey. *Arch Gen Psychiatry* 53:159–168
- Mantymaa M, Puura K, Luoma I et al. (2003), Infant-mother interaction as a predictor of child's chronic health problems. *Child Care Health Dev* 29:181–191
- Martin CM, Uhlmann V, Killalea A, Sheils O, O'Leary JJ (2002), Detection of measles virus in children with ileo-colonic lymphoid nodular hyperplasia, enterocolitis and developmental disorder. *Mol Psychiatry* 7:S47–S48
- McDade TW (2002), Status incongruity in Samoan youth: a biocultural analysis of culture change, stress, and immune function. *Med Anthropol Q* 16:123–150
- McEwen BS (2002), The neurobiology and neuroendocrinology of stress. Implications for post-traumatic stress disorder from a basic science perspective. *Psychiatr Clin North Am* 25:469–494
- Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA (2002), Clinical depression and inflammatory risk markers for coronary heart disease. *Am J Cardiol* 90:1279–1283
- Miller RJ, Sutherland AG, Hutchinson JD, Alexander DA (2001), C-reactive protein and interleukin 6 receptor in post-traumatic stress disorder: a pilot study. *Cytokine* 13:253–255

- Moffitt TE (1993), Adolescence-limited and life-course-persistent-offending: a complementary pair of developmental theories. In: *Developmental Theories of Crime and Delinquency*, Thornberry TP, ed. New Brunswick, NJ: Transaction, pp 11–55
- Moffitt TE, Caspi A, Harrington H, Milne BJ (2002), Males on the life-course persistent and adolescence-limited antisocial pathways: follow-up at age 26. *Dev Psychopathol* 14:179–207
- Mold C, Gewurz H, DuClos TW (1999), Regulation of complement activation by C-reactive protein. *Immunopharmacology* 42:23–30
- Morris DL, Montgomery SM, Thompson NP, Ebrahim S, Pounder RE, Wakefield AJ (2000), Measles vaccination and inflammatory bowel disease: a national British Cohort Study. *Am J Gastroenterol* 95:3507–3512
- Murch SH, Anthony A, Casson DH et al. (2004), Retraction of an interpretation. *Lancet* 363:750
- Murphy BE (1991), Steroids and depression. *J Steroid Biochem Mol Biol* 38:537–559
- Muthen B, Muthen LK (2000), Integrating person-centered and variable-centered analyses: growth mixture modeling with latent trajectory classes. *Alcohol Clin Exp Res* 24:882–891
- Nagin DS, Tremblay RE (2001), Analyzing developmental trajectories of distinct but related behaviors: a group-based method. *Psychol Methods* 6:18–34
- National Research Council and Institute of Medicine (2001), Juvenile Crime, Juvenile Justice. Panel on Juvenile Crime: Prevention, Treatment, and Control, McCord J, Widom CS, Crowell NA, eds. Washington, DC: National Academies Press
- Nelson KB, Bauman ML (2003), Thimerosal and autism? *Pediatrics* 111:674–679
- Nemeroff CB, Widerlov E, Bissette G et al. (1984), Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science* 226:1342–1344
- Noble KK, Miyasaka K (2004), Letter to the editor. *N Engl J Med* 348:952–953
- Oomen HA, Schipperrijn AJ, Drexhage HA (1996), The prevalence of affective disorder and in particular of a rapid cycling of bipolar disorder in patients with abnormal thyroid function tests. *Clin Endocrinol* 45:215–223
- Opler MG, Brown AS, Graziano J et al. (2004), Prenatal lead exposure, delta-aminolevulinic acid, and schizophrenia. *Environ Health Perspect* 112:548–552
- Orvaschel H, Lewinsohn PM, Seeley JR (1995), Continuity of psychopathology in a community sample of adolescents. *J Am Acad Child Adolesc Psychiatry* 34:1525–1535
- Patten SB (2003), Recall bias and major depression lifetime prevalence. *Soc Psychiatry Psychiatr Epidemiol* 38:290–296
- Paykel ES (2000), Not an age of depression after all? Incidence rates may be stable over time. *Psychol Med* 30:489–490
- Pharoah PD, Stevenson CJ, Cooke RI, Stevenson RC (1994), Prevalence of behaviour disorders in low birthweight infants. *Arch Dis Child* 70:271–274
- Phillips DI, Barker DJ, Osmond C (1993), Infant feeding, fetal growth and adult thyroid function. *Acta Endocrinol* 129:134–138
- Pichichero ME, Cernichiari E, Lopreiato J, Treanor J (2002), Mercury concentrations and metabolism in infants receiving vaccines containing thimerosal: a descriptive study. *Lancet* 360:1737–1741
- Pickles A, Pickering K, Simonoff E, Silberg J, Meyer J, Maes H (1998), Genetic “clocks” and “soft” events: a twin model for pubertal development and other recalled sequences of developmental milestones, transitions, or ages at onset. *Behav Genet* 28:243–253
- Pine DS, Cohen P, Gurley D, Brook J, Ma Y (1998), The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Arch Gen Psychiatry* 55:56–64
- Raine A, Moffitt TE, Caspi A, Loeber R, Stouthamer-Loeber M, Lynam D (2005), Neurocognitive impairments in boys on the life-course persistent antisocial path. *J Abnorm Psychol* 114:38–49
- Ridker PM, Buring JE, Cook NR, Rifai N (2003), C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. *Circulation* 107:391–397
- Risch N, Burchard E, Ziv E, Tang H (2002), Categorization of humans in biomedical research: genes, race and disease. *Genome Biol* 3:1–12
- Robins L (1999), A 70-year history of conduct disorder: variations in definition, prevalence, and correlates. In: *Historical and Geographical Influences on Psychopathology*, Cohen P, Slomkowski C, Robins L, eds. Mahwah, NJ: Lawrence J. Erlbaum Associates, pp 37–56
- Roose SP, Glassman AH, Seidman SN (2001), Relationship between depression and other medical illnesses. *JAMA* 286:1687–1690
- Rothman KJ, Greenland S (1998), *Modern Epidemiology*, 2nd ed., Rothman KJ, Greenland S, eds. Philadelphia: Lippincott-Raven
- Rutter M, Caspi A, Moffitt T (2003), Using sex differences in psychopathology to study causal mechanisms: unifying issues and research strategies. *J Child Psychol Psychiatry* 44:1092–1115
- Rutter M, Garmezay N (1983), Developmental psychopathology. In: *Handbook of Child Psychology, Volume 4*, Mussen P, ed. New York: John Wiley & Sons, pp 775–911
- Rutter M, Giller H, Hagell A (1998), *Antisocial Behavior by Young People*. New York: Cambridge University Press
- Rutter M, Silberg T, O'Connor T, Simonoff E (1999a), Genetics and child psychiatry: II. Empirical research findings. *J Child Psychol Psychiatry* 40:19–56
- Rutter M, Silberg J, O'Connor, Simonoff E (1999b), Genetics and child psychiatry: I. Advances in quantitative and molecular genetics. *J Child Psychol Psychiatry* 40:3–18
- Rutter M, Sroufe LA (2000), Developmental psychopathology: concepts and challenges. *Dev Psychopathol* 12:265–296
- Saigal S, Pinelli J, Hoult L, Kim MM, Boyle M (2003), Psychopathology and social competencies of adolescents who were extremely low birth weight. *Pediatrics* 111:969–975
- Sakkas PN, Soldatos CR, Bergiannaki JD, Paparrigopoulos TJ, Stefanis CN (1998), Growth hormone secretion during sleep in male depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry* 22:467–483
- Sanford M, Boyle MH, Szatmari P, Offord DR, Jamieson E, Spinner M (1999), Age-of-onset classification of conduct disorder: reliability and validity in a prospective cohort study. *J Am Acad Child Adolesc Psychiatry* 38:992–999
- Sarid O, Anson O, Yaari A, Margalith M (2001), Epstein-Barr virus specific salivary antibodies as related to stress caused by examinations. *J Med Virol* 64:149–156
- Schwartz S (1998), The role of values in the nature/nurture debate about psychiatric disorders. *Soc Psychiatry Psychiatr Epidemiol* 33:356–362
- Silberg J, Rutter M, Eaves L (2001), Genetic and environmental influences on the temporal association between earlier anxiety and later depression in girls. *Biol Psychiatry* 49:1040–1049
- Silove D, Manicavasagar V, Curtis J, Blaszczynski A (1996), Is early separation anxiety a risk factor for adult panic disorder? A critical review. *Compr Psychiatry* 37:167–179
- Simon GE, Vonkorff M, Ustun TB, Gater R, Gureje O, Sartorius N (1995), Is the lifetime risk of depression actually increasing? *J Clin Epidemiol* 48:1109–1118
- Simonoff E, Pickles A, Meyer JM et al. (1997), The Virginia Twin Study of adolescent behavioral development: influences of age, sex and impairment on rates of disorder. *Arch Gen Psychiatry* 54:801–808
- Singer B, Ryff CD (1999), Hierarchies of life histories and associated health risks. *Ann N Y Acad Sci* 896:96–115
- Smeeth L, Cook C, Fombonne E et al. (2004), MMR vaccination and pervasive developmental disorders: a case-control study. *Lancet* 364:963–969
- Snidman N, Kagan J, Riordan L, Shannon DC (1995), Cardiac function and behavioral reactivity during infancy. *Psychophysiology* 32:199–207
- Sommerfelt K, Ellertsen B, Markestad T (1993), Personality and behaviour in eight-year-old, non-handicapped children with birth weight under 1500 g. *Acta Paediatr* 82:723–728
- Sommerfelt K, Troland K, Ellertsen B, Markestad T (1996), Behavioral problems in low-birthweight preschoolers. *Dev Med Child Neurol* 38:927–940
- Spoth RL, Kavanagh KA, Dishion TJ (2002), Family-centered preventive intervention science: toward benefits to larger populations of children, youth, and families. *Prev Sci* 3:145–152

- Stroufe LA, Rutter M (1984), The domain of developmental psychopathology. *Child Dev* 55:17–29
- Stehr-Green P, Tull P, Stellfeld M, Mortenson P-B, Simpson D (2003), Autism and thimerosal-containing vaccines: lack of consistent evidence for an association. *Am J Prev Med* 25:101–106
- Stepoe A, Lundwall K, Croleby M (2000), Gender, family structure and cardiovascular activity during the working day and evening. *Soc Sci Med* 50:531–539
- Stouthamer-Loeber M, Drinkwater M, Loeber R (1999), Family functioning profiles, early onset of offending, and disadvantaged neighborhoods. *Int J Child Fam Welfare* 3:247–256
- Strickland PL, Deakin JW, Percival C, Dixon J, Gater RA, Goldberg DP (2002), Bio-social origins of depression in the community: interactions between social adversity, cortisol and serotonin neurotransmission. *Br J Psychiatry* 180:168–173
- Sullivan ML (1998), Integrating qualitative and quantitative methods in the study of developmental psychopathology in context. *Dev Psychopathol* 19:377–393
- Sung M, Erkanli A, Angold A, Costello E (2004), Effects of age at first substance use and psychiatric comorbidity on the development of substance use disorders. *Drug Alcohol Depend* 75:287–299
- Susser M, Susser E (1996), Choosing a future for epidemiology: 2. From black box to chinese boxes and eco-epidemiology. *Am J Public Health* 86:674–677
- Swan G, Hudmon K, Jack L et al. (2003), Environmental and genetic determinants of tobacco use: methodology for a multidisciplinary, longitudinal family-based investigation. *Cancer Epidemiol Biomarkers Prev* 12:994–1005
- Tamakoshi K, Yatsuya H, Kondo T et al. (2003), The metabolic syndrome is associated with elevated circulating C-reactive protein in healthy reference range, a systemic low-grade inflammatory state. *Int J Obes Relat Metab Disord* 27:443–449
- Taylor B, Miller E, Farrington CP et al. (1999), Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. *Lancet* 353:2026–2029
- Thompson C, Syddall H, Rodin I, Osmond C, Barker DJ (2001), Birth weight and the risk of depressive disorder in late life. *Br J Psychiatry* 179:450–455
- Tolan PH, Thomas P (1995), The implications of age of onset for delinquency risk II: longitudinal data. *J Abnorm Child Psychol* 23:1995
- Tremblay RE (2004), The development of human physical aggression: how important is early childhood? In: *Social and Moral Development: Emerging Evidence on the Toddler Years*, Leavitt LA, Hall DB, eds. Brunswick, NJ: Johnson & Johnson Pediatric Institute, pp 221–38
- Tremblay RE, Nagin DS, Seguin JR et al. (2004), Physical aggression during early childhood: trajectories and predictors. *Pediatrics* 114:e43–e50
- Uhlmann V, Martin CM, Sheils O et al. (2002), Potential viral pathogenic mechanism for new variant inflammatory bowel disease. *Mol Pathol* 55:84–90
- Van den Veyver IB, Zoghbi HY (2002), Genetic basis of Rett syndrome. *Ment Retard Dev Disabil Res Rev* 8:82–86
- Vega W, Aguilar-Gaxiola S, Andrade L et al. (2002), Prevalence and age on onset for drug use in seven international sites: results from the International Consortium of Psychiatric Epidemiology. *Drug Alcohol Depend* 68:285–297
- Verstraeten T, Davis RL, DeStefano F et al. Vaccine Safety Datalink Team (2003), Safety of thimerosal-containing vaccines: a two-phased study of computerized health maintenance organization databases. *Pediatrics* 112:1039–1048
- Wakefield A (1999), MMR vaccination and autism. *Lancet* 1999:949–950
- Wakefield AJ, Anthony A, Murch SH et al. (2000), Enterocolitis in children with developmental disorders. *Am J Gastroenterol* 95:2285–95
- Wakefield AJ, Anthony A, Schepelmann S et al. Royal Free Hospital School of Medicine (1998a), Persistent measles virus (MV) infection and immunodeficiency in children with autism, ileo-colonic lymphonodular hyperplasia and non-specific colitis. *Gut* 42:A86
- Wakefield AJ, Montgomery SM (2000), Measles virus as a risk for inflammatory bowel disease: an unusually tolerant approach. *Am J Gastroenterol* 95:1389–1392
- Wakefield AJ, Murch SH, Anthony A et al. (1998b), Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 351:637–641
- Wakefield AJ, Puleston JM, Montgomery SM, Anthony A, O'Leary JJ, Murch SH (2002), Review article: the concept of entero-colonic encephalopathy, autism and opioid receptor ligands. *Aliment Pharmacol Ther* 16: 663–674
- Whitaker AG, Rossem RV, Feldman JF et al. (1997), Psychiatric outcomes in low-birth-weight children at age 6 years: relation to neonatal cranial ultrasound abnormalities. *Arch Gen Psychiatry* 54:847–856
- Wickramaratne PJ, Weissman MM, Leaf PJ, Holford TR (1989), Age, period, and cohort effects on the risk of major depression: results from five United States communities. *J Clin Epidemiol* 43:333–344
- Wittchen HU, Knauper B, Kessler RC (1994), Lifetime risk of depression. *Br J Psychiatry* 26(suppl):16–22
- Wright LB, Treiber F, Davis H, Bunch C, Strong WB (1998), The role of maternal hostility and family environment upon cardiovascular functioning among youth two years later: socioeconomic and ethnic differences. *Ethn Dis* 8:367–376
- Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C (2003), Prevalence of autism in a US metropolitan area. *JAMA* 289:49–55