

INTRODUCTION

BACKGROUND OF THE CHILD HEALTH AND DEVELOPMENT STUDIES

General Information

The Child Health and Development Studies were designed and initiated in 1959 by Dr. J. Yerushalmy, Professor of Biostatistics at the University of California, Berkeley. Under his skillful, imaginative, and stimulating directorship, which continued until his death in 1973, a rich database of information on human reproduction and child development was established, and an abundance of investigations were performed and published. Dr. Bea J. van den Berg, who has been Director of the Studies since 1973, has greatly extended the database and significantly expanded the areas open to investigation.

Initially, the Child Health and Development Studies were conducted on a cooperative basis. The participating agencies were the Division of Biostatistics of the School of Public Health, University of California, Berkeley; the Kaiser Foundation Research Institute; and the Permanente Medical Group. Until June 1, 1972, the Kaiser Foundation Research Institute had grantee responsibilities; after that date, administrative responsibilities were transferred to the University of California, Berkeley. Since 1959, the Child Health and Development Studies have been funded primarily by grants and contracts from the National Institutes of Health.

The original objectives of the Child Health and Development Studies, as they were formulated by Dr. Yerushalmy, were as follows: "...to investigate the relationships of biologic, genetic, medical, and environmental factors in the parents--including events in pregnancy, labor, and delivery--to the normal and abnormal development of the offspring; to investigate the relationships of these factors to pregnancy loss in the form of early fetal death, perinatal mortality, infant and childhood mortality, and to the incidence of congenital anomalies; to provide detailed growth curves for children suitable for the study of differences in growth rate according to the above factors; to provide estimates of illness and injury rates in infants and children; to accumulate a large number of matings in which the detailed blood group typings in the different systems are known for the woman, her husband, and the offspring suitable for investigation of blood group incompatibilities producing potential disease in the infant; to investigate the relationships of physical and mental development in early childhood to those during the period of puberty and adolescence."

In addition to the investigations indicated by these objectives, the data have also been shown to be suitable for a wide variety of studies on the women without regard to their offspring.

The Child Health and Development Studies are based on prospective longitudinal observations of women, their pregnancies and deliveries, and the development of the children born from these pregnancies. After exploring the research possibilities of various populations, the choice was made to use the local membership of a prepaid health system, the Kaiser Foundation Health Plan. Kaiser provides comprehensive medical care to members at medical center facilities throughout California. The characteristics inherent in this population and advantageous for a survey are as follows: the population receives all medical care at Kaiser facilities; medical care is equally available for all members;

reports of medical services rendered by physicians in the various specialties are assembled in a single file for each patient; and the population is socioeconomically broadly based: only the extremes--the very indigent and the very affluent--are not represented. Since these data reflect a primarily middle class population, they present an interesting contrast to observations based on populations of lower socioeconomic status, the varied ethnic composition of this population also makes its use highly valuable.

The data, which were assembled over a period of 20 years, have been used for a large number of biomedical studies. More than 200 publications have resulted from these analyses, and the titles of articles included in the attached publication list provide an idea of the topics that have been explored.

Enrollment Process

Members of the Kaiser Foundation Health Plan residing in the East Bay of the San Francisco Bay Area were enrolled in the Child Health and Development Studies during pregnancy when they first contacted participating Kaiser facilities regarding a confirmed or possible pregnancy. Enrollment started in June 1959 and ended in September 1966. In all, some 20,500 pregnancies were enrolled prospectively into the Studies.

Criteria for Prospective Study Group Membership

The original target population of the Child Health and Development Studies included all members of the Kaiser Health Plan who became pregnant and planned to use the facilities of the Oakland Kaiser Foundation Hospital and/or the Kaiser clinics in Richmond, Hayward, or Oakland during the enrollment period. However, from August 1, 1964 on, women who began their prenatal care at the Richmond or Hayward Kaiser clinics were excluded from the target population; due to financial constraints.

Throughout the enrollment period, every effort was made to identify all pregnancies in the target population. These efforts generated nine subgroups; the label for each subgroup indicates either why individuals could not be included in the prospective study group or what a patient's interview status was if she was included in the prospective study group. The first four subgroups, Patient Categories 1 through 4, include women who did not meet the criteria for our prospective study group. The remaining subgroups, Patient Categories 5 through 9, met the criteria but differed in interview status. The criteria for the prospective study group were as follows:

- 1) The woman had to contact Kaiser Foundation Hospital in Oakland or one of the Kaiser clinics in Richmond, Hayward, or Oakland with regard to confirmation of pregnancy and/or prenatal care, within the enrollment period;
- 2) A study interview and/or laboratory work for the woman had to be initiated at one of the facilities mentioned in Item 1 above;
- 3) The woman had to be in prenatal care at one of the Kaiser facilities in Northern California and subsequently end her pregnancy while still under the care of physicians belonging to a Kaiser facility in Northern California.

Members of the target population who did not meet these criteria fell into three categories: women who delivered at facilities other than those specified, women who were eventually determined not to be pregnant, and women who came in for the first time during the process of miscarrying. Data files on these women are incomplete and differ in quality from the data compiled on the prospective study group. Since non-cooperating hospitals were not following the Child Health and Development Studies reporting protocols, they could not provide complete delivery information.

Women who came in for the first time in the process of aborting or immediately following a spontaneous abortion at home could not always be contacted. When the Child Health and Development Studies staff were able to contact them, the possibility that their answers to certain questions might be influenced by the knowledge of their fetal loss could not be ignored. Since information on patients who did not meet the criteria of the prospective study group differs from that compiled on the prospective study group, it is maintained separately and is classified as data available only by special arrangement.

To encourage all members of the target population to participate in the Child Health and Development Studies, Dr. Yerushalmy arranged for the laboratory of the Child Health and Development Studies to be the official lab for all routine prenatal lab work; services were free to the patients. This procedure greatly aided the Studies and resulted in enrollment of nearly 100% of eligible gravidas. Initially, the physicians at the participating Kaiser ObGyn clinics gave the patients a brief explanation of the Child Health and Development Studies at their first visit and referred them to CHDS for lab work. When the women came in for lab work, they were weighed and measured, and 30 cc of blood was drawn. They were also given a detailed account of the policies and objectives of the Child Health and Development Studies, and they were asked to have their husbands come in to have a sample of blood drawn. Basic information was obtained from the women, and they were then interviewed in detail if time permitted. If time was limited, an interview appointment was arranged.

It was decided after only a couple of months that earlier contact with the gravidas was desirable. To accomplish this, a procedure was instituted in which copies of all Kaiser pregnancy confirmation appointment slips were sent to the Child Health and Development Studies when appointments were made at the cooperating facilities. These slips were given to the interviewers, who then contacted the women, talked with them about the Child Health and Development Studies, and set up early appointments for lab work and interviews. In some cases, women came in for lab work before they had been contacted by an interviewer. In this situation, the original routine described above was followed.

Definition of Patient Categories

This enrollment ultimately gave rise to seven of the nine patient categories previously mentioned. Women who started through the normal processing but delivered at a non-participating facility were classified as members of Patient Category 1. Women who started through the normal processing but were later determined not to be pregnant were classified as belonging to Patient Category 2.

Not all women who proceeded through the enrollment processing were interviewed in detail. As a result, they were placed into five separate categories. Patient Category 5 consisted of women who were

unmarried minors; it was considered inappropriate to ask for detailed interview information from them. A few women did not wish to be interviewed in detail; they were classified as Patient Category 6 and are referred to as having refused cooperation. Women who were cooperative but were not interviewed, for any of a variety of reasons (insufficient time, interpreter unavailable, interviewer unavailable, etc.), were put into Patient Category 7. The majority of cases in this category were registered at either Richmond or Hayward the clinic, where interviewers were not always available.

Women who went through the normal processing and were interviewed in detail were classified as members of either Patient Category 8 or Patient Category 9, depending on whether they were interviewed before or after delivery. Those interviewed before delivery, Patient Category 9, account for 77% of the prospective study group. Only Patient Categories 5 through 9 are included in the database.

Patients who never began the normal processing routine were put into Patient Categories 3 and 4. Pregnancies ending in a fetal loss before prenatal care was initiated were classified as belonging to Patient Category 3. These cases were detected via pathology and emergency room reports. Gravidas in Patient Category 4 were not part of the target population (see Flow Chart 1). Instead, they represent gravidas who were dropped from the target population when users of the Richmond and Hayward clinics were excluded from that group. If users of these clinics had been enrolled in CHDS when they were part of the target population and subsequently returned with another pregnancy when they were no longer included in the target population, they were placed into Patient Category 4. Although these women were not interviewed during the later pregnancy, CHDS did have earlier interviews about the family and was able to abstract the medical records pertaining to the pregnancies assigned to Patient Category 4. These "record study" cases were maintained in order to have a larger pool of information on sibling pairs for selected analyses. Information on cases in Patient Category 4 is available only by special arrangement.

Patient Identification Numbers (CHDS Number)

When a woman was first enrolled in the Child Health and Development Studies, she was assigned a six-digit identification number (CHDS Number). The first five digits uniquely identified the woman; the sixth digit identified her individual study pregnancies, not necessarily the parity of her child. Thus the first time a woman entered the Child Health and Development Studies, the sixth digit of her identifying number would be "1." When she subsequently returned during her next pregnancy, the first five digits would be the same, but the sixth digit would be a "2." Similarly, the sixth digit was increased by one each time the woman returned with another pregnancy. The first five digits of the CHDS Number are ordered chronologically with regard to the time a woman first entered the study.

The children were given the same six-digit number as their mother, with a seventh digit to indicate the plurality of the birth. In this way, the offspring of multiple pregnancies could be uniquely identified.

In some instances, the sixth digit of the CHDS Number does not conform to the sequence of a woman's pregnancies. When a patient had a pregnancy outside of Patient Categories 5 through 9, the sixth digit

of her CHDS Number was not necessarily in the same sequence as her pregnancies themselves. Do not use the sixth digit of the identification number for analyses depending on the sequence of births, since there are a few inversions. The actual pregnancy order is given in the BASIC file.

Interview During Pregnancy

In the enrollment process, great emphasis was placed upon obtaining detailed interview information from each gravida. The interviewing was done by a team of professionally trained interviewers who put great effort into obtaining reliable data. This objective was achieved by gaining rapport with the patients, by making sure they understood the questions, and by guaranteeing that their responses would be completely confidential.

Over the enrollment period, several different interview forms were used. The first form was designed for use during the first trimester of pregnancy. It was revised eight times between 1959 and 1965 in an effort to obtain as much pertinent and accurate information as possible from each patient. In general, this form covered a wide range of medical, genetic, and environmental issues. Among these were a very detailed reproductive history of the gravida and data on illnesses and injuries pertaining to the gravida, her husband, and her children. A special effort was made to elicit accurate information on congenital anomalies in the children. Information was obtained on ethnic background, financial and occupational status, housing and living conditions, and attitudes toward the pregnancy. A general overview of the areas of revision is shown in Table 1.

The second interview form was designed for use during the second trimester; it was introduced in May of 1960 and was used through the end of the intake period. The purpose of this interview form was primarily to identify changes that had occurred after the earlier interview; the opportunity was also used to add a few general questions. If for some reason the gravida could not be interviewed until late in pregnancy, the two interview forms were combined.

Since the interview was quite time-consuming, a special interview was developed for women who were in the prospective study group more than once. Rather than repeat all basic family information, this "repeater interview" asked questions only about the current pregnancy and events which had transpired between the last pregnancy and the current one. This interview was in use from November 1962 through 1966.

The interview is the source document for several data files. Changes in the interview that had an effect on coded items are indicated in the extended notes on each file. Since some gravidas did not complete the interview because of time constraints and others did not answer questions for a variety of reasons, the number of women who did not answer varies from question to question. The women were classified as having been interviewed if they had completed the interview at least through the section on reproductive history. When a woman did not participate in an interview, the receptionist filled out a "face sheet" which reported the name, age, race, and date of birth of the gravida and her husband, and the gravida's LMP.

The Gravida Registry Card

In the initial processing of each patient, a gravida registry card was prepared. It encompassed basic information on the patient and was routinely updated throughout the pregnancy. The interview provided the gravida registry card with reproductive history information and data on ethnic background, occupation, and education. It also provided two key dates: the date of the last regular menstrual period and the estimated date of delivery. Information that was added to the gravida registry card as the pregnancy progressed included dates on which blood specimens were drawn for the National Institutes of Health; dates on which blood specimens from the gravida and her husband were sent to the Diamond Blood Grouping Laboratory; resulting blood types for the ABO-Rh systems; prenatal appointments; and all contacts between the Child Health and Development Studies and the patient. When the pregnancy ended, information on the outcome of the pregnancy, the day and hour of birth, and the sex and birthweight of the child was added. Notations regarding the availability of cord blood and placental tissue samples were also entered on the record. When the gross placenta description and delivery report were received, this information was also noted on the record.

The Pediatric Card

As information on the outcome of each pregnancy in the Child Health and Development Studies was received, a pediatric card was made up for each infant. Separate files of these cards were maintained for live births, stillbirths, and neonatal deaths. Pediatric cards were made up with much the same basic format as the gravida registry cards, with additional information on date and time of birth, length of gestation, birthweight, length at birth, head circumference, sex, and race. The first entry in the body of the card was taken from the birth hospitalization record, and it gave information regarding the condition of the baby at birth, type of delivery if abnormal, treatment or tests given, congenital anomalies, birth marks, breathing difficulties, molding of head, forceps marks, hematomas, jaundice, transfusions, type of resuscitation, if any, birth injuries, etc.

Information was added to the pediatric card for every visit the child made to any Kaiser clinic, as well as for any hospitalization or any special examination he or she had. All entries on the card were recorded by date and included diagnosed conditions, injuries, developmental problems, or other problems the child was noted to have. If there were no problems, the notation of a routine check-up was entered. Any tests, x-rays, treatments, prescriptions, lab work, or immunizations were also recorded, as was the name of the physician who saw the child at each visit.

The basic goal was to abstract all Kaiser medical record information for at least the first five years of each child's life, but the abstracting covered a much longer period for those children born during the early years of the study. Some pediatric cards cover a period of over 12 years. Abstracting ended in May of 1972.

Sources of Information

As indicated previously, a large portion of the data collected by the Child Health and Development Studies was derived from the interview with the mother during pregnancy and from the mother's and

child's Kaiser medical charts. The interview process was previously discussed. The Kaiser chart encompassed all services rendered to the patient at a given Kaiser facility. Copies of specialty or emergency services rendered outside the Kaiser system were also included in the chart. Patients who used more than one Kaiser facility had charts at each location where medical care was sought. When there was any indication that our patients had used more than one Kaiser facility, the charts of all of these facilities were obtained and abstracted. The children's charts were requested from Kaiser regularly, and each chart was seen and abstracted at least once a year. The mothers' charts were requested on a schedule based on the date they delivered. All deliveries to women in the prospective study group that occurred within a single year were considered a birth cohort. The charts for each birth cohort were requested and abstracted in batches according to CHDS Number

Other records the Child Health and Development Studies routinely received from Kaiser included appointment lists from the Obstetrics and Gynecology clinics, hospital admission and discharge lists, delivery room dictations, pathology reports pertaining to fetal losses, and autopsy reports on all deaths (stillbirths, neonatal deaths, and deaths of older children). The appointment lists and admittance and discharge lists helped the study keep track of its patients. The delivery dictation, which followed a fixed protocol, was a special tape recording made by the obstetrician as soon as possible after delivery. It provided more information on the delivery than was usually included in the medical chart. Autopsies provided the study with information on congenital malformations confirmed or noted only at death, and on causes of death. Pathology reports were used to determine whether or not a patient was pregnant (pregnancy tests were also used) and whether or not observed fetal tissues were normal.

Routine laboratory procedures set up by the Child Health and Development Studies produced additional sources of information. The blood specimens taken from the gravida, her husband, and the infant were sent to the Diamond Blood Grouping Laboratory, in Boston, MA, for typing in ABO, D, Cc, Ee, MN, Ss, Kell, Duffy, Lutheran, and P systems. Serum samples, ideally taken from the gravidas in each of the three trimesters of pregnancy and also post partum, were frozen for future serological studies. Specially trained members of the Child Health and Development Studies staff who were either physicians or graduate students in the biological sciences routinely did gross placental examinations.

Another major source of information was the data compiled at special examinations given by the Child Health and Development Studies. These examinations, which pertained to certain subgroups of study children, can be divided into two classifications: those that encompassed a large number of children, and those that were confined to relatively small groups. The former, so-called "developmental examinations" were given to subcohorts of children; eligibility for these subcohorts was determined by birth date and place of residence. The children examined in the smaller groups were selected on the basis of a characteristic of interest. These included prematurity, being a twin, having a very small head circumference at birth, being either very short or very tall for chronological age, having a heart murmur or heart disease, or having unusual difficulty in school.

A great deal of information was collected on the subcohorts of children who took developmental examinations. These examinations were given to two cohorts of 5-year-olds, two cohorts of 9-11-year-olds, and one cohort of 15-17-year-olds. Most of the information derived from these examinations has

been coded and is accessible on computer files. The type of information collected and the selection criteria for each subcohort are indicated in the brief descriptions which follow.

At their fifth birthday, some of the children born between June 1960 and April 1963, and all those born between April 1964 and April 1966 who were still living in the East Bay Area were invited for special developmental examinations and follow-up interviews. In the first examination group (those born between June 1960 and April 1963), some 4,000 children were included. Over 3,000 children (born between April 1964 and April 1966) participated in the second examination, which utilized a modified, extended protocol. Both examinations included a general physical examination and tests of vision, hearing, speech, and cognitive ability, and in the second examination, a 42-item inventory completed by the mothers on the child's behavior and the mother/child relationship.

From April 1971 until April 1972, some 3,600 children who were born between April 1960 and April 1963 were examined at their ninth, tenth, or eleventh birthday. This examination included anthropometrics (weight, standing and sitting height, biacromial and bi-iliac distance, head circumference, chest depth and breadth, and triceps and subscapular skinfolds), and cognitive ability tests (Peabody Picture Vocabulary Test and Raven Progressive Matrices). In addition to an interview on the health and well-being of the family, the mothers of the 9-11-year-old children responded to a 100-item inventory about the child's behavior and the mother/child relationship. A cognitive ability test for the mother (Peabody Picture Vocabulary Test) was also included. Blood pressure measurements and screening of vision, hearing, and speech were done for a separate sample of 698 children at nine years of age.

In July 1977, examinations of 15-17-year-olds started. The main objective of the adolescent study was to investigate precursors of high blood pressure. The data collected included several measurements of blood pressure, lung function tests, anthropometric measurements, and interviews and questionnaires regarding health history and life-style items. Also, a cognitive ability test was administered. The mothers of these teenagers also participated in the examinations, with a protocol similar to that of the adolescents.

An overview of how the children participating in the 5-year-old examinations relate to the total prospective study group can be seen in Flow Chart 2. Flow Chart 3 indicates how many children participated in both the first examination of 5-year-olds and the examination of 9-11-year-olds; these children were the ones who were eligible for the examinations at ages 15 to 17.

Follow-Up Procedures

If a child was not being seen routinely at Kaiser, the Child Health and Development Studies follow-up unit tried to ascertain his or her health status. This procedure introduced several additional sources of information for the study. These included standard health questionnaires filled out by the child's non-Kaiser physician, standard health questionnaires filled out by the child's parents, and death certificates obtained from the authorities having jurisdiction in the case of a study child's death.

The follow-up unit followed fixed procedures in obtaining information about the health of study children. If a child was under the age of two years and had not been seen at a Kaiser facility for six

months, the follow-up unit immediately started to track him or her down. Older children were not checked on until a period of twelve months had passed. These procedures did not apply however, if the child had been adopted, the mother was classified as "refused coöperation," or the mother had been an unmarried minor at the time of her child's birth.

A sequence of steps was devised to make contact. The computer was of great assistance with the first follow-up step. We had programs written to alert us each month about the numbers that were "delinquent" according to the above criteria. These programs produced address labels for routine first contact letters. If a letter was returned because of a wrong address, or if we did not receive a reply within six weeks, we proceeded to the next step, which was contact by phone. If this was unsuccessful, a number of additional procedures were utilized. First, the references given by the woman when she was first interviewed were contacted. If still unsuccessful, contacts were made with the Department of Motor Vehicles, unions, the husband's employer, the wife's employer, neighbors, schools, the health department, and credit bureaus. In difficult cases, a field worker was sent out to talk with those who might know the whereabouts of the missing child. Where financial hardship appeared to have prevented a family from bringing the child in for an examination, the Child Health and Development Studies paid for the cost of the visit.

A certain attrition rate is to be expected from a large cohort study, even with intensive follow-up of the children. The loss rates for this study are, however, very low; for example, at the age of one year, we did not know the status of only 48 children out of 19,044 liveborn infants, an attrition rate of 0.2 percent. By the time the children reached their fifth birthday, 89.4 percent were still observed (68.2 percent were still Kaiser Health Plan members and 21.2 percent were otherwise in contact with the follow-up unit); 3.2 percent had died or had been adopted or institutionalized; only 7.4 percent had been lost from observation.

Generation of Coded Files

Many codes have been developed to process the vast amounts of collected data. Coded items are grouped into files which are representative of closely related data and are often based on a specific source document. Some files have one record per case, and others have a variable number of records per case. In addition, the number of cases varies from file to file. The Overview of Data Files, which precedes this chapter, briefly describes each file included in the database and gives source information and the number of cases included in the file.

The codes were developed over a 20-year timespan. Those that were developed at the very beginning of the study occasionally tended to squeeze data into single columns inappropriately. As data processing became more sophisticated, the majority of items that had been forced into single columns were recoded. A few items recoded only for special studies were never transferred to the main files. Consequently, some odd groupings still remain, but they are few in number.

The collection and reduction of data were very closely supervised. Abstracting from medical records and coding from various documents was generally done twice; any differences were then reconciled.

The computerized files were edited routinely. The resulting body of data thus has a very high level of accuracy.

In the process of coding the data, many unusual situations were encountered. When a precise definition or detailed explanation is necessary to understand an item, it is explained in the notes which accompany the individual files. These notes are intended as a supplement to the variable names and descriptions found in the SPSSX documentation. These notes provide background information on how the file was compiled, the individuals to whom it pertains, and clarifying remarks on individual codes. The notes for each file should be reviewed in conjunction with the SPSSX documentation to ensure proper analysis of the data.

Several files contain coded items that have extremely long codes pertaining to diagnoses and prescribed drugs. These items have been listed separately in the notes for the primary file for which they were developed so that they can be described in detail. Specifically, there are three general codes: the maternal conditions code, the drug code, and the congenital anomaly code. The maternal conditions code and the drug code are included as part of the documentation for the Maternal Conditions and Drugs Abstract file (MATCOND). The drug code is also used in the Child's Prescribed Drugs file (CHDRUGS). The congenital anomaly code is included in the documentation for the Congenital Anomalies file (ANOMALY), and it is also used in the Previous Pregnancies and Children file (PREPROD) and the Child Morbidity file (CHMORBID). The maternal conditions code and the congenital anomaly code were both originally based on the seventh revision of The International Lists of Diseases and Causes of Death. These codes were expanded to meet the needs of the study, and the congenital anomaly code was later adapted to some of the changes which appeared in the eighth revision of The International Lists of Diseases and Causes of Death. The drug code was based on information found in the Physicians' Desk Reference for the years 1959 through 1972. It assigns numbers to each drug that was abstracted for members of the study.

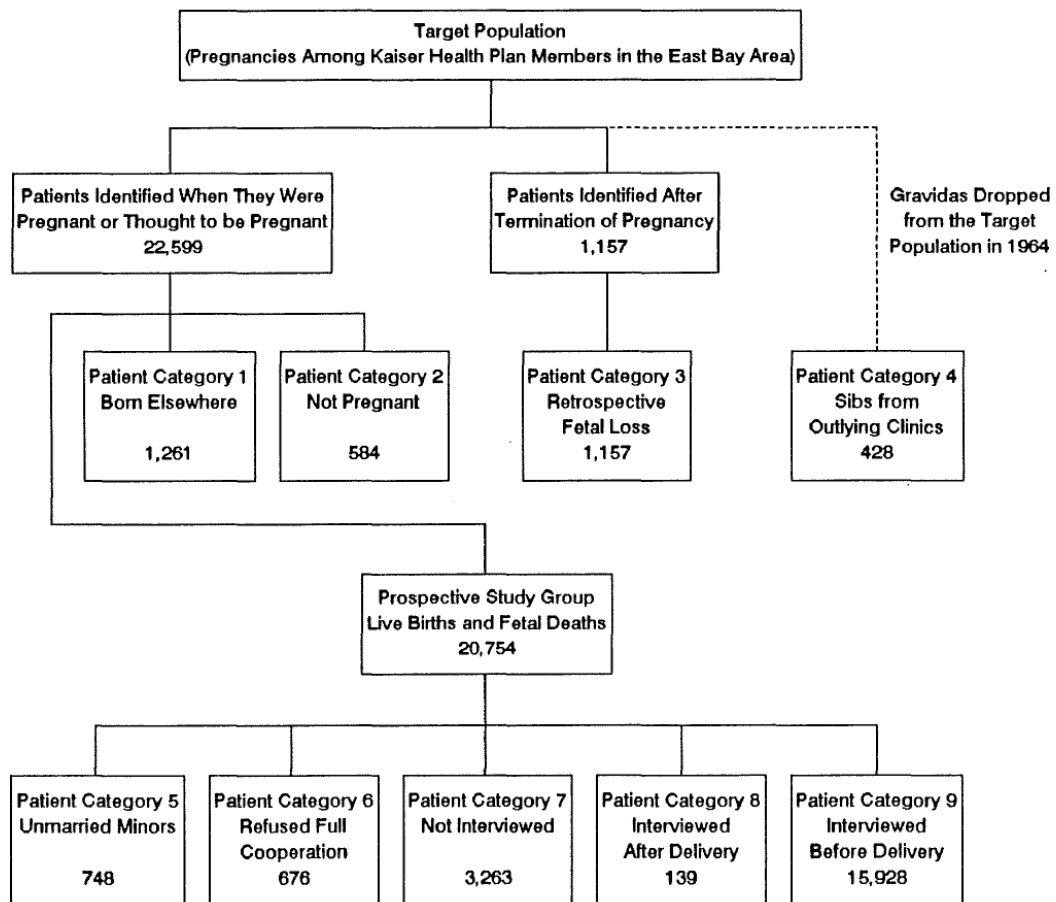
TABLE 1

History of Revisions of Pregnancy Interview Form
Child Health and Development Studies

June 1, 1959	Original Form:	Used in conjunction with the Family Health History (FHH) questionnaire. Birthdate of gravida was added some weeks later.
August 17, 1959	First Revision:	Birthdate of gravida, date of next appointment, and interviewer's comments were added to the interview. Place of birth was moved to the front page.
January 25, 1960	Second Revision:	The format of the front page was changed.
March 31, 1960	Third Revision:	The interview was expanded from 10 pages to 17 pages. Questions on health and pre-existing conditions were expanded, covering pages 4-8. Reproductive history was asked in more detail, and the child's health chart was included in the

		body of the interview since the FHH was no longer used. Questions on husband's smoking and drinking habits were also included.
April 27, 1960	Fourth Revision:	Questions on health and health conditions of relatives were asked in more detail. (These have never been coded.)
(May, 1960 Second Interview)		
June 15, 1960	Fifth Revision:	Questions on husband's race and nationality were added.
January 23, 1961	Sixth Revision:	A separate page for gravida's health information was added to interview.
June 30, 1961	Seventh Revision (or "Blue Book"):	Complete change of format. Questions on rubella exposure, twins in family, relatives participating in the study, drugs and medicines taken, and date of marriage were added.
April 20, 1965	Eighth Revision:	Additional detail was asked concerning previous marriage(s) and date of marriage(s), use of contraceptives, and drinking habits of both gravida and husband.

FIGURE 1
Relationship Between Patient Categories and Target Population⁴



⁴The numbers shown refer to the numbers of live births and fetal deaths among women in each category.

FIGURE 2
Status of Prospective Study Groups Through Five Years of Age

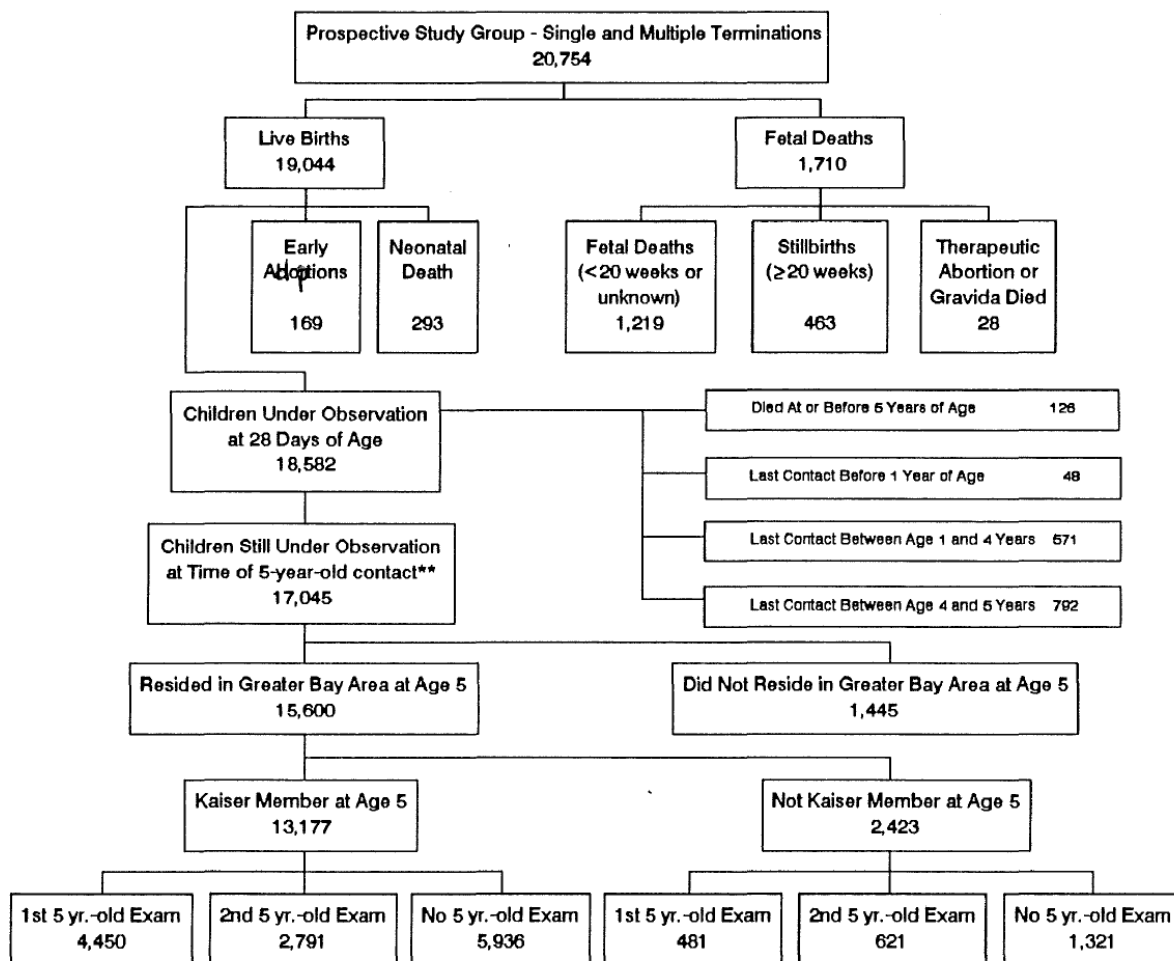
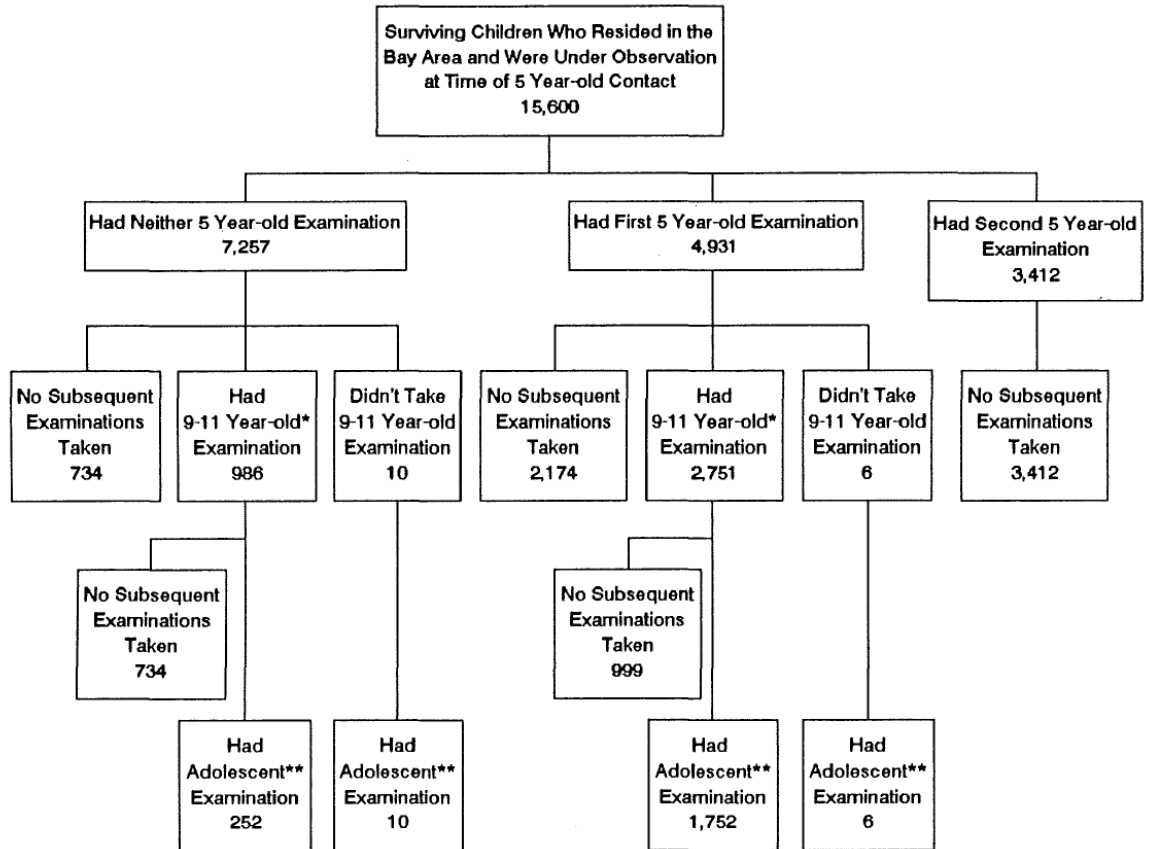


FIGURE 3
Relationships Between Examination Groups: 5-Year-Olds, 9-11-Year-Olds, and Adolescents



* Total who took 9-11 year-old examination: 3,737

** Total who took adolescent examination: 2,020