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What can Large Population-Based Birth Cohort Study Ask about Past, Present and Future of Children with Disorders of Development, Learning, and Behavior

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Abstract

A large cohort consisting of all subjects born to mothers from community provides “natural” selection into different exposures and is powerful resource for epidemiologic research. Large population-based birth cohort with detailed systematic information already recorded as part of longitudinal medical care, historic and current school data, detailed birth certificate data, and all three resources available for every member of the birth cohort, are extremely rare. Our population-based birth cohort consists of all children born 1976–2000 to mothers residing in Olmsted County, Minnesota, at the child’s birth (N=39,890). In this paper, we provide a comprehensive report of the

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Contributors

All the authors contributed to the work and take responsibility for it. Precisely, Dr. Katusic designed the study, directed every step of its implementation, including obtaining permission to access all 41 school resources, developed strategies for quality assurance, and completed all the requirements for IRB approvals. Specialists in child development disorders, Dr. Colligan, Dr. Myers, Dr. Voigt, and Dr. Stoeckel were part of the whole, long process helping in supervision and advising in all study activities. Dr. Yoshimasu helped conduct the literature review and contributed to the preparation of the discussion of the text. Ms. Weaver designed the study’s analytic strategies and completed statistical analysis. All the authors provided critical revisions of the manuscript.

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Ethics Approval

Institutional Review Board #PR09-008216-06; Title: “The Epidemiology of Childhood Neurodevelopmental Disorders in a Population-Based Birth Cohort (1976–2000).”

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Method describing the identification, the characteristics, and longitudinal follow up of each child (and family members) from the birth cohort, wealth of complementary resources of data, and study measures and designs (retrospective, combined retrospective/prospective). In last decade or so, we obtained scientific and clinically needed answers for incidence rates, potential risk/protective factors, treatment, comorbidities, outcomes, cost/utilization and potential biases (that are always assessed and clinically interpreted) of many Developmental Learning and Behavioral Disorders (DLBD) including Learning and Attention-Deficit/Hyperactivity Disorders, Intellectual Disability, Speech-Language Impairment and Autism Spectrum Disorder. Many current and future questions related to Developmental Learning and Behavioral Disorders are remaining to be answered. The Olmsted County Birth Cohort (OCBC) is an example of a comprehensive, contemporary epidemiologic research model for the development of similar research infrastructures, and its current and future results are important for replication and comparison with other population-based retrospective and prospective birth cohort studies.

Keywords

Clinical epidemiology; Cohort studies; Longitudinal studies; Paediatric; Research Design in Epidemiology

Introduction

The cohort study design has been a powerful resource for epidemiologic research from the time first described.[1, 2] A large cohort consisting of all subjects born to mothers from a community provides “natural” selection into different exposures, avoiding biases found in studies based on referral cohorts.[3]

Large population-based birth cohorts with detailed systematic information already recorded as part of longitudinal routine medical care (prenatal, perinatal, postnatal throughout childhood/adulthood, with detailed medical information on parents and siblings, are extremely rare.[4, 5] These longitudinal routinely collected medical care data allow to address past, present and future health, risk factors and outcomes of children with Developmental Learning and Behavioral Disorders (DLBDs).

DLBDs comprise a significant component of chronic childhood illnesses, with incidence rates by age 19 years of 9% for Reading Disorder (RD),[6] 0.9% for Intellectual Disability, [7] 9% for Attention-Deficit/Hyperactivity Disorder (ADHD),[8] 11% for Written-Language Disorder (WLD),[9] 11% for Math Learning Disorder (MLD),[10] and 1.46% for Autism Spectrum Disorder (ASD).[11] Thomas Insel stated that mental disorders are the predominant non-communicable conditions of adolescents.[12] It is estimated that 43% of US children have chronic health conditions, including mental health problems.[13]

This paper has two primary purposes: 1) to provide detailed descriptions of: methods used to identify every member of a population-based birth cohort, study resources, data available on every member, and capability of longitudinal retrospective/prospective studies; 2) to emphasize the importance of this rigorous epidemiologic scientific approach in pediatric research related to DLBDs.

Methods

Study setting

Olmsted County, Minnesota, is 90 miles southeast of Minneapolis-St. Paul, the closest urban center. According to U.S. census data in 2000, the Olmsted County population is comparable to the U.S. regarding median age, household income, and gender distribution.[14] The Olmsted County population is more racially homogeneous than the U.S. (whites 90.3% vs. 75.1%) allowing investigations to concentrate on other possible risk factors (e.g. biological characteristics, comorbidities, SES) and minimizing potential confounding due to race and ethnicity.

Study resources

The Rochester Epidemiology Project (REP) medical record linkage system—

The REP provides longitudinal medical data for virtually all individuals who resided in Olmsted County, Minnesota, from 1966 to the present, regardless of age, sex, disease, socioeconomic, or insurance status.[5, 15, 16]

The REP is widely recognized as a unique resource for conducting population-based epidemiologic research. Since 1907, every Mayo patient has been assigned a unique identifier. Detailed information from every encounter at Mayo Clinic and its two affiliated hospitals are recorded as part of routine medical practice, and are contained in the patient based medical record. Following data are part of medical record: the details from primary care office, specialty clinic, emergency room visits, hospital in-patient and out-patient admissions, psychology/psychiatry reports, laboratory, radiology, pathology results, social services reports, and correspondences with private tutorial/interventional facilities. Diagnoses assigned at each encounter are coded and entered into continuously updated computer files. Under the auspices of the REP, the diagnostic index and record linkage was expanded to include Olmsted Medical Center, affiliated hospitals, and other private practitioners.[5, 16, 17]

School Resources—Both Mayo Clinic Institutional Review Board and Independent School District (ISD) No. 535 school board approved a contractual research agreement allowing access to cumulative, richly documented school records of all birth cohort members registered at any of the 41 public, parochial, private schools, including moved from the school district, home schooled, deceased, or graduated. Conditions and procedures developed to conduct studies, follow Minnesota Law concerning data privacy and Federal Law concerning disclosure of personally identifiable information from educational records without prior consent. From 1916, ISD #535 have archived school records on all children who ever attended school system in Olmsted County. The rich, detailed school resources data, available for every birth cohort member are important addition to REP medical record linkage resources described above.

State Birth Certificate Data – Minnesota Department of Health (MDH)—Detailed birth certificate data (demographic, biological, socioeconomic, risk/protective factors) are

available for every child. Access to electronically available birth certificate data is approved by MDH and Mayo Clinic, on a study by study basis.[18]

1976–2000 Olmsted County birth cohort (OCBC) – identification and follow-up

The population-based birth cohort consists of all children born from January 1, 1976, to December 31, 2000, to mothers who were residents of Olmsted County at the time of child's birth.

We utilized iterative processes based on name variants, sex, and date of birth, to link the birth certificates with REP medical records. This process can be complicated if the names are incomplete ("Baby boy", "Baby girl"), spelled differently or changed as a result of adoption or parental marital status and clerical errors in the recording of information. After electronic matching, additional manual verification was performed. This same iterative process was employed to link members of the birth cohort with school records (electronic and manual matching).

The REP resources include the construction of a REP timeline for each person using addresses associated with dates of medical visits.[19] In addition to REP, school registration information was used to enable us to define study inclusion criteria specific to each study, (e.g. "In Study" or "Not In Study") and to longitudinally follow every "In Study" OCBC member. For example, for the "Epidemiology of ASD" study, the "cut off" at 3 years was chosen since ASD like problems can be recognized with more certainty at or after age 3. Further, the REP receives electronic death certificates within Minnesota and from the National Death Index source.

OCBC is a dynamic birth cohort, and depending on the research/clinical topics, the time frame of the cohort and the age cut-off established for a particular study, can be modified and expanded.

1976 – 2000 Olmsted County birth cohort – identification of the child's family members

Identification and linkage to the medical and school records of the parents, siblings and other members of the family can be done using the same resources (birth records-MDH, REP medical records, school records) and matching (electronic, manual) processes employed for identification of birth cohort subjects.

1976 – 2000 Olmsted County birth cohort – baseline characteristics and potential bias issues

In a study involving a population-based birth cohort, potential biases are extremely important to identify and address.[20] Although Olmsted County is relatively stable,[15] a major source of potential bias could be migration from Olmsted County. Depending on the age cut-off established for a particular study, birth cohort members are either "In Study" or "Not In Study" and migration bias needs to be addressed using detailed birth certificate data available on every member of the birth cohort. These baseline characteristics include: child's demographic and pregnancy/delivery data. Similarly, within the "In Study" group, subsequent migration may occur and are addressed in the same manner. If study design

involves a current status assessment, it is imperative to assess bias by comparing participants and non-participants using, besides birth certificate data, medical data related to particular clinical topic. The extent and direction of potential biases are always statistically assess and clinically interpreted.

Results

Table 1 summarizes the number of subjects in the 1976 – 2000 OCBC, comprising of live births to mothers who were residents of Olmsted County at the time of the infant's birth. This period was chosen to study Autism Spectrum Disorder, its incident rates/trends and other epidemiologic topics of clinical interest. Of the 43,215 subjects, access to medical records for research was available for 39,890 (92.3%) and among these subjects, 31,220 (78.3%) were still in the community after 3 years of age ("In Study" subjects). "Not in Study" subjects either moved or died prior to age 3 years. To address potential bias issues between "In Study" and "Not in Study" subjects, birth certificate characteristics will be used (Table 2).

On all birth cohort children (43,215), we have detailed birth certificate data grouped into: 1. Biological risk/protective factors or 2. Socioeconomic risk/protective factors. We grouped the biological factors into child factors, parent factors and pregnancy/labor/delivery data and socioeconomical factors, for example, included marital status, years of education of father or mother, number of siblings in the family... (Table 2)

School resources data, on all birth cohort children, can be collected for any retrospective, current or future studies (Table 3). These detailed data are either in electronic or in paper format. The cumulative school records include all school assessments, individual, group IQ and achievement tests results, educational intervention reports, school outcomes, notes related to any type of difficulty in learning, performance, or behavior, documented by teachers, parents, school psychologist, physicians, social workers, school nurses, counselors, and correspondence with private tutorial/intervention facilities.

The characteristics of OCBC, time and cost of assembling it, "dynamic" capabilities, resources available, subject, as well as, three kinds of study designs for longitudinal and "life span" follow up are presented in Table 4a.

Table 4b presents the comprehensive list of measures that large population-based Olmsted County Birth Cohort can ASK and get ANSWERS for. The answers for these measures can be achieved through three different epidemiologic designs and hypothesis driven studies of clinical importance for children with Developmental Learning and Behavioral Disorders (DLBDs).

Discussion

The quality and quantity of pediatric research is inadequate in many areas, including lower scientific rigor, compared to adult research. Further, there is a need for rigorous designs involving "larger study population and longer time-frame." [23] Stroll et al. emphasized that long term neurodevelopmental outcomes of childhood chronic illness are needed as

mounting evidence confirms a need for a transformation of childhood research.[24] Thomson et al. stated that there is a lack of information on etiology, risk/protective factors, onset, early symptoms, comorbidity, incidence rates, course and trend of child psychiatry conditions, adding that the best potential answer is to do huge population based, longitudinally followed, birth cohort epidemiological studies.[4]

Because of REP and its medical records linkage system with historical depth of data, Olmsted County, Minnesota, is one of the few places in the world where the occurrences, natural history and determinants of health/disease can be accurately described, longitudinally followed and analyzed in a defined population. In addition to the REP, the availability of comprehensive school, and detailed birth certificate records, make this a unique population for pediatric research. By identifying the population-based Olmsted County birth cohorts, REP was enriched and poised for epidemiologic studies on pediatric topics, especially related to DLBDs.

The foundation of our long-term, ongoing comprehensive epidemiologic studies related to DLBD is OCBC, *assembled in approximately 6 months, costing considerably less than establishing a prospective birth cohort* – huge contrast to recently halted National Children Study.[25] OCBC can always be expanded (*dynamic capabilities*). To address possible anesthetic associated neurotoxicity in humans by exploring, through retrospective/prospective approach, the long-term outcomes (e.g. LD, ADHD, Speech/Language problems) updated OCBC (2000 – 2007) study was implemented.[18] Further, different targeted sub - OCBCs can be created depending on clinical characteristics. For our current NIH funded Autism Spectrum Disorder (ASD) epidemiology study (RO1 MH093522), targeted “In Study” population consisted of all who stayed in Olmsted County after 3 years of age (age when ASD symptoms can be recognized with more certainty). The *mothers, fathers, siblings, and other family members* of individuals in the OCBC can be identified, and longitudinal medical, school and detailed birth certificate records can be used for research purposes.

Three epidemiology designs can be implemented for OCBC studies: *retrospective, combined retrospective/prospective and prospective only*. *Retrospective* designs can be completed accurately, and in detail, due to the availability of longitudinal medical records with information recorded as part of routine medical practice, from birth until migration, graduation, last follow-up during childhood/adulthood, or death. Cumulative school records add additional detailed longitudinal information. Lastly, the length of time members of OCBC are covered by the medical record linkage system, allows to study early life exposures and later outcomes without relying on questionnaires and memory.[19]

Every OCBC *retrospective* study has strict research steps including: retrieval of an electronic list of potential diagnostic codes of interest, a detailed protocol for the abstraction process, strict abstractor training and explicitly-defined operational research criteria modeled on the current clinical diagnostic criteria.[26] These carefully planned and executed research steps allow us to ask and get answers for many topics of clinical interest. We studied *incidence rates and time trends* for Intellectual Disability, Learning Disabilities (RD, WLD, MLD), ADHD.[6–10] *Incidence*, a measure of singular importance in epidemiology, is primarily

used for studying relationships between etiological factors and development of specific medical conditions by implementing unique case – cohort design.[27] The use of incident cases in exploring *potential risk/protective factors* minimizes many biases that are encountered in studies based on prevalent cases.[3] This approach was used to study possible *environmental early risk factors* for ADHD Incident case.[28] *Comorbidity* among DLBDs is high.[29, 30]. We confirmed that childhood ADHD is strongly associated with broad range of psychiatric disorders.[31, 32] The same was found among mothers of ADHD cases compared to mothers of ADHD controls.[33] Other clinically important topics that we looked for the answers so far, include long-term stimulant medication *treatment* and *risk* for substance abuse among ADHD cases,[34, 35] *gender* issues among RD and ADHD incident cases,[36, 37] LD and ADHD *outcomes* among late preterm infants,[38] alcohol and drug abuse among ADHD cases,[35] and *cost/utilization studies* of ADHD incident cases.[39] The *retrospective* epidemiologic design utilized in all of the above studies is less expensive, less time consuming, and less prone to bias issues than prospective studies.[40]

Epidemiologic design that is currently being conducted is a *combined retrospective/prospective epidemiologic* approach involving current status assessment (prospective face to face evaluation) of retrospectively-identified childhood cases. This approach saves time and money. Lawlor et al. concept of “revitalization of historical pregnancy birth cohort” suggests that there are benefits to a combined retrospective/prospective approach in longitudinal studies.[41] Five hundred potential ASD cases (R01MH093522) have been *identified retrospectively* from 1976 – 2000 OCBC and *prospectively assessed* as adults through a 4-hour battery of tests. The study of relationships among psychological tests (behavior), neuroimaging and neurophysiology studies (biomarkers), and genotypes across diagnostic categories may provide a framework for transformation of current DSM nosology of mental disorders to an etiology and pathophysiology-based classification system. This is one of the goals of the Research Domain Criteria (RDoC) approach initiated by NIMH.[12, 42] *Biological specimen collection* was performed. So far, saliva from 514 potential ASD cases, as well as blood from 711 ADHD cases/controls (previous ADHD study) have been stored for future studies.

There are few large population-based birth cohort studies related to long-term neurodevelopmental outcomes. In contrast to our OCBC combined retrospective/prospective approach, three population-based birth cohort studies from Norway,[43] Denmark,[44] and Avon (England)[45] are long-term prospective studies with pregnant mothers recruited from general population. These studies required long, complicated preparation phases, recruitment of approximately 100,000 (Norway, Denmark) and 15,000 (Avon) subjects, and found high costs and opposition to ambitious projects. Even though these countries have a variety of excellent registers related to health, social conditions, occupational history, and family conditions, the studies are lacking in depth and historical details. Therefore, they rely on questionnaires or telephone interviews which depend on memory/recall. Strengths of these study designs include the frequency of data collected, availability of repeated measures, establishment of specific sub-cohorts, and extensive bio bank collections. So far, even though there are an impressive number of papers published (e.g. > 700 from Avon study), there are many limitations in methodologies, including low response rates and bias issues, all stated by authors themselves.

Although our population-based OCBC study offers many important strengths, it can be subject to potential biases. The extent and direction of the possible biases are always statistically assessed and clinically interpreted. One source of bias is loss of study subjects because of migration before “cut off age” determined by the study topic. We evaluated potential migration biases using detailed birth certificate information for sub-cohort 1976 – 1982 and found that in the context of the large number of children who remained in the community, the slight differences should not compromise our findings.[46] Our adult current-status assessment of ADHD incident cases yielded a high participation rate (63%) and among participants, only high school graduation rates were different.[47] During the retrospective component of our studies, it is possible that a few childhood incident cases could be missed. However, our systematic, multi-stage, multi-resource process (complementary medical, school, and private facilities records), together with precisely defined operational research criteria modeled on the current clinical diagnosis criteria, and our experience from previous retrospective studies[6–10] minimize the possibility that incident cases will be missed. While identified risk/protective factors will not establish etiology, they will provide information concerning association between potential risk factors and childhood illness. Finally, Olmsted County has historically been primarily a white community, with a percent of white population higher than in the U.S. (95% vs. 80%); however, this is changing, especially for younger age (~30% were non-white in 2009).[14] Even though there is no single community in the U.S. or in any single study, including the Framingham study, that is completely representative of the entire U.S.,[14] our unique population based retrospective/prospective approach establishes a comprehensive model for future studies and allows replication and comparisons.

Conclusion

To best study childhood Developmental Learning and Behavioral Disorders, potential early life risk factors, neurodevelopmental trajectories, and long-term outcomes, an experienced, well integrated, multi-disciplinary team and rigorous comprehensive epidemiologic research program are essential. Important features of this approach include: 1. A large population-based, birth cohort; 2. Several unique, complementary sources of information for every child (medical, school, birth certificate records, additional resources when needed); 3. Incident case identification; 4. Implementation of three epidemiologic designs: retrospective, combined retrospective/prospective (adolescent/adult face to face assessment of retrospectively identified childhood incident cases), and prospective; 5. Current status assessment (e.g. neuroimaging, neurophysiology, genetic and other laboratory tests, psychological testing, bio-specimen collection); and 6. The evaluation of potential risk factors involving case/cohort design.

Doctor Paneth stated, “Thanks to the scientific rigor of the Framingham study millions of lives have been saved-children deserve no less.”[25] Through scientifically sound epidemiologic research, Olmsted County Birth Cohort has been contributing to the critical pediatrician goal of trying to find a way to prevent DLBDs, to help children who are already affected, assisting their families and improving long-term public health.

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Summary Box

What is already known on this subject

The quality and quantity of pediatric research is inadequate in many areas, including scientific rigor, compared to adult research. There are few large population-based birth cohort studies related to neurodevelopmental outcomes, but all of them are prospective studies with complicated preparation phase, opposition to ambitious projects, high cost, consuming long-time and with many limitations in methodologies all stated by authors themselves.

What this study adds

Our study is an example how research on childhood Developmental Learning and Behavioral Disorders (DLBDs) can be done. Beside the establishment of large population-based birth cohort, and existence of several unique complementary sources of longitudinally routinely collected information, available for each child, the implementation of two epidemiologic designs, retrospective and combined retrospective/prospective is important. These two designs are less expensive, less time consuming (faster results) and less prone to bias issues than prospective birth cohort studies. The ultimate goal of our sound epidemiologic method is to contribute to prevention of DLBDs, help children already affected and to improve long-term public health.

Table 1

Population-based 1976–2000 Olmsted County Birth Cohort (OCBC)

Category ^a	1976–1980		1981–1995		1996–2000		1976–2000 ^b		Total (n=43215)
	Male (n=3906)	Female (n=3645)	Male (n=13793)	Female (n=13052)	Male (n=4528)	Female (n=4291)	Male (n=22227)	Female (n=20988)	
Denied research Authorization, n ^c	225	244	954	914	499	489	1678	1647	3325
Not in study, n	903	881	2801	2486	836	763	4540	4130	8670
Deceased before 3 years ^d	50	34	138	100	20	26	208	160	368
Moved before 3 years ^d	853	847	2663	2386	816	737	4332	3970	8302
In study, n (%) ^e	2778 (75.5%)	2520 (74.1%)	10038 (78.2%)	9652 (79.5%)	3193 (79.3%)	3039 (79.9%)	16009 (77.9%)	15211 (78.6%)	31220 (78.3%)

^aBirth cohort requirement for the study: “Autism Spectrum Disorder (ASD): Birth Cohort 1976 – 2000, Epidemiology and Adult Status”.^bThis period 1976 – 2000 was chosen to study rare disorders and their incident rates/trends and other epidemiologic topics of clinical interest.^cIn 1996, the State of Minnesota passed a new law requiring each patient to provide general written authorization if they choose to allow researchers permission to review their medical record[21, 22].^dThe cutoff at 3 years of age was chosen since Autism Spectrum Disorder (ASD)-like problems can be recognized with more certainty at or after age 3.^eFinal status (i.e. deceased, moved, or never moved) will be determined for each specific future study. The percentage “In Study” is based on the total number of “Not in Study” and “In Study” subjects in each column.

Table 2

Population-Based 1976–2000 Olmsted County Birth Cohort (OCBC) – **BIRTH CERTIFICATE DATA**

Birth Certificate Data ^a	
Biological Risk/Protective Factors	Socioeconomic Risk/Protective Factors
Child factors: sex, child’s race, birth weight, prematurity, Apgar Score-1 min, Apgar Score-5 min, multiple births	Father, mother: name, marital status, age, race, years of education
Parent factors: mother’s age-father’s age: 15–19 (young), 20–34, 35+ (old), mother’s and father’s race	Legitimacy
Pregnancy/labor/delivery factors: pregnancy complications, labor/delivery complications, operative procedure required, birth injuries congenital anomalies, Intensive Care Unit stay, number of prenatal visits, month of pregnancy in which prenatal care began	Places of deliver: hospital, home, other
	Number of siblings in family; number of children previously born alive; number of children previously born alive, now dead
	Number of pregnancies terminated after 20 weeks
	Number of pregnancies terminated before 20 weeks
	Number of prenatal visits
	Month of pregnancy in which prenatal care began
	Address at birth

^aBirth certificate data available for every member of the OCBC

Table 3Population-Based 1976–2000 Olmsted County Birth Cohort (OCBC) – **SCHOOL RESOURCES DATA**

School Resources ^a		
DATA		DESCRIPTION
Outcomes		Drop out; expulsions; abuse/neglect – mother, father, child; alcohol/drug abuse – mother, father, child; absenteeism; frequency of school changes; high school graduation status
School Achievement Test Results		<ul style="list-style-type: none"> Group: Ability and Achievement Individual: Ability and Achievement
Medical Information		Immunizations; medication if reported to school nurse; major diseases if reported to school nurse
Child Developmental and Behavioral Problems		Disability classification ("Handicap Codes") determined by school's special education professional team
Individual Education Plan (IEP)		Details of goals, services, start and end date of each IEP
Enrollment in Chapter I/Title I Program		Surrogate for socioeconomic status
Family Information at age 3–5	Father	Names, years of education, degree, English as a second language, married, divorced, remarried, single, dead
	Mother	
	Siblings	Name, birth date, biological, half, adopted names, sex, order
	Child living with	Both biological parents, biological father and step-mother, biological mother and step-father, biological father only, biological mother only, other. . .

^a All members of the OCBC registered at any 41 public, parochial, private schools have these detailed data

Table 4

a. Population-Based 1976–2000 Olmsted County Birth Cohorts (OCBC): CHARACTERISTICS	
Time period of births	1976 – 2000
No. of births	43,215
Time to assemble OCBC	Approximately 6 months
Cost of assembling OCBC	Minimal compared to cost for assembling prospective cohorts
“Dynamic” capabilities	<ul style="list-style-type: none"> - OCBC can be expanded - Different targeted sub-OCBC can be created depending on clinical topics
Resources available	<ul style="list-style-type: none"> - REP medical record linkage system and medical records - ISD^a 535 school records - Detailed Minnesota birth certificate data - If needed for a specific study, further data can be collected via mail, telephone, or in-person interviews
Subjects	<ul style="list-style-type: none"> - Birth cohort children - Mothers - Fathers - Siblings born before or after the time period of the cohort - Other family members
Study designs for longitudinal/life span follow-up of subjects	<ul style="list-style-type: none"> - Retrospective only - Combined retrospective/prospective - Prospective only

b. Population Based 1976 – 2000 Olmsted County Birth Cohorts (OCBCs): STUDY MEASURES and the DESIGNS				
Measures	Descriptions	Designs		
		retrospective only	retrospective /prospective ^a	prospective only ^b
Incidence	<ul style="list-style-type: none"> • rates • trends over time • rare diseases 	+		
Incident case	important for the analyses of the association between potential risk factors and childhood illness	+		
Bias issues	• migration y/n	+	+	
	• participation y/n		+	
Risk/protective factors	case-control(randomly selected controls from the same birth cohort)	+		
	case - cohort design	+	+	+
Environmental risk factors	<ul style="list-style-type: none"> • during pregnancy • childhood: 0–3 yr 	+	+	+

b. Population Based 1976 – 2000 Olmsted County Birth Cohorts (OCBCs): STUDY MEASURES and the DESIGNS				
Measures	Descriptions	Designs		
		retrospective only	retrospective /prospective ^a	prospective only ^b
	<ul style="list-style-type: none"> 3 yr – 19 yr 			
Comorbidities	related to specific childhood chronic issues (e.g. DLBD) ^c	+	+	+
Treatment	<ul style="list-style-type: none"> during pregnancy childhood: 0–3 yr 3 yr – 19 yr 	+	+	+
Outcomes	<ul style="list-style-type: none"> pre, peri, postnatal neurodevelopment (e.g. ASD^d, ADHD^e, LD^f, ID^g...) Adulthood long-term 	+	+	+
Bio specimens collections	<ul style="list-style-type: none"> child mother father 	+	+	+

^aISD, Independent school district

^aThe main epidemiologic design to be utilized in the future studies. Face to face evaluations of adolescence/adult (**prospective part**) of **retrospectively** identified childhood incident cases.

^bIf clinical research requires, prospective only design can be organized, planned, and done.

^cDLBD – Developmental Learning and Behavioral Disorders

^dASD – Autism Spectrum Disorder

^eADHD – Attention Deficit/Hyperactivity Disorder

^fLD – Learning Disability

^gID – Intellectual Disability