8 Comorbidity and Intellectual Disability

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Comorbidity has been defined as the "existence or occurrence of any additional entity during the clinical course of a patient who has the index disease under study" (Feinstein, 1970) Comorbidity is commonly used to refer to the presence of a second or multiple conditions alongside a primary condition of interest. In a technical context, the term refers to the greater than chance likelihood that the presence of one condition will be accompanied by a second or multiple conditions. The presence of the comorbidities would be observed in the population at a higher rate than the product of the base rates would suggest. In this chapter, we concentrate on comorbidity in the context of developmental neuropsychiatric disorders primarily in children.

Comorbidity is often anticipated as a component of many disorders (Burd, Klug, Martsolf, & Kerbeshian, 2003; Feinstein, 1970; Kerbeshian & Burd, 2000). For example, people with intellectual disability (ID) may also have increased rates of attention deficit hyperactivity disorder autism and epilepsy in comparison to people without ID (Burd et al., 2003; Burd, Li, Kerbeshian, Klug, & Freeman, 2009; Kerbeshian & Burd, 2000; Peng, Hatlestad, Klug, Kerbeshian, & Burd, 2009; Weyrauch, Schwartz, Hart, Klug, & Burd, 2017 May). Comorbidities are important from a clinical standpoint as they influence disease activity, prognosis, medication choice, adverse effects, treatment response, patient compliance, and health care costs (Aslam & Khan, 2018). Comorbidities often have a major negative impact on quality of life, increasing functional disability, independent of disease activity. Comorbidities increase the risk for suboptimal care of coexisting disorders and the psychosocial milieu that accompany these comorbidities.

Diagnostic approach is central to understanding comorbidity. Traditionally, diagnosticians could be conceptualized as "lumpers" who *perceive* a broad phenotype encompassing multiple impairments or various behavior disorders as components of the phenotype. Lumpers tend to see conditions as hierarchical in nature, with

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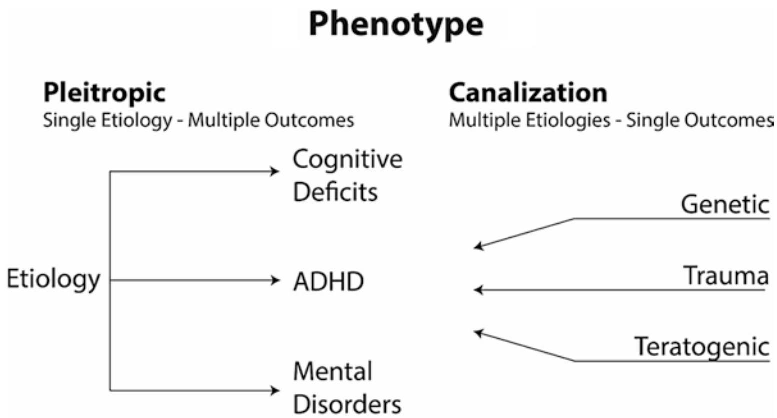

Fig. 8.1 Description of the two most common approaches to diagnoses of neurobehavioral disorders

diagnoses of greater severity, complexity, or impact trumping and incorporating diagnoses of lesser severity, complexity, or impact. Examples of this dynamic can be seen when autism spectrum disorder trumps the specific semantic pragmatic language disorder often present in people with ASD, or in instances where trisomy 21 eclipses problems related to prenatal alcohol exposure. Pleiotropy is roughly the genetic equivalent of the concept of multipotentiality (Fig. 8.1). The term pleiotropy reflects the idea that a common element or a single gene may lead to multiple alternate outcomes or phenotypes, presumably modified by the background of other genes or elements, or epigenetic factors. The concept of equifinality is that of different genes or elements merging into a common outcome or phenotype. The concept of phenocopy also has a similar effect. Canalization refers to a measure of resistance to change of outcome from a single element or a gene, irrespective of the influence of background elements of other genes, epigenetics, or other modifying factors. For example, heavy prenatal use of alcohol may lead to a certain configuration of the eyes and the face, but not to a third eye. Two eyes are heavily canalized, even if there are congenital cataracts, anisophthalmia, etc.

Alternatively, other diagnosticians utilize a broad approach where multiple *different* causes result in a constrained but recognizable pattern or disease phenotype. This approach is *equifinality or convergent homology* canalization (Fig. 8.2). Common examples are genetic causes or environmental causes (prenatal alcohol exposure), intellectual disability, autism spectrum disorders, or cerebral palsy. In practice most clinicians utilize the two approaches together and provide a useful approach to understanding clinically relevant factors that may clarify etiological diagnosis or inform treatment planning (Fig. 8.2). An example of this combined approach can be seen in the diagnosis of fetal alcohol spectrum disorders. Prenatal alcohol exposure is the causal etiology of FASD; however, smoking, maternal depression, prematurity, and drug use are other important elements in the epidemiological causal chain of events, and merit consideration in the diagnosis of fetal alcohol spectrum disorders. These additional elements would be considered as effect modifiers for prenatal alcohol exposure modifying the phenotype both during pregnancy and during postnatal development.

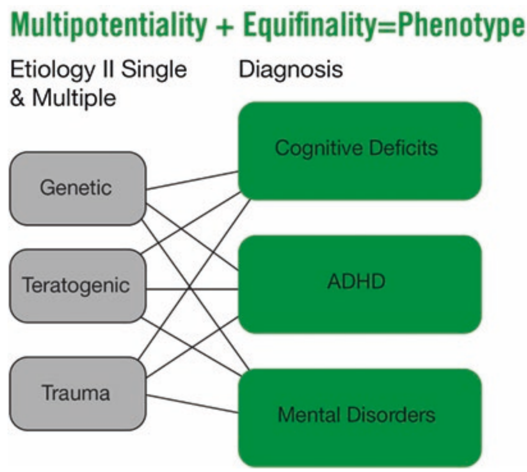

Fig. 8.2 Graphic representation of the components in the construct of multipotentiality

The phenotype of fetal alcohol spectrum disorders is highly variable and is both age and development dependent (Johnson, Moyer, Klug, & Burd, 2017 online first; Weyrauch et al., 2017 May). Clear examples of this variability are the increased risk for development of a substance use disorder *and* contact with the juvenile justice system for individuals with fetal alcohol spectrum disorders. These factors are not apparent in infancy but emerge during childhood and adolescence and may appear as longitudinal comorbidity. In clinical practice it is important to be aware of changes in phenotype in response to age and development. For example, it is important to understand that individuals with FASD have increased rates of contact with juvenile corrections and substance use disorders, and consequently monitor their behavior for signs of issue. These problems are foreseeable risks and should not surprise parents of these children when they reach adolescence. It is important to note that while the risk for these problems is increased in these populations, the problems are not inevitable.

Adverse childhood experiences are frequently seen concurrently with FASD. Adverse childhood events are important effect modifiers, which increases the risk for a variety of problematic health outcomes throughout the life span. In a study comparing FASD participants against non-FASD controls we found large increases in rates of adverse events in patients with FASD compared to controls (in preparation). We examined the role of adverse childhood experiences in people with FASD and the number of comorbid neuropsychiatric disorders compared to the number of adverse childhood experiences and comorbid diagnoses in a group of non-FASD controls. This relationship is summarized in Figs. 8.3 and 8.4.

Children with FASD who had multiple diagnoses also had higher ACE scores. A visual depiction of the relationship between ACEs and the number of diagnoses is presented as a nomogram (Fig. 8.3).

The 10 traditional adverse childhood experiences (ACEs) and placement in foster care or residential care programs making a total of 12 possible variables.

The number of adverse childhood experiences appears to be an important effect modifier of risk for comorbid neurodevelopmental disorders in people with FASD but is much less important for non-FASD controls.

In Fig. 8.5 we present a disease specification approach that is also central to the issue of comorbidity. The broad phenome of conditions of interest (childhood developmental disorders) can be examined by the study of multiple phenotypes (phenomics), which comprises a catalogue of phenotypes used to diagnose the different expressions of diseases and disorders.

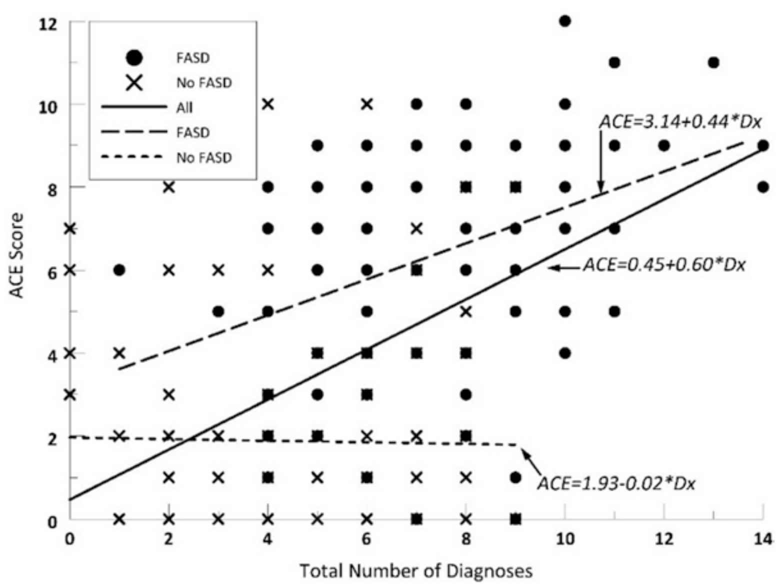

Fig. 8.3 The relationship between adverse childhood experience and comorbid neurobehavioral diagnoses

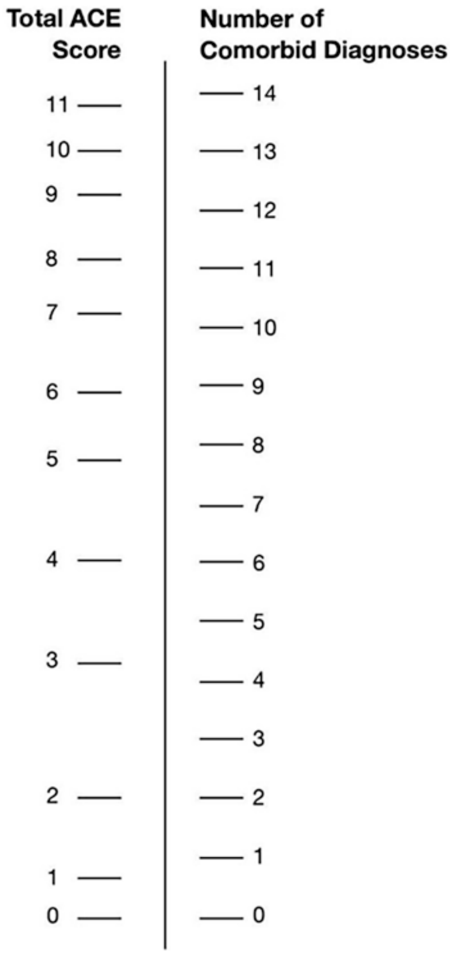

Fig. 8.4 A nomogram depicting the relationship between increasing (ACE) rates of adverse childhood experiences and associated comorbid neurobehavioral disorders

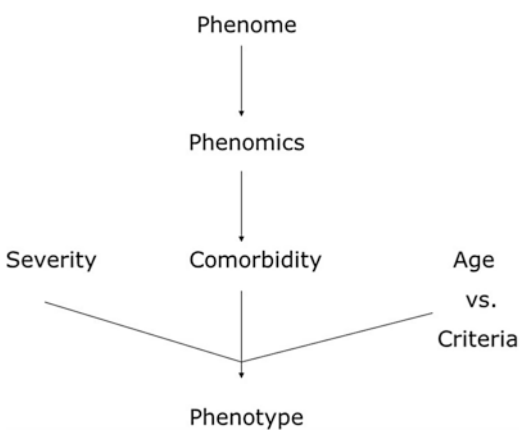

Fig. 8.5 Relationship between all diagnosis phenome and individual disease phenotype in a patient

Most neurodevelopmental disorders have multiple diagnostic features (nosology) that comprise a diagnosis, and these features are typically assessed dimensionally (mild, moderate, severe, or on a symptom diagnostic spectrum such as motor tic disorder, vocal tic disorder, and Tourette syndrome) and on categorical (yes or no) criteria. Figure 8.6 presents the concept of intellectual disability as a comorbid finding in fetal alcohol spectrum disorders and its impact.

Fetal alcohol spectrum disorders and autism spectrum disorders are clear examples of dimensional diagnostic categories which have evolved from more specific categorical diagnoses such as fetal alcohol syndrome, fetal alcohol effects, or alcohol related neurodevelopmental disorders. Autistic disorder, childhood disintegrative disorder, PDDNOS, infantile autism, or childhood onset pervasive developmental disorder also reflects the shift to appreciation of a phenotypic spectrum (Burd, Fisher, & Kerbeshian, 1988; Burd, Fisher, & Kerbeshian, 1989; Fisher, Burd, & Kerbeshian, 1987).

The impact of comorbidity on diagnostic boundaries has profound implications when studying the prevalence, etiology, diagnostic clarity, treatment strategies, and prevention for disorders. A conceptual overview of comorbidity expression suggests that several components merit consideration. Following is a list of the eight components of a comorbidity logic model.

Logic model components of comorbidity
1. Comorbidity increases the complexity of care.
2. Adversity increases the risk for comorbidity.
3. Comorbidity increases the risk for additional comorbidity (the complexity principle).
4. Increasing comorbidity increases diagnostic uncertainty.
5. The prevalence of comorbidity increases with age.
6. Increasing comorbidity increases service utilization and cost of care.
7. Comorbidity decreases access to evidence-based treatments.
8. Comorbidity decreases the likelihood of optimal outcomes.

In clinical practice or research settings, the complexity model may be a function of categorical diagnostic symptom counting (e.g., identification of multiple discreet diagnoses) versus use of

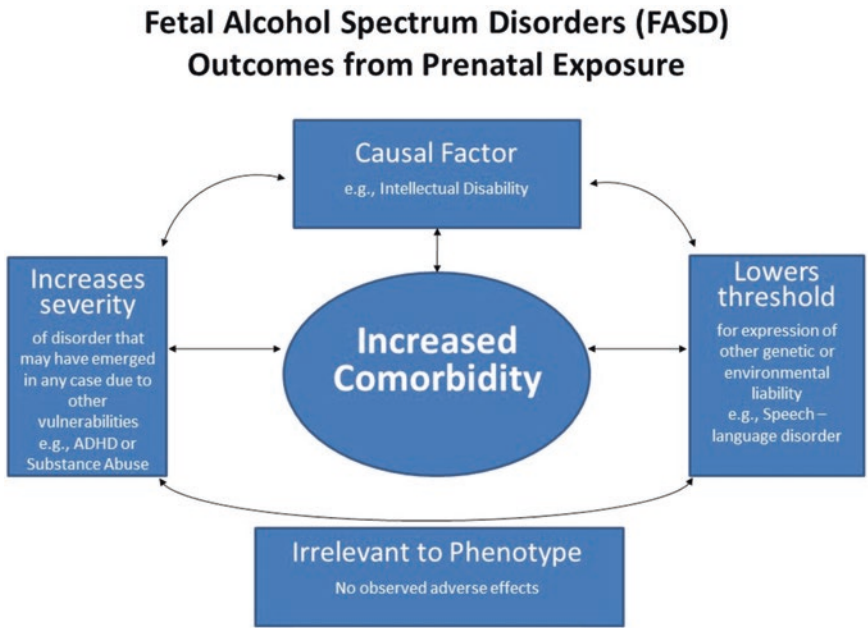

Fig. 8.6 Graphic presentation of factors influencing comorbidity in fetal alcohol spectrum disorders

a broad diagnostic category to subsume the comorbid diagnoses. For example, the overlap of some symptoms of ADHD with symptoms of a manic episode will require fewer additional manic symptom criteria in an ADHD child to make a diagnosis of mania, than in a child without ADHD. Symptoms may be double counted and reduce the threshold for additional comorbidities.

We will provide a brief discussion of each of the logic model components. Where appropriate, we will utilize health claims data and our clinical experience to illustrate each of the comorbidity components. The health claims data and our patient registries have been utilized within other studies of cost and service utilization and phenotype specification (Burd et al., 2001; Burd et al., 2002; Burd, Klug, Coumbe, & Kerbeshian, 2003a; Burd, Klug, Coumbe, & Kerbeshian, 2003b; Peng et al., 2009). For this analysis, we utilized inpatient and outpatient data on 179,873 unique individuals collected over the past two years. The sample's average age was 9.8 years (s.d. 5.4) and ages ranged from 1 year 18 years. This data excluded infants, thus accounting for childbirth expenses, which would skew the results. Just over half of participants (51.1%) were male. The average number of claims per child in the two-year period was 5.1 (s.d. 6.0) and ranged from 1 to 180. We identified 30 individual behavioral diagnoses and the major diagnostic category (MDC) for each claim using the ICD-9 3 digit designations. The average number of behavioral diagnoses per child was 0.14 (s.d. 0.57) and ranged from 0 to 13. After analyzing this data, several conclusions were reached, which are discussed below.

Comorbidity Increases Complexity of Care

It's often difficult for patients or families to decide which diagnoses are priorities for their limited time and funds. Multiple comorbid disorders often require multiple care providers. If a patient sees multiple providers, which one(s) should parents/caregivers prioritize (e.g., home programs for physical therapy, sensory impairments, medications, and/or mental health treatments)? How many appointments at how many different locations are reasonable? Is buying eyeglasses more important than medication for sleep? Patients and caretakers can be overwhelmed by multiple, often conflicting treatment recommendations for patients with comorbidity. This can lead to problems with anger, discouragement, and huge financial burdens for families and health care funders.

In Fig. 8.7 below we present a hypothetical situation depicting increasing complexity of care for a child with increasing comorbidity. The child is born to a mother who was abused and has alcohol use disorder. The father has ADHD, abuses alcohol, and has anger management issues.

This sequence of developmental events increases complexity of care and the cost of care.

Adversity Increases Prevalence and Risk of Comorbidity in Neuropsychiatric Disorders

Prevalence rates of common neurodevelopmental disorders are seen at elevated rates among children with exposure to adverse childhood events (Weyrauch et al., 2017 May). We used claims data for 1506 children with ID to find common comorbid diagnoses. ADHD is by far the most prevalent comorbid condition (42%), and is roughly four times as prevalent as other disorders. Several other disorders were also prevalent among people with ID (Fig. 8.8).

Children with ID are at far greater risk for these comorbidities, when compared to children without ID. However, the risk for a disease doesn't always follow prevalence, meaning that the comorbid disease that children with ID have the most frequently (ADHD) is not the one they are at the most risk for (conduct disorder) (Fig. 8.8). ADHD is very prevalent in children with ID and they are 10 times more likely to have ADHD than other children. However, children with ID are almost 16 times more likely to develop conduct disorder than other children, and 12 times more likely to have an ICD-defined emotional disorder (Fig. 8.9).

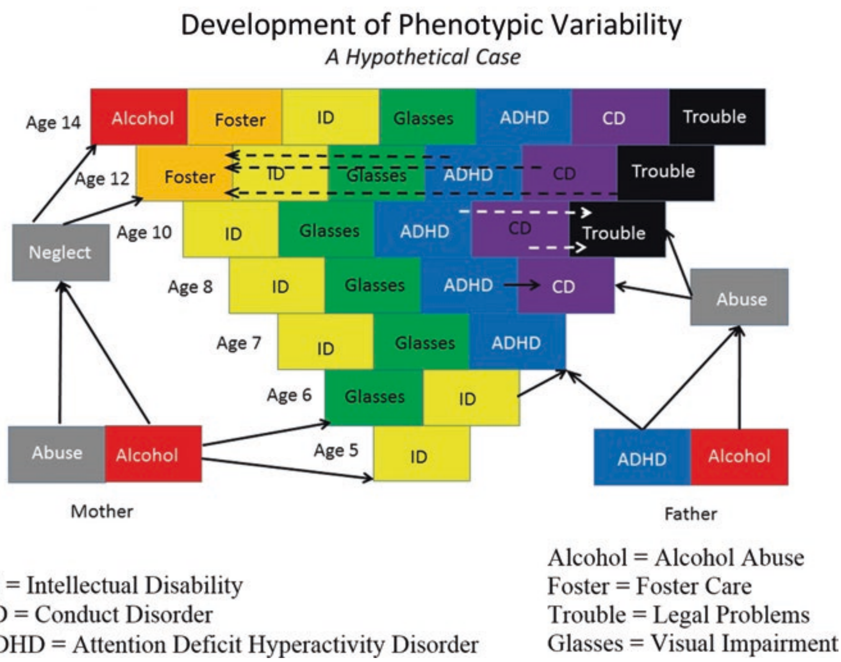

Fig. 8.7 Increasing complexity of ID and the individual phenotype of a person with ID with age. Age 5: The child is diagnosed with an intellectual disability, possibly related to maternal drinking during pregnancy. Age 6: The child needs glasses. Age 7: The child has been diagnosed with ADHD, as is the father. Age 8: The child is abused by the father. Learning and behavior issues emerge at school. Age 10: The child develops conduct disorder. Age 12: Neglect and abuse by the parents, trouble in school, and increasing behavioral impairments lead to foster care placement. Age 14: Substance abuse emerges as a concern. *ID* intellectual disability, *CD* conduct disorder, *ADHD* attention deficit hyperactivity disorder, *Alcohol* alcohol abuse, *Foster* foster care, *Trouble* legal problems, *Glasses* visual impairment

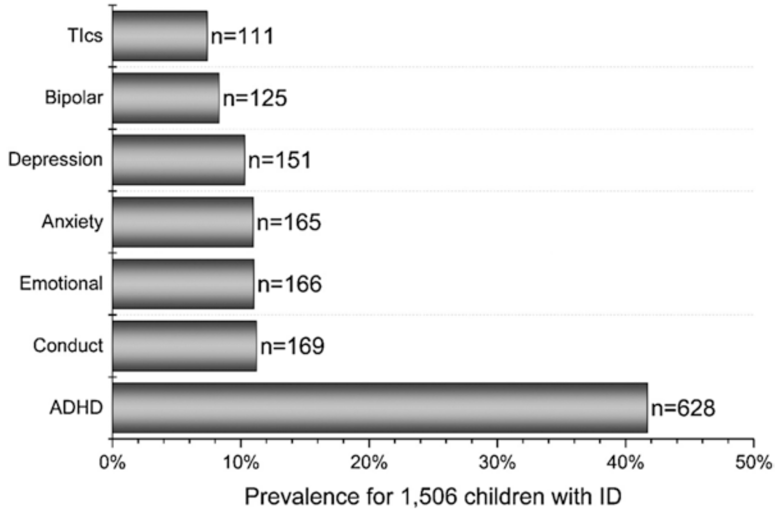

Fig. 8.8 Prevalence of seven most common comorbid behavioral diagnoses for children with ID

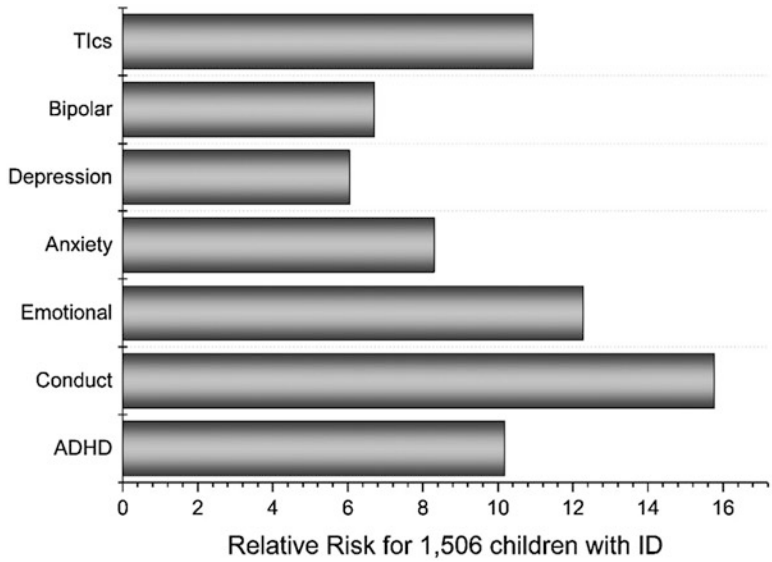

Fig. 8.9 Relative risks of seven most common comorbid behavioral diagnoses for children with ID

Comorbidity Increases Risk for Additional Comorbidities (The Complexity Principle)

Over the past 30 years, we have often observed that the presence of one comorbidity increases the risk for another comorbid disorder. We have described this as the complexity principle. We demonstrate this principle using health claims data for people with ID. As ADHD was the most prevalent comorbid diagnosis seen in children with ID (41.7%) we divided the ID children into those without ADHD (n = 878) and those with ADHD (n = 628). Figure 8.10 shows the risk of emotional disorder, anxiety, and depression diagnoses for these two groups. ID children with ADHD have a much higher risk of these additional comorbid diagnoses than those without ADHD.

For example, the risk of conduct disorder is 6.6 times more likely for ID children and 28.6 times more likely for ID children with ADHD (compared to children without ID). This means that children with ID and ADHD have over 4 times the risk for conduct disorder than a child

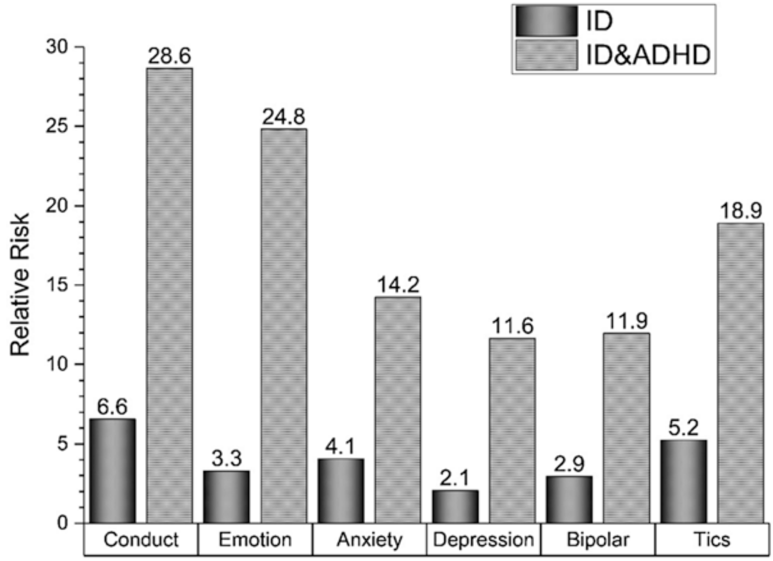

Fig. 8.10 Relative risk of having a second comorbid condition given ADHD previously exists for 1056 children with ID

who just had ID (28.6 compared to 6.6). A child with ID and ADHD is 25 times more likely to have an emotional disorder compared to children without ID, which is 7 times more likely than those with just ID (24.8–3.3). Having ADHD increases the risk of these common conditions by 3.5 (anxiety) to 7.5 times for ICD-defined behavioral and emotional disorders.

This demonstrates that just having one comorbid condition (e.g., ADHD) as well as an existing condition (e.g., ID) greatly increases the likelihood of having another comorbid condition (e.g., conduct or emotional disorder). The likelihood of complexity extends from these examples of having two comorbid conditions to having three or even four comorbid conditions. Figure 8.11 shows 878 children with ID only (left side), and 628 with ID and ADHD (right side). The prevalences of having conduct disorder, anxiety, or emotional disorder diagnoses as second, third, or fourth comorbid conditions are shown in the diagrams inside each box. Though the box on the left (ID only) is larger than the shaded box on the right (ID and ADHD) because it represents more children (878 vs. 628), the figures inside are smaller on the left side indicating only 98 children with ID have a lower prevalence of conduct disorder, anxiety, and emotional disorder as comorbid conditions (compared to 276 on the right, ID and ADHD). As demonstrated in Fig. 8.12, the presence of ADHD alongside ID increases the risk for multiple other neurodevelopmental disorders.

About 5% (3.6% + 0.23% + 0.23% + 0.57%) of the ID children have conduct disorder while 20% (10.2% + 1.9% + 3.8% + 4.5%) of children with ID and ADHD children have conduct disorder (over four times as many). Similarly, 5.4% (4.3% + 0.23% + 0.23% + 0.57%) of children with ID have anxiety and 18.8% (9.6% + 1.9% + 3.8% + 3.5%) of children with ID and ADHD have anxiety. ICD-defined emotional disorders increase from 3% in children with ID only to 22.3% in children with ID and ADHD.

Complexity increases for both groups, when viewing children with two of these comorbid conditions. For the conditions of conduct disorder and anxiety disorder, there are 0.46% (0.23% + 0.23%) of the children with ID and both of those comorbidities, and 5.7% (1.9% + 3.8%) of the children with ID and ADHD have conduct disorder and anxiety, a 12-fold increase. For a combination of anxiety and emotional disorder, 0.8% (0.23% + 0.57%) of children with ID have those two comorbidities, and when ADHD is added as a comorbidity, 7.3% (3.8% + 3.5%) of children have the two additional

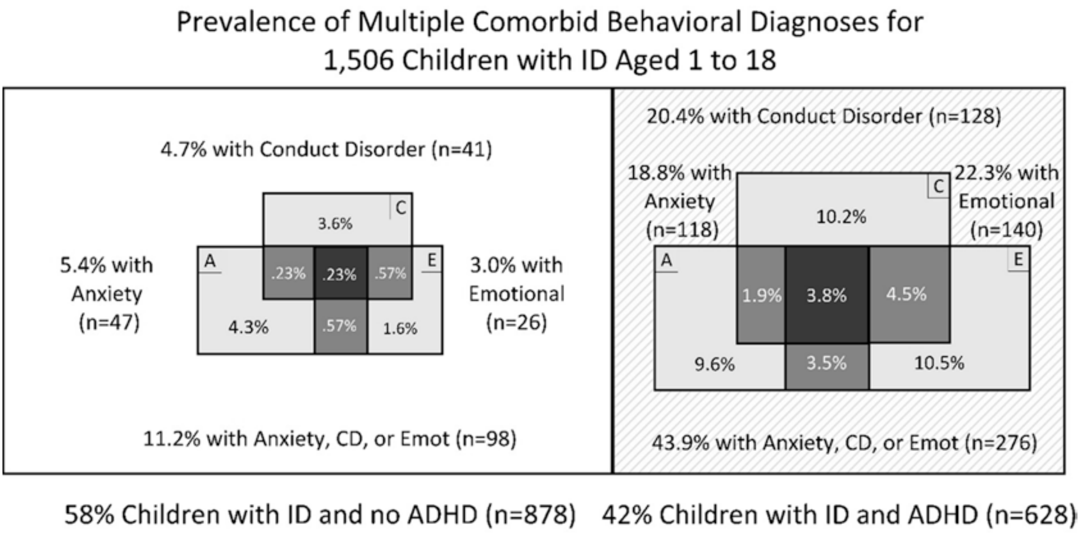

Fig. 8.11 Prevalence of one to three additional comorbid conditions beyond ADHD for children with ID

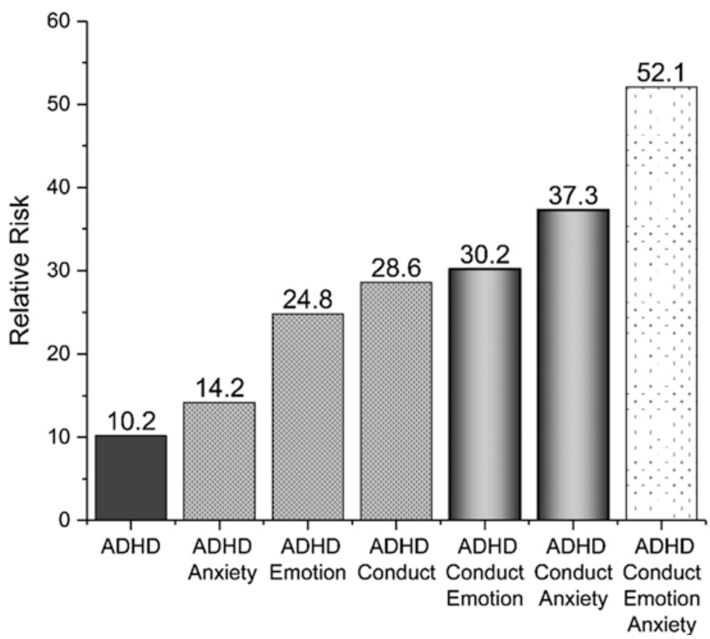

Fig. 8.12 Relative risk of multiple comorbid conditions in children with ID

comorbidities. Adding more complexity (three of these diseases are comorbid together among both groups of children), we observe that 0.23% of the children with ID have three comorbidities of conduct disorder, emotional disorder, and anxiety disorders (center square). 3.8% or over 16 times that many children with ID and ADHD as a fourth comorbidity have those three diagnoses.

The increase in the likelihood of complexity can also be seen with the relative risks of having one, two, three, or four diagnoses (Fig. 8.12). A child with ID is 10 times more likely to have ADHD than a child without ID (first black bar). The child with ID is 14 to 29 times more likely to have a second comorbid disease, (anxiety, emotional disorder, or conduct disorder, three light gray bars) in addition to ADHD. A child with ID is 30 to 37 times more likely to have two comorbid diseases in addition to ADHD (two vertical striped bars). And finally, a child with ID is over fifty times more likely to have ADHD, anxiety, emotional, and conduct disorder in comparison to a child without ID.

Increasing Comorbidity Increases Diagnostic Uncertainty

As we have demonstrated above, children with ID or other behavioral illnesses are more likely to have comorbid illness, often more than one. Figure 8.13 shows the prevalence of children with two or more MDCs in the two years of claims data gathered. 47% of children with a behavioral diagnosis had two or more MDCs compared to 53% of those without a behavioral diagnosis. This trend quickly changed and children with behavioral diagnoses were more likely to have 3 or more (30 vs. 25%), 4 or more (19 vs. 11%), or even up to 7 or more MDCs. Children with ID (line) were even more likely to have multiple MDCs in the time span with 65% having just two or more MDCs.

There was a high likelihood for children within the sample to have multiple behavioral diagnoses (Fig. 8.14). 71% of children with depression had two or more behavioral diagnoses. This was also true for 59% of children with ID and 39% of children with ADHD. The probability of having three or more comorbidities ranged from 21% to 45% in this sample.

Comorbidity increases diagnostic complexity by presenting multiple disorders simultaneously. Clinicians often diagnose only the most distinctive disorders at the time of the evaluation. It is not uncommon for people to receive multiple different diagnoses as they move from clinician to clinician, and resultantly they often lose an appreciation for the whole child or the child within the context of the family, as they focus on the multiplicity of segmented diagnoses. This is similar to treating parts of the elephant rather than the whole elephant.

In a study of fetal alcohol spectrum disorder (FASD) we used our FASD patient registry to query the health claims data for information on cost of care and utilization. However, only about 8% of patients on the FASD registry could be identified by diagnosis in the claims data. This is partially because FASD was not specified in the ICD or DSM. The FASD registry contained many patients with 10 or more diagnoses. In the claims data, the diagnosis entered was often the reason for the visit (otitis media, headache). Since FASD was not entered in the registry, our ability to track cost of care, comorbid disorders, or service utilization and to aggregate this data by patient was limited. Even for more severe health related visits in the health claims data (surgical procedures, extensive diagnostic evaluations) FASD was usually not identifiable in the claims data. Children were often noted to have intellectual disability, seizure disorders, attention deficit hyperactivity disorder, or speech and language disorders, but FASD was not a diagnosis included for the visit. We were surprised by this since FASD is likely to be crucial in diagnostic formulation and in treatment planning (*FASD: Diagnosis informed care,* Unpublished manuscript).

The Prevalence of Comorbidity Increases with Age

Recognition of comorbidity is closely related to and dependent on both age and development. Figure 8.15 shows how the average age of children increases as the number of behavioral diagnoses increases. The average age for children with one behavioral diagnosis is 11.4. As the number of diagnoses increases over 8 comorbid conditions, mean age increases to 14.6 years.

Many of the comorbidities we see among patients we care for may have been present earlier but could not be diagnosed until later in

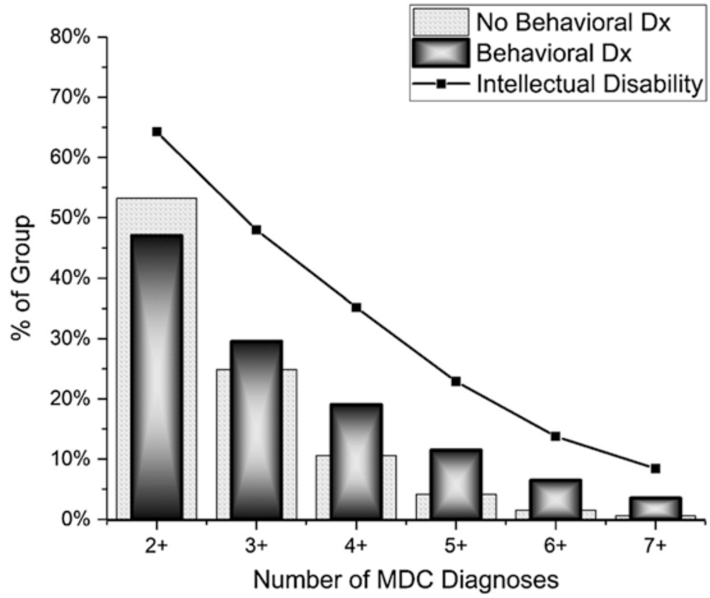

Fig. 8.13 Prevalence of children with multiple MDC diagnoses

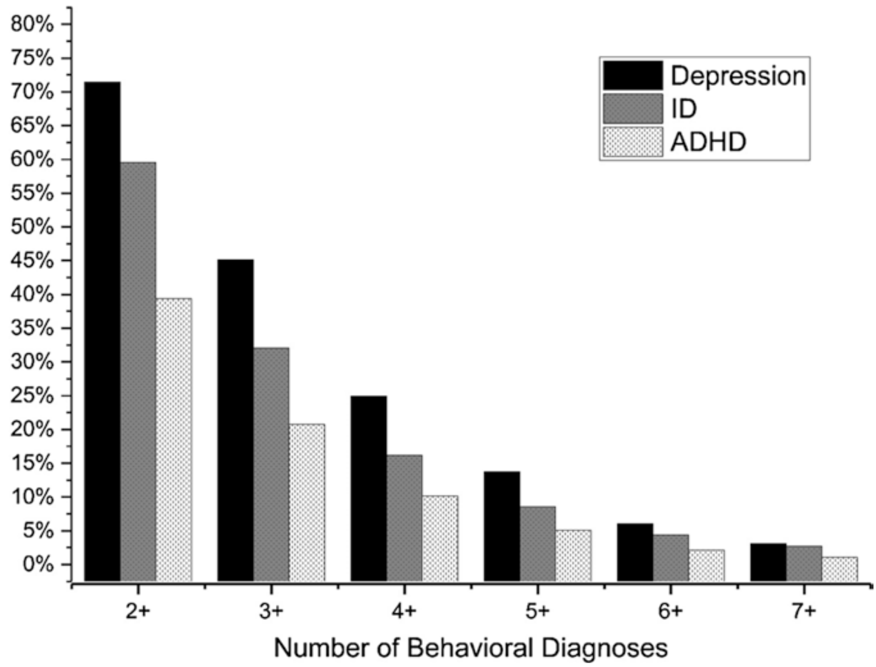

Fig. 8.14 Prevalence of children with multiple behavioral diagnoses by diagnoses

development. Attention deficit hyperactivity disorder, depression, speech and language disorders, and severe mental disorders are relevant examples. The development dependent expression of many of the key criteria for diagnosis is a key to understanding comorbidity (people must achieve a certain developmental level in order for us to reliably diagnose some problems). This duration of effect could be considered as heterotypic continuity, or alternatively longitudinal comorbidity. A classic example of this is seen in the identification of speech or language disorders in children

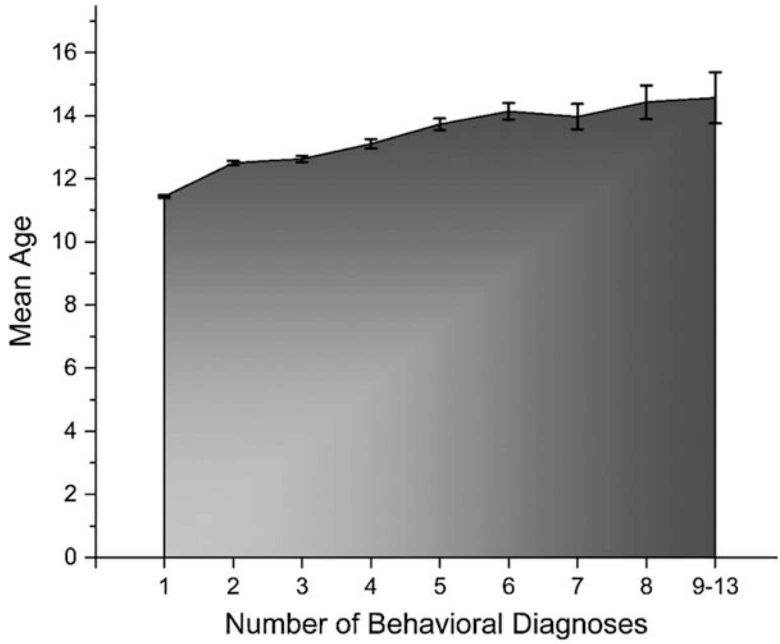

Fig. 8.15 Relationship between mean age and number of behavioral diagnoses for 15,366 children

under 12 months of age or the diagnosis of depression in infancy. A child must have reached a certain age in order to be able to reliably respond to questions about hallucinations or delusions in order for them to receive a diagnosis of some mental disorders. In some cases, children will not be able to express these problems until they reach adolescence. The expression of comorbidity can be limited by developmental impairments. For example, some complex clinical syndromes will be difficult to diagnose in the presence of severe intellectual disability (externalizing disorders or memory impairments).

Increasing Comorbidity Increases Service Utilization and Cost of Care

As is observed in routine health care, people with complicated diagnoses are seen to have higher costs of care. This observation remains true for children with comorbidity. When analyzing the total cost per year (including inpatient and outpatient costs) for 22,994 children with behavioral illness and 1506 with ID, we found the distribution of costs to be highly skewed (Fig. 8.16a). Transforming the data with logarithms showed two distributions of costs, valued under or over approximately 50,000 (Fig. 8.16b). This pattern was similar for the 1506 children with ID, so logarithmic transformations and categories of high and low were used for cost estimates.

Figure 8.17 (four parts) shows the scatter diagrams with regression lines using the number of behavioral diagnoses to predict yearly cost for low spenders (<=$50,000) and high spenders (>$50,000). The top two figures are for lower costs of care, 884 children with ID and 12,535 children with behavioral disorders. Lower costs significantly increase as the number of behavioral diagnoses increases for both groups. The correlation of diagnoses to cost was $r = 0.312$ for ID children and $r = 0.515$ for children with behavioral illness. The bottom two figures are for higher annual costs of care (<$50,000) for both children with ID and behavioral illnesses. The bottom two figures are for higher costs of care, 622 children with ID and 3581 children with behavioral illness. Though the relationships were different, higher costs also significantly increased as the number of behavioral diagnoses increased. Number of behavioral illnesses was significantly correlated with cost for ID children ($r = 0.0841$) and children with behavioral illnesses ($r = 0.123$).

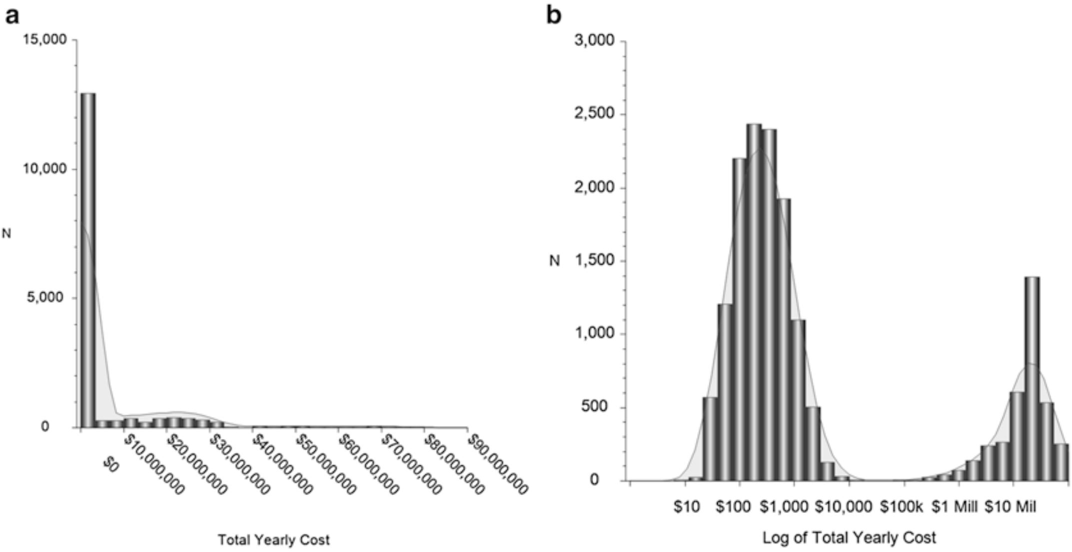

Fig. 8.16 Histograms of number of children in cost categories, original (**a**) and after a logarithmic transformation (**b**)

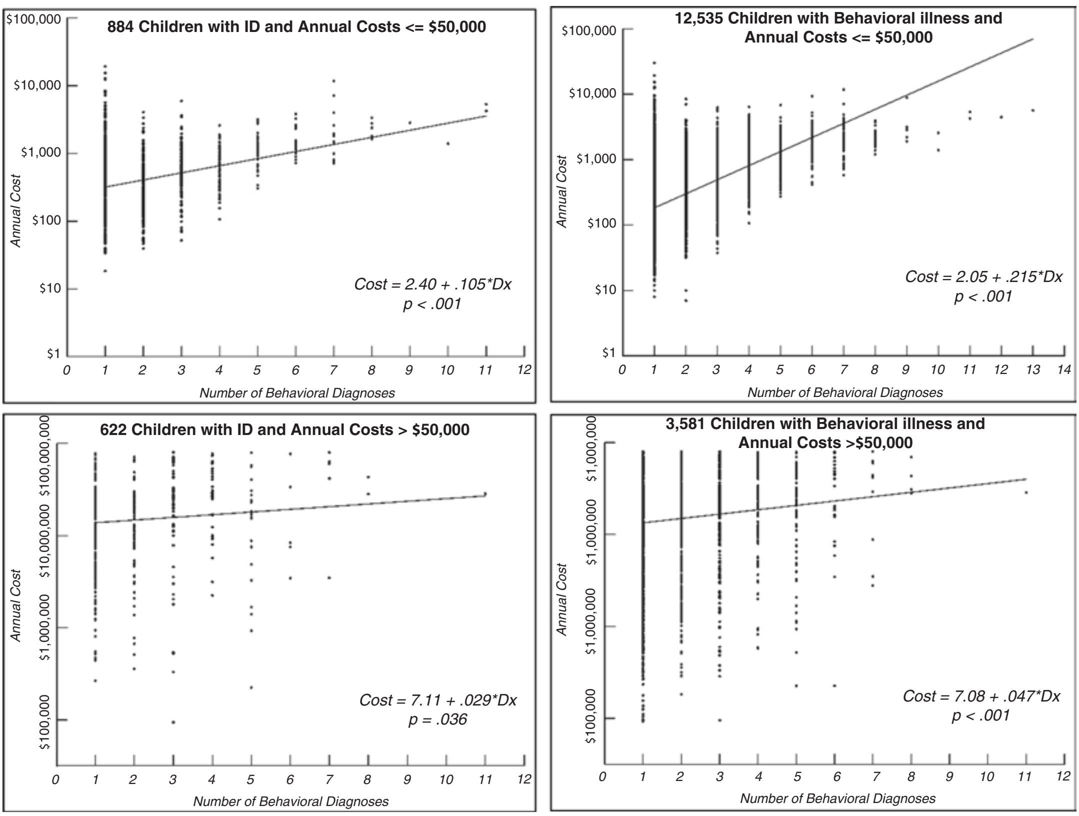

Fig. 8.17 Relationship between number of behavioral diagnoses and increased cost for children with ID or behavioral illnesses

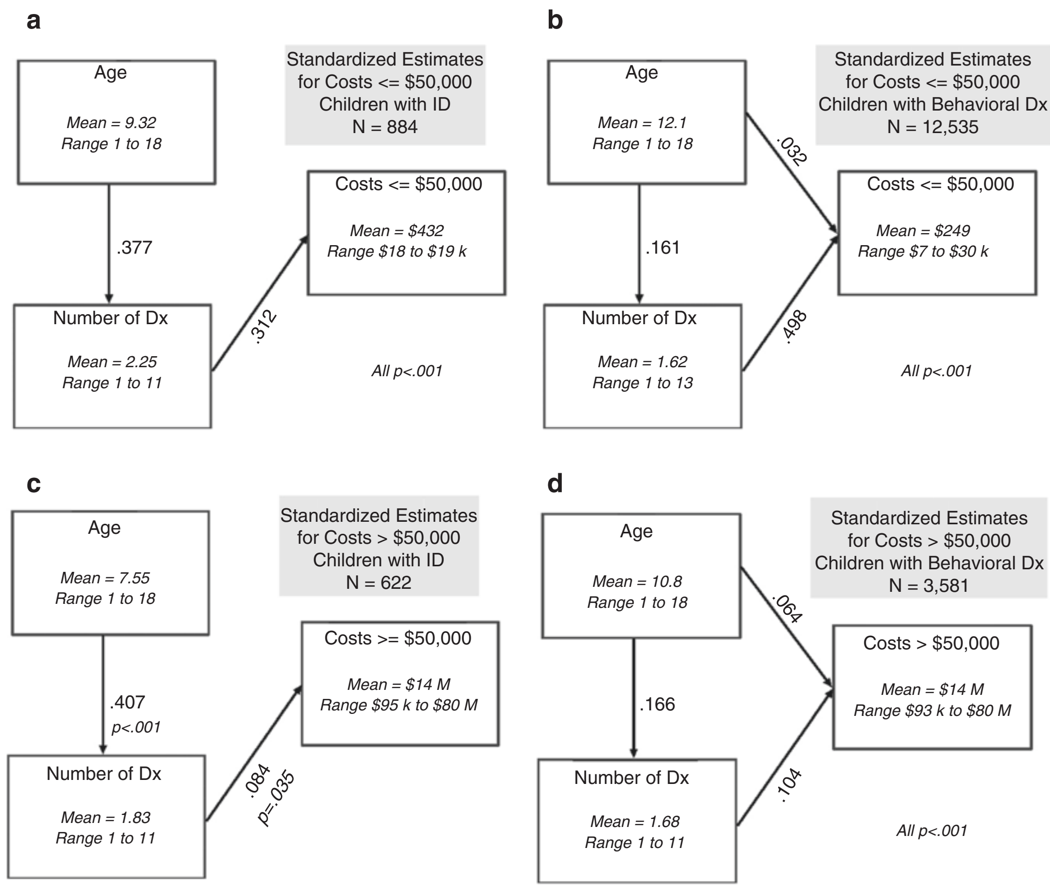

Fig. 8.18 Significant paths relating age and number of diagnoses to high and low costs for children with ID and diagnosed behavior disorder

Age was found to be related to number of behavioral diagnoses (older children had more diagnoses) (Fig. 8.18). Age may also directly or indirectly related to annual cost. Path diagrams can be useful to estimate and understand the full relationships between age, number of diagnoses, and expenses for participants within the high cost and low cost group. The four quadrants of Fig. 8.18 show how age and number of behavioral diagnoses relate to high and low annual costs for children with behavioral diagnoses and ID.

All diagrams show a relationship between age and number of comorbid diagnoses, the relationship is stronger (0.377 and 0.407) for children with ID (a and c). Also, all diagrams show a relationship between number of diagnoses a child has and their annual costs, though this relationship is stronger for children with lower (no expensive hospitalizations) costs (0.312 and 0.498) (a, b, c, d). This creates an indirect relationship between age and annual cost. Age has a direct relationship to annual cost for children with behavioral diagnoses (0.032 and 0.064).

Increasing Comorbidity Decreases Access to Evidence-Based Treatments

In most treatment studies participants are carefully selected to allow for precise examination of the intervention within a minimum sample size. Children with two or more disorders are often excluded from studies and as a result we have limited information on clinical presentation of complex developmental disorders in children and adults.

As a result, we have limited information on the benefits of multiple simultaneous treatments or the risks (adverse effects) from multiple interventions at the same time. This is an area of considerable concern. Do we spend huge amounts of money on interventions which negatively effect (affect) outcomes when delivered together? Are we selecting the optimal mix of treatments that maximize efficiency and benefits when used together? Equally importantly, how do we attribute either harm or benefit when a child is exposed to three, four, or more treatments at the same time? Put another way: Do we have sufficient variance in treatment response to detect either benefit or harm from 3 to 5 treatments utilized simultaneously?

Currently, we seem to operate with the belief that more intervention is better. For example: early intervention services in the home, center-based speech/language therapy, occupational therapy, preschool, and clinical behavior management with medication for sleep and separate medication for attention deficit hyperactivity disorder. This may be a form of therapeutic splitting influenced by both strategies to enhance reimbursement and therapeutic boundaries. Costs are enhanced, but it may be that this is the ideal combination with each intervention enhancing and optimizing the others. It may also be possible that this is just unnecessary duplication (e.g., the structure in preschool, occupational therapy, behavioral consultation, medication, and speech/language interventions overlap). Thus, only 1 or 2 of these interventions may account for the gains and medication or behavior consultation is unnecessary.

Increasing Comorbidity Decreases the Likelihood of Optimal Outcomes

Both the natural history and response to treatment for neurodevelopmental disorders are poorly understood (Burd et al., 2001; Burd et al., 2002; Burd et al., 2003a; Burd et al., 2003b; Kerbeshian & Burd, 2000). The impact of multiple disorders in clinical practice can also result in long-term impacts which can increase the risk for both additional comorbidity or long-term impairment from the combined effects of the disorders (Burd et al., 2003; Burd, 2016). Intellectual disability can have effects on long-term outcomes, and when these effects are combined with additional effects such as comorbid cerebral palsy, attention deficit hyperactivity disorder, or visual impairment, it is clear that more comorbidity nearly always results in additional impairment.

Discussion

Comorbidity increases both cost and utilization of services. The complexity principle is an important concept related to this finding. Increasing comorbidity increases the risk for additional comorbidity and the complexity of care. To illustrate this point, consider a young child who needs speech and language therapy and thus increases the demand on caretakers or parents. This child also needs occupational therapy, physical therapy, early intervention, frequent pediatric visits for multiple medication management, who wears glasses and has a hearing aid represents a huge increase in demand on the child's caretakers. These demands will affect which jobs the parents are able to do, and which promotions that they can accept compared to parents who don't have a child with multiple comorbid conditions.

We conclude with a brief discussion of several key points that have surfaced in this manuscript.

1. We enroll children in developmental therapies using an assumption of endless benefit. We have yet to clearly define benefits or adverse outcomes from multiple simultaneous therapies. We use therapy or multiple therapies as benign interventions and currently associate no downside from using multiple therapies concurrently.
2. Complexity increases both cost and utilization of services. Increasing comorbidity increases complexity which increases both service utilization and cost of care. For example, we have reviewed cases recently where children were sent home after multi-disciplinary assessments with dozens of recommendations.

Parents are forced to choose between what care the child needs and what care can be realistically provided. These choices are difficult as they pose limited affordable treatment options against the numerous treatments that were recommended. The level of care that can be implemented may be determined by travel schedule to different therapies, available time, and financial costs of these therapies. This is especially relevant for families with other children or where more than one child has ongoing health needs.

3. The uncovered or uncompensated cost of these therapies has been largely understudied. This concern applies even if services are funded by health insurance in countries with government-funded care. The implications of parents spending large amounts of money early in the child's life on therapies, travel, and time off from work, where the outcome is highly individualized, often limits funds they have for the care of themselves or other family members and for these children as they become older. Many parents describe this experience as "it's just often too much to hear about." They report feeling overwhelmed by the demands from multiple health care providers and rarely have access to someone to help them prioritize recommendations and to help allocate their resources.
4. Morbidity risk is somewhat predictable for some diagnoses but highly variable in expression. ADHD prevalence is increased in ID. But only some individuals with ID have ADHD. Monitoring for comorbidity should be built into routine care plans with systematic monitoring included within the context of ongoing care. A useful and emerging example is the understanding that increased adverse childhood events increase the risk for other neuropsychiatric diagnoses (submitted). There is an urgent need for strategies which assess whether or not we can prevent or diminish the prevalence and impact these comorbid conditions with early developmental interventions. The optimal developmental timing for these services also merits further examination. Further data regarding the intensity of services and what combinations are most effective or harmful could also be practically utilized.
5. Additionally, we need to optimize strategies and developmental interventions to most effectively treat comorbidity. For example, many children end up on multiple medications to treat multiple comorbid disorders. In some cases, these medications have an evidence-base for individual disorders (attention deficit hyperactivity disorder, depression, or obsessive compulsive disorder) in children. However, large-scale trials of routine clinical populations where children present three, four, five, or six of these other conditions are lacking. Studies of this type will require huge strategic investments in the future. We have very limited understanding of the potential benefits and risks of polypharmacy. Some agencies and parents refuse medications (especially for mental health diagnoses) even when the medications are well studied and offer demonstrable benefits. This seems to be biologically naïve and attributes a huge amount of a child's developmental impairments to disturbed emotions and relationships. This is often viewed by parents as blame. This is especially prominent in foster care where there is a growing mandate to avoid using medications for young children. Under careful examination, it is clear that this mandate applies mainly to mental health application, and is not seen similarly in regard to general medications. Psychological therapies face less critical assessment, despite possessing less evidence of efficacy for developing children.
6. Identification of optimal strategies early in the developmental course to reduce phenotype severity early in life is still limited. Can either early intervention or optimal intervention strategies prevent comorbidity from developing? Could this lead to a reduction in phenotype severity in the future? In populations of children with multiple complex disorders, we need better evidence to guide our practice. These conclusions suggest that a shift in our research practice is needed. It's time to embrace complexity and to begin studies capable of providing evidence to guide our care for these children and their families.

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