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In the United States 1995-1997

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Abstract

Sudden infant death syndrome (SIDS) constitutes an increasing proportion of infant deaths, and twins have a higher risk of SIDS than singletons.

This retrospective cohort study, based on the 1995-1997 Matched Multiple Birth File of the United States, examined risk factors of SIDS and non-SIDS deaths using generalized estimating equations, and investigated competing risks of SIDS using survival analysis.

The three unique characteristics of twins, namely birth weight discordance, birth order within pairs, and sex combinations, were not associated with SIDS, while they were related to non-SIDS deaths. Lower maternal education, younger maternal age, and maternal smoking during pregnancy were the strongest risk factors of SIDS among twins. Preterm birth and fetal growth restriction were determinants of infant deaths, including both SIDS and non-SIDS deaths.

In conclusion, social factors and common biological factors are important risk factors for SIDS among twins while the biological factors unique to twins are not.

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Table of Contents

1. INTRODUCTION 1

1.1 Background 1

1.2 Research Objectives 5

2. LITERATURE REVIEW 6

2.1 Public Health Importance of SIDS 6

2.1.1 Leading cause of infant death 6

2.1.2 Gaps in SIDS research and prevention 6

2.2 Introduction of SIDS 7

2.2.1 Definition 7

2.2.2 Diagnosis 8

2.2.3 Incidence 9

2.3 Risk Factors of SIDS 9

2.3.1 Infant factors 10

2.3.2 Maternal factors 14

2.3.3 Sleeping environmental factors 18

2.3.4 Genetic consideration 19

2.4 Pathophysiology of SIDS 20

2.4.1 Respiratory theories 21

2.4.2 Cardiovascular theories 22

2.4.3 Central and peripheral nervous system theories 22

2.4.4 Gastrointestinal theories 24

2.4.5 Microbiological theories 24

2.4.6 Miscellaneous theories 26

2.5 Triple-risk Model and Multifactorial Concept 26

2.6 SIDS in Twins 28

2.7 Unique Characteristics of Twins with SIDS and Non-SIDS 29

2.7.1 Birth weight discordance 29

2.7.2 Birth order within twin pairs 31

2.7.3 Sex combinations 33
2.8 Recommended Interventions to Decrease SIDS 34

3. METHODOLOGY 35
3.1 Study Design 35
3.2 Material 35
3.2.1 Twins data 35
3.2.2 Study populations 39
3.3 Variables of Interest 39
3.3.1 Dependent variables 39
3.3.2 Independent variables 41
3.3.2.1 Primary exposure variables 41
3.3.2.2 Established confounding variables 42
3.3.2.3 Potential confounding variables 43
3.4 Statistical Analysis 44
3.4.1 GEE analysis for the risk factors of SIDS 44
3.4.1.1 Populations for SIDS and non-SIDS study.....45
3.4.1.2 Data description and rates of SIDS and non-SIDS 46
3.4.1.3 GEE method 46
3.4.1.4 Univariable analysis 52
3.4.1.5 Multivariable analysis 52
3.4.1.6 Test of confounders 53
3.4.1.7 Interaction test 53
3.4.1.8 Model evaluation 54
3.4.1.9 Power analysis 55
3.4.2 Competing risks analysis of SIDS 56
3.4.2.1 Main causes of infant death by functional groups 56
3.4.2.2 Smaller and larger twin populations 57
3.4.2.3 Incidence rates of main causes of infant death in smaller and larger twins 58
3.4.2.4 Method of competing risks analysis 58

3.4.2.5 Comparison of log survivor curves by main causes of infant death 60
3.4.2.6 Risk factors with main causes of infant death in smaller and larger twins 61
3.5 Missing Values 61

4. RESULTS 62
4.1 Eligible Study Twin Population 62
4.2 GEE Analysis for the Risk Factors of SIDS 62
4.2.1 Data sets 62
4.2.1.1 Data set for SIDS study.....62
4.2.1.2 Data set for non-SIDS study.....63
4.2.2 Rates of SIDS and non-SIDS deaths 63
4.2.3 Risk factors of SIDS 69
4.2.3.1 Crude and adjusted odds ratios 69
4.2.3.2 Confounders 69
4.2.3.3 Interactions 72
4.2.3.4 Model evaluation 72
4.2.3.5 Power analysis 72
4.2.4 Risk factors of non-SIDS 72
4.2.5 Comparison of risk factors between SIDS and non-SIDS 73
4.3 Competing Risks by Survival Analysis 76
4.3.1 Smaller and larger twin data sets 76
4.3.2 Main causes of infant death by functional groups 77
4.3.3 Comparison of log survivor curves 77
4.3.4 Competing risks for main causes of infant death 81
4.3.4.1 Competing risks in smaller twins 81
4.3.4.2 Competing risks in larger twins 82
4.3.4.3 Comparison of competing risks between smaller and larger twins 85
4.3.4.4 Test proportionality 86

5. DISCUSSION 92

5.1 Summary of Key Findings and Implications 92

5.2 Interpretation of the Findings 93

5.2.1 SIDS death rate in twins 93

5.2.2 Birth weight discordance with SIDS 93

5.2.3 Birth order with SIDS 95

5.2.4 Sex combinations with SIDS 97

5.2.5 Important infant factors with SIDS 98

5.2.6 Important maternal factors with SIDS 99

5.2.7 Other risk factors with SIDS 102

5.2.8 SIDS and other main causes of infant death 103

5.2.9 Comparison between smaller and larger twins 104

5.3 Strengths of Methodology 104

5.3.1 Large administrative data set 104

5.3.2 Comparison of general association 104

5.3.3 Study controls 105

5.3.4 SIDS – postperinatal death or postneonatal death 106

5.3.5 Quality of the study 106

5.4 Limitations 107

5.4.1 Key variables 107

5.4.2 Non-sampling errors 107

5.4.3 Accuracy of information 108

5.4.4 Event number 109

5.4.5 Missing values 109

5.5 Conclusion and Future Work 109

REFERENCE 111

APPENDICES ..... I-XIV

List of Tables

Table-1: Summary of risk factors for SIDS 11
Table-2: Observations and variables in the study data set 35
Table-3: Percentage distribution of maternal and infant characteristics in twins with SIDS and non-SIDS deaths.....65
Table-4: Comparison of odds ratios and 95 percent confidence intervals for SIDS and non-SIDS deaths 70
Table-5: Study power analysis 73
Table-6: Distribution of infant death and death rates by five main causes of infant death in smaller and larger twins 77
Table-7: Comparison of significant adjusted hazard ratios and 95 percent confidence intervals in smaller twins for five main causes of infant death 83
Table-8: Comparison of significant adjusted hazard ratios and 95 percent confidence intervals in larger twins for five main causes of infant death 84

List of Charts

Chart-1: Scheme of the study methodology 36
Chart-2: Composition of eligible study twin population and populations for SIDS and non-SIDS study.....45

List of Figures

Figure-1: Comparison of death rates between SIDS and non-SIDS across the three primary exposure variables 67
Figure-2: Comparison of death rates between SIDS and non-SIDS across the various variables other than three primary exposure variables 68
Figure-3: Comparison of significant adjusted odds ratios between SIDS and Non-SIDS 74
Figure-4: Log survivor plot for five main causes of infant death in smaller twins 78
Figure-5: Log survivor plot for five main causes of infant death in larger twins 79
Figure-6: Significant adjusted hazard ratios for three twin characteristics in smaller and larger twins 87
Figure-7: Significant adjusted hazard ratios for six maternal variables in smaller and larger twins 88
Figure-8: Significant adjusted hazard ratios for three infant physiological variables in smaller and larger twins 89
Figure-9: Significant adjusted hazard ratios for 5-minute APGAR score in smaller and larger twins 90
Figure-10: Significant adjusted hazard ratios for four other variables in smaller and larger twins 91

1. INTRODUCTION

1.1 Background

Sudden infant death syndrome (SIDS) is defined as "the sudden death of any infant or young child which is unexpected by history, and in which a thorough postmortem examination fails to demonstrate an adequate cause for death."(1). Although SIDS rates are greatly variable in different countries due to various reasons, the incidence trend of SIDS has generally been downward (2,3). Through the national "back-to-sleep" campaigns, the SIDS incidence fell from 1.0 to 0.5 per 1000 live births in Canada (2), and decreased from 1.4 to 0.8 per 1000 live births in the United States during the 1990s (3).

However, SIDS is the leading cause of infant death in the postneonatal period (28-364 days) (4,5). It accounts for 40 to 60 percent of all deaths that occur after the first month of life and before the first birthday, and constitutes an increasing proportion of the total infant deaths as the number of other causes of death declines (6). Since 1990, the proportion of SIDS increased during the first month after birth and after six months of age (7). Thus, SIDS prevention is an increasingly important public health issue.

The underlying causes of SIDS are not clearly understood. However, investigators have identified a list of risk factors for SIDS during the past three decades: a prone sleeping position, soft bedding, overheating of infants, maternal age less than 20 years, black race, maternal education less than 12 years, unmarried status, multiple births, more than two previous pregnancies, birth weight less than 2500g, gestational age at birth less than 37 completed weeks, male gender, 5-minute APGAR score less than 7, late onset of prenatal care, and maternal smoking during pregnancy (8-12). Studies on perinatal risk factors of SIDS, such as mode of delivery and pregnancy complications have yielded

inconsistent results (13-15). After specific environmental risk factors were identified, community awareness campaigns were implemented and resulted in a large decline in SIDS in many countries (16).

Although the knowledge about various risk factors has saved thousands of lives, it is a challenge to understand the mechanisms behind these risk factors (7). There has been considerable controversy in the literature regarding the mechanisms of SIDS, owing to variations in research design and heterogeneity in the pathophysiology of SIDS (17). Since each risk factor affects infants in a particular way, SIDS infants are quite a heterogeneous population with subgroups of unique predispositions and characteristics (18). Instead of the traditional single-cause theories of SIDS, a triple-risk model and then a multifactorial concept were proposed to integrate complex individual susceptibilities with developmental stages and environmental factors (19,20). Since SIDS is a developmental disorder and its origins are during fetal development (21), it has been suggested that pregnancy-related factors could play an important role in SIDS through a suboptimal intrauterine environment, "hypoxic conditions" in the fetus or the newborn, and then inadequate development of the "brain-cardio-respiratory axis" (15,22). Therefore, identifying prenatal and perinatal factors that increase the risk for SIDS would be helpful to identify vulnerable infants.

Since 1980, the number of twin births has relatively increased 42% in the United States due to the delay in pregnancy and an increase in the use of assisted reproductive technology (4). Twins have a 2- to 4-fold increased risk for SIDS compared with singletons (8,23-25). Compared with singletons, twins have three unique characteristics: birth weight discordance, birth order within twin pairs, and sex combinations. The rates

of low birth weight and preterm birth in twins are also much higher than those in singletons (24,26). Previous studies demonstrated that the three unique characteristics contribute to the mortality and morbidity among twins: firstly, birth weight discordance was an important determinant of fetal and neonatal deaths as well as postnatal morbidity (27-30); secondly, second-born twins had increased perinatal mortality rate (24,31) and were more vulnerable to labor and delivery complications than first-born twins (32); and thirdly male twins had 20% to 30% higher infant mortality rates than female twins and like sex twins had an increased risk of mortality than unlike sex twins (24). However, whether these three unique factors in twins are associated with SIDS, a postperinatal infant death (7-364 days), has not been appropriately examined.

Previous studies found that the birth weight discordance tended to be larger among twin pairs in which one or both twins died of SIDS than those in which both twins survived (5,23). In addition, if the birth weights of twins in a pair were significantly different, it was usually the smaller twin who died of SIDS (23,33). But these studies did not establish a clinically important threshold correlating birth weight discordance with SIDS. Studies of the birth order as a risk factor of SIDS produced inconsistent results (24,33,34). There are three types of twin pairs in terms of sex combinations, Male-Male (M-M), Female-Female (F-F), and Male-Female (M-F) / Female-Male (F-M). Since the risk of SIDS was higher in males than that in females, the assessment of the relationship between sex combinations and SIDS may be biased towards M-M > M-F/F-M > F-F (8). However, inverse results have been observed in a large-scale study (5). The first part of this thesis focuses on the association between SIDS and these three unique characteristics in twins (birth weight discordance, birth order within twin pairs and sex combinations),

with established risk factors as confounders. Most previously identified risk factors are not specific for SIDS but for infant deaths in general (10,35). In the second part of the thesis, the risk effect for SIDS is compared with that for non-SIDS infant deaths for all risk factors detected in two twin populations which are from the same twin data set.

Previous studies have suggested that three fourths of twin deaths occur in the neonatal period (0 to 27 days) and that the leading cause of neonatal deaths is prematurity (24). The age-at-death distribution distinguishes SIDS from other main causes of death during infancy: SIDS occurs in the first six months of life with a peak between two and four months of age (6,35). It is not clearly understood, however, whether, and to what extent, the age-dependent SIDS incidence mortality is affected by competing causes of infant death such as prematurity in the twin population in terms of various risk factors. In the third part of the thesis, the distribution of age at death and the magnitude of risk effects of various risk factors for SIDS are compared with those for other main causes of infant death, grouped by the International Collaborative Effort (ICE) classification system (36).

It is known that the identification of various risk factors for SIDS could lead to early detection of the unfavorable conditions among twins and the development of effective prevention. Because of the large population, our study allowed us to adequately examine the association between a number of risk factors and SIDS in twin births, specify the risk factors for SIDS by comparing the risk effects between SIDS and non-SIDS deaths, and differentiate SIDS from other main causes of infant death. Furthermore, mothers and families of twins with a high risk of SIDS could be provided with special counseling services for the special care needs of twins in the vulnerable stage. Our study results could also help to shed light into the mechanism of SIDS among twins.

1.2 Research Objectives

1) To assess whether the increased birth weight discordance, second-born birth order within twin pairs and Male-Male sex combination are risk factors for SIDS among twins.

2) To compare the effects of various risk factors for SIDS and non-SIDS deaths.

3) To examine whether the risks of other main causes of infant death affect the risk of SIDS occurring.

2. LITERATURE REVIEW

2.1 Public Health Importance of SIDS

"What greater pain can mortals bear than this; to see their children die before their eyes?"

Attributed to Euripides 480-406 BC (37)

2.1.1 Leading cause of infant death

In Canada, three infants are reported to die of SIDS per week on average (38). In the United States, nearly 3000 SIDS-related deaths occur in a year (2). SIDS is the leading cause of infant death in postneonatal period (28-364 days) (4,5). It accounts for 40 to 60 percent of all deaths that occur after the first month of life and before the first birthday, and constitutes an increasing proportion of the total infant deaths as the number of other causes of infant death declines in these countries (6). Since 1990, the proportion of SIDS increased during the first month after birth and after six months of age (7). Regrettably, SIDS is a tragedy that results in the breakup of marriages, self-accusation from the victims' parents, and deterioration in the quality of family life (38,39). Thus, SIDS prevention has become a more and more important public health issue.

2.1.2 Gaps in SIDS research and prevention

Community awareness campaigns have significantly reduced deaths from SIDS in many countries (16). For example, the incidence of SIDS has decreased more than 50% in western countries after the national "back-to-sleep" campaigns in last decade (40).

Despite these major successes, SIDS remains a significant public health concern. In the United States, the rate of SIDS remains two to three times higher than the lowest rates in other industrialized countries (2). Many infants who died of SIDS after the "back-to-

sleep" campaigns were still found sleeping prone (41). Infants whose deaths are now attributed to SIDS often come from socially disadvantaged groups, in which it may be difficult to investigate the causes and take counsel (40). SIDS deaths are still investigated poorly in many jurisdictions without fulfilling the requirements of recognized SIDS definitions or following accepted protocols for autopsy and death scene investigation (42). Single-cause theories of SIDS continue to be expounded through the media without appropriate peer review, causing considerable parental confusion and anxiety (17). Until the underlying cause or causes of SIDS are found, research can only identify risk factors and suggest how to reduce these risks (38).

As a result, research should concentrate on identifying the characteristics of particular subgroups of SIDS infants (18), exploring the increased relative importance of risk factors which might not require prone sleep for their deleterious impact (43), and investigating multifactorial mechanisms behind risk factors (20,44). Prevention strategies should pay careful attention to providing additional targeted efforts for certain subpopulations, especially for infants at high risk of SIDS (2).

2.2 Introduction of SIDS

2.2.1 Definition

In 1969, at the Second International Conference on Causes of Sudden Death in Infants, SIDS was defined as "the sudden death of any infant or young child, which is unexpected by history, and in which a thorough postmortem examination fails to demonstrate an adequate cause for death" (1). Although the debate continues about this definition by exclusion, it has been the dominating one during the last 30 years (7).

Since many natural and unnatural diseases and conditions may cause unexpected infant death with only very subtle presenting symptoms and minimal or no postmortem signs, the National Institute of Child Health and Human Development (NICHD) of the United States revised the definition in 1989, as "the sudden death of an infant under one year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history" (45). This definition requires a compulsory death scene investigation performed before SIDS diagnosis. Consequently, the SIDS rates declined, while other causes of sudden infant death have become more prominent after further investigations, such as deaths due to neglect, abuse and murder (7). Despite the usefulness of this definition, it has not been accepted universally mainly due to different legislation and cultural traditions (17).

2.2.2 Diagnosis

SIDS was accepted as a diagnosis on death certificates first in the UK in 1971 and "sudden infant death" was given a separate coding in the World Health Organization's (WHO) International Classification of Diseases (ICD) (coding number 798.0) after 1979 (37).

As mentioned in the definition above, SIDS should be diagnosed based on the exclusion of other causes of sudden infant death only after they have been sought scrupulously. This exclusion demands expertise in forensic medicine, pediatric pathology, neuropathology, radiology, pediatrics, microbiology, and toxicology (7). Although the examination of unexpected infant deaths has progressed considerably, SIDS still appears to be a difficult, contentious, and emotive term which is used very easily as a

"diagnostic dustbin" to disguise incomplete investigations and inaccurate conclusions (46). However, as a registered cause of death, SIDS should not be abolished. Otherwise, pathologists would have to apply vague diagnoses again, which would harm the research on SIDS (7).

2.2.3 Incidence

The first rate of SIDS was reported from England and Wales in 1965 and was1.4 per 1000 live births (47). The first reported Canadian rate was 3 per1000 live births from Ontario in 1969 (47).

SIDS rates show great variations among different countries. The WHO reported SIDS rates in 22 countries in 1996 ranging from 2.25 per 1000 live births in Belgium to 0.05 per 1000 live births in Portugal (48). The reasons for the variation are most likely problems with the classification of SIDS and the difficulties with reporting in some countries (7).

The trend in the incidence of SIDS has generally been downward and has likely been influenced by multiple factors, such as the use of varying definitions and sampling methods as well as the reductions in placing babies prone for sleep. Through the national "back-to-sleep" campaigns, the incidence of SIDS fell from 1.0 to 0.5 per 1000 live births in Canada (2), and decreased from 1.4 to 0.8 per 1000 live births in the United States during the 1990s (3).

2.3 Risk Factors of SIDS

Even though the cause of SIDS is still not fully understood, reducing exposure to modifiable risk factors has helped to lower the incidence of SIDS, a complex disorder. However, except for the age-at-death distribution, most previously identified risk factors

are not specific for SIDS but for infant deaths in general (10,35). This section presents the summary of various risk factors for SIDS in Table 1 with further description in detail.

2.3.1 Infant factors

Age at death: SIDS shows a unique age distribution, i.e. most deaths occur after the first month of life to six months of age with a peak between two and four months of age, which distinguishes SIDS from other main causes of infant death (6,14,35,49). Approximately 80% of SIDS deaths occur in the first six months of life (49,50). A general consensus of the upper age limit is one year (45). However, the typical age peak has become less significant with the recent decrease in the rate of SIDS, particularly with increased proportions of unexplained deaths during the first month after birth and after six months of age (7). The age of death in SIDS is independent of other risk factors and is the only universal epidemiological characteristic of SIDS (47).

Gender: SIDS generally affects 30-50% more males than females (51-53). Some studies found a somewhat greater proportion of males affected, usually around 55% (14,54). An odds ratio (OR) of 1.47 (95% CI: 1.40-1.53) for males to females was reported in the United States (15) and an OR of 1.47 (1.26-1.70) was ever reported in Canada (55). This phenomenon could be attributed to a greater prevalence of the prone sleeping position in males, even after the "back-to-sleep" campaigns (54), or a lag in maturation of active sleep in males compared with females at risk (56). However, a 5-year survey in Washington State found that 51 % of SIDS cases were males, consistent with 1.05 of the male/female ratio at birth (57). Further, higher rates in males have been observed for all infant mortality not just SIDS (47).

Table 1 – Summary of risk factors for SIDS (continue)

Factor	Association*	Comment
Infant factors		
Age at death	↑	80% of SIDS deaths occurring by 6 months with a peak at 2-4 months of age; Unique age-at-death distribution distinguishing SIDS from other causes of infant death
Male	↑	OR of 1.47 (95%CI: 1.40-1.53) for males to females in the United States; Higher risk in males observed for all infant mortality
Preterm births	↑	Unadjusted OR of 3.7 (2.1-7.6) and adjusted OR of 2.3 (1.0-5.3) for preterm births (28-32 weeks) to term births (≥38 weeks); Proportion of preterm infants in those dying of SIDS increased from 12% to 34% before and after the "back-to-sleep" campaigns; An important contributor to SIDS;
Fetal growth restriction	↑	Adjusted OR of 1.40 (1.30-1.50) for fetal growth restriction (birth weight-for-gestational-age < 10^{th} percentile, ≥10^{th} percentile as reference); An important contributor to SIDS
Higher parity /birth order	↑	Unadjusted OR of 1.6 (1.1-2.4) and adjusted OR of 1.4 (0.9-2.1) for higher parity (≥3) compared with lower parity (<3); Association becoming weaker after adjusting for maternal education
Low APGAR score	↑	Adjusted ORs of 2.2 (1.0-4.8) and 1.2 (0.3-4.9) for low 1-minute and 5-minute APGAR scores (<7) compared with the normal APGAR (≥7)
Maternal factors		
African-American	↑	Adjusted OR of 1.93 (1.83, 2.03) for black mothers to white mothers in the United States; Association becoming weaker after controlling for socioeconomic factors
Young maternal age	↑	The incidence of SIDS of 5.2 per 1000 live births in infants of mothers younger than 20 years; Adjusted OR of 2.24 (2.04-2.47) for young mother (<20 years) to elder mother (≥35 years); SIDS risk decreasing as maternal age increasing
Single mothers	↑	OR decreased to 0.9 (0.6-1.5) for single mothers to married mothers after controlling for family income

Factor	Association*	Comment
Maternal factors		
Low maternal education	↑	Adjusted OR of 2.23 (1.96-2.54) for maternal education less than 12 years to that more than 16 years; Maternal education used as an index of social status
Multiple births	↑	Relative risk of 2 for SIDS in twins compared with singletons
Late or no prenatal care	↑	2-3 times higher risk as compared with those who had early prenatal care; The effect of inadequate prenatal care on SIDS reduced after controlling for socioeconomic status and maternal age
Smoking	↑	Adjusted OR of 3.19 (3.03-3.37) for smoking to non-smoking; Relative risk of 3 for maternal smoking exposure to unexposure before "back-to-sleep" campaigns and relative risk of 5 after the campaigns; A dose-response relationship; An important risk factor and importance relatively increasing after "back-to-sleep" campaigns
Other maternal factors	—	Including chronic diseases, pregnancy complications, and mode of delivery
Sleeping environmental factors		
Supine sleeping position	↓	Overall OR of 2.72 (2.27-3.26) for the association between prone sleep position and SIDS; Relative risk of 4.47 (1.3-15.4) for prone sleeping after adjusting for infant birth weight and maternal age in a prospective study; Prone sleeping position: a well established risk factor; Side sleeping position: becoming more important as prone sleeping declines
Overheating	↑	Significantly and independently related to SIDS
Bed sharing	↑	Related to a raised risk of SIDS
Genetic consideration	—	Different distribution of polymorphisms for some genes between SIDS infants and controls

* ↑ Increased risk; ↓ Decreased risk; — Inconclusive or no apparent association

Gestation: Prematurity is an important contributor to SIDS identified by many studies (14,15,50,51,58-60). Compared with term births, an unadjusted OR of 3.7 (2.1-7.6) for preterm (28-32 weeks) and an adjusted OR of 2.3 (1.0-5.1) were reported in a large study in the United States (51) while an unadjusted OR of 5.7 (3.5-9.4) for preterm (<37 weeks) was reported in a study in Nordic countries (50). The percentage of preterm births in all SIDS victims rose from 14% in 1956 to 18% in 1979, compared to the population rates for prematurity of 8% and 5%, respectively (47). Thus it has been suggested that the rise in SIDS rates may be due to the increase in low birth weight infants surviving the neonatal period (47). Some recent studies showed that prematurity became a more important risk factor after the "back-to-sleep" campaigns, and reported that the proportion of preterm infants in those dying of SIDS increased from 12% before the campaigns to 34% after the campaigns (58,59).

Birth weight and birth weight-for-gestational-age: Infants with a birth weight less than 1500g and of 1500-2499g were about four and three times, respectively, more likely to die of SIDS than those with a birth weight of more than 2500g (61). Low birth weight is determined by a shortened gestational age or a slower fetal growth or a combination of the two. As a result, in epidemiological studies, preterm birth and fetal growth restriction should be considered instead in the analysis (58). Infants of extremely low birth weight nearly are always preterm (47). Fetal growth restriction (birth weight-for-gestational-age $<10^{th}$ percentile) is one of the major determinants of infant mortality and morbidity, including SIDS (14,15,49-51,62). An unadjusted OR for fetal growth restriction of 3.1 (2.0-4.9) ($\geq 10^{th}$ percentile as reference) was reported in a Nordic study (50) and an adjusted OR of 1.40 (1.30-1.50) was reported in a recent American study (15).

Birth order and Parity: Previous studies reported that there was an increasing incidence of SIDS with increasing parity or birth order (9,14,51,60,63). However, the association became weaker when the effect of maternal education was accounted for (unadjusted OR of 1.6 (1.1-2.4) and adjusted OR of 1.4 (0.9-2.1) for parity ≥3) (51). Spiers et al found that the risk of SIDS decreased with increasing birth order after the live births were stratified by the sibship size (64). It might be related to socioeconomic strain in the care environment or increased risk of infection from siblings (65). In addition, multiparity may affect a particular pregnancy by causing low birth weight if the interval between pregnancies is brief (9,66).

APGAR score: APGAR score is a useful measure for resuscitation and a predictor of the infant's chances of surviving the first year of life (67). The NICHD epidemiological study, using 7 of 1-minute APGAR as a cut-off, found no difference in SIDS risk for APGAR <7 compared with APGAR ≥7 when gestational age, race and birth weight were controlled for (60). However, another study of 148 autopsied SIDS infants found associations between low 1-minute and 5-minute APGAR scores (<7) and the risk of SIDS with ORs of 2.2 (1.0-4.8) and 1.2 (0.3-4.9) respectively, after adjusting for labor and delivery complications (13). Haas and colleagues observed a significant association of low 5-minute APGAR score with "possible SIDS" but not for "classic SIDS" (10).

2.3.2 Maternal factors

Maternal race: African-American and Native American infants have the highest rates of SIDS, ranging from 2.5 to 6.0 per 1000 live births in the United States while whites, Asians and Pacific Islanders have the lowest rates, ranging from 1.0 to 2.5 per 1000 live births (14,57,60). Some researchers strongly suggested that the high SIDS rate in the

blacks and Native Americans was socioeconomic in origin because they found an adjusted OR reduced to 1 (0.7-1.3) for black American mothers to white mothers and adjusted relative risk (RR) diminished to 1.82 (1.28-2.58) for Native Americans once socioeconomic factors such as income and the level of maternal education had been controlled for (51,57). However, a recent American study reported an adjusted OR of 1.93 (1.83-2.03) for black mothers to white mothers (15). Differences in SIDS rates among different racial groups may also be related to differences in childcare practices, for example, Asian infants may benefit from their parents' supine sleep preference (68). On the other hand, less reduction in the prevalence of prone positioning among blacks after the "back-to-sleep" campaigns may explain the continued disadvantages from black families (40).

Maternal age: Many studies reported a higher incidence of SIDS in mothers with an age less than 20 years (14,15,52,60,63,69). The incidence of SIDS was reported to rise from 1.0 per1000 live births in infants of mothers at 30 to 34 years of age to 5.2 for mothers younger than 20 years (69). NICHD study reported that 75% of SIDS mothers were teenagers at the time of their first births, which yielded ORs of 4.4 and 3.3 compared with controls matched on age and controls matched on age, birth weight and race, respectively (60). An adjusted OR of 2.24 (2.04-2.47) for young mothers (<20 years) to elder mothers (≥35 years) was reported in a recent American study (15). Unlike the U-shaped distribution in overall postneonatal mortality (higher rates at both younger and older maternal ages), the rate of SIDS declines continuously with increasing maternal age (14,47,52,69).

Marital status: It was reported that 59% of the SIDS mothers were unmarried, yielding the ORs of 3.9 and 2.5 compared with controls matched on age and controls matched on age, birth weight and race, respectively (60). However, Kraus and colleagues found that maternal marital status was not associated with SIDS because the OR reduced to 0.9 (0.6-1.5) once family income had been adjusted for (51). Therefore the effect of single mothers may be influenced through several other risk factors, particularly young mothers and poor socioeconomic status (47).

Maternal education: Maternal education is frequently used as an index of social status, and there appears to be a protective effect of high maternal education on SIDS occurrences (9,11,15,51,60). The NICHD study found that 57% of SIDS mothers had not finished high school, associated with ORs of 2.7 and 2.6 compared with the two control groups (60). A recent study in the United States reported the adjusted OR of 2.23 (1.96-2.54) for maternal education less than 12 years to that more than 16 years (15). Malloy and Freeman reported that, compared with twin pregnancies in which both twins survived, pregnancies in which one or both twins died of SIDS were more prevalent among mothers with less than 12 years of education (5). However, two Nordic studies found that low maternal education was not a significant risk factor after adjusting for maternal age, parity, and smoking habits (52,70).

Multiple births: Infants of multiple births are at a moderately increased risk of SIDS than singletons (9,51). This may be due to prematurity or small birth size (5). The mortality rates of twins for most causes of death were 6 to 15 times those of singletons, whereas the risk of SIDS in twins was only twice that of singletons (47).

Prenatal care: SIDS infants occurred more frequently in mothers who delayed their first prenatal visits or had fewer prenatal visits, with two to three times higher risk compared with those who had early prenatal care (14,51,60,63). After controlling for socioeconomic status and maternal age, the effect of inadequate prenatal care on SIDS was reduced (14).

Smoking: Many studies found that cigarette smoking during pregnancy was an important risk factor of SIDS, and there was a dose-response relationship (60,71). Furthermore, it appears that as prone sleeping is reduced, the relative importance of smoking increases (58,59). The studies showed that infants with intrauterine exposure to cigarette smoking were three times more likely to die of SIDS than those unexposed before the "back-to-sleep" campaigns and five times more likely after the campaigns (65). A recent study reported an adjusted OR of 3.19 (3.03-3.37) for mothers smoking during pregnancy to those not smoking in the United State (15). Although the exact mechanism of smoking on the occurrence of SIDS is not clearly understood, cigarette smoking during pregnancy may execute its effect on SIDS, at least in part, through its effect on prematurity and intrauterine growth retardation (66). Impaired arousal has also been demonstrated in infants exposed to tobacco smoke (72).

Others maternal factors: Moderate maternal anemia and chronic hypertension that could contribute to chronic utero hypoxia due to decreased uterine blood flow were found more frequently in the mothers of SIDS infants (14). Various pregnancy complications that could cause antenatal hypoxia for the fetus such as eclampsia, placenta previa, and abruptio placenta were associated with an increased risk for SIDS in some studies (13,15). No increased risk of SIDS associated with meconium staining was observed in a

large American SIDS cooperative study (60). Cesarean section rates did not differ between SIDS cases and controls (14). However, these findings were neither sensitive nor specific to SIDS, i.e. they were risk factors for infant mortality in general.

2.3.3 Sleeping environmental factors

Several case-control studies have shown that the prone sleeping position increased the risk of SIDS in different countries (14,47,68). The first prospective study of the prone position from Tasmania in 1991 reported a relative risk of SIDS of 4.47 (1.3-15.4) for prone sleeping after adjusting for infant birth weight and maternal age (73). In the same year, a meta-analysis was published including 19 case-control studies, most of which showed a positive association between the prone sleep position and SIDS with an overall OR of 2.72 (2.27-3.26) (74).

In response to these research results, national campaigns against sleeping prone in infants started in major industrialized countries from 1986 to 1994. After the campaigns, these countries reported a marked decline in prone sleeping position as well as a striking reduction in SIDS rates (16,40). On the other hand, there was no increase in deaths due to aspiration after the "back-to-sleep" campaigns (75).

Although it is the most important risk factor of SIDS ever reported, the prone position is not a sufficient cause of SIDS, because infants dying of SIDS have died in other sleeping positions (47) and 99% of infants who sleep prone will survive (17). The mechanism of death in prone sleeping is more complex than simple smothering and involves contributions from a number of factors, such as unfavorable ratio of ventilation and perfusion caused by the prone position (76). In addition, infants who sleep on their sides also have an increased risk of SIDS, as they may roll on to their abdomens (77).

Other than sleeping positions, overheating of infants caused by heavy wrapping with bed clothing or environmental hyperthermia is significantly and independently correlated to SIDS (78). Bed sharing is also associated with a raised risk of SIDS because of overlying, hyperthermia, passive smoking and alcohol consumption by parents (71).

Oyen and colleagues observed the strong combined effects of prone and side sleeping with low birth weight, preterm, and intrauterine growth retardation as well as the effects of the combined presence of nonsupine sleeping positions with smoking in pregnancy, young maternal age, higher parity, low level of maternal education, and single motherhood (50). The researchers suggested that SIDS might be triggered by nonsupine sleeping in the infants with prenatal risk factors during a vulnerable period of postnatal development (50).

2.3.4 Genetic consideration

Genetic studies identified some genes for which the distribution of polymorphisms differ between infants dying of SIDS and controls, such as the cardiac ion channel associated with a long QT syndrome, serotonin transporter (5-HTT) affecting breathing, cardiovascular and circadian regulation, complement C4 and interleukin-10 related to infection and inflammation (65). However, there is neither a cost-effective way existing to screen for any of these genetic polymorphisms in early infancy nor a specific clinical abnormality or phenotype delineated for the polymorphisms identified in SIDS infants (65). The actual risk of SIDS in individual infants seems determined by complex interactions between genetic and environmental risk factors (65).

2.4 Pathophysiology of SIDS

Although studies on the risk factors of SIDS have led to public health measures that have saved thousands of lives, it is a challenge to understand the mechanisms behind risk factors such as the prone sleeping position. Certainly, information about risk factors may help to generate new hypotheses of possible mechanisms of SIDS (7).

Various etiologic theories have been proposed, ranging from the earliest explanation of accidental suffocation caused by overlaying many thousands of years ago to an alternative theory of enlarged thymus glands pressing the upper airway in the late 19th century, and to the current triple-risk model (17). There has been considerable controversy in the literature regarding the contribution of various abnormalities to the mechanisms of SIDS. This reflects the variation in the quality of different investigations and also suggests considerable heterogeneity in pathophysiology of SIDS. SIDS victims do not all exhibit the same kinds of functional impairments or developmental delays. So far it is not clearly understood how various predisposing factors interrelate and how individuals react differently to a variety of stresses (17).

SIDS is a developmental disorder and its origins are during fetal development (21). It has been suggested that pregnancy-related factors could play an important role in SIDS through a suboptimal intrauterine environment (22), in which "hypoxic conditions" either in the fetus or in the newborn influence the adequate development of the "brain-cardio-respiratory axis" and eventually contribute to the development of SIDS (15). Therefore, identifying certain prenatal and perinatal factors with an increased risk of SIDS would be helpful to identify vulnerable infants (18).

The following information attempts to summarize the available evidence for and against different theories for SIDS.

2.4.1 Respiratory theories

The apparent plausibility of airway obstruction, underlying defects in respiratory control, and failure of arousal in early infancy has generated a number of hypotheses implicating respiratory failure in the causation of SIDS (79). These theories have been classified into the categories of obstructive, central, mixed and expiratory apnea (17). There has been considerable research about the infant respiratory physiology in SIDS, however, often with apparently conflicting results.

In a study by Kahn et al, 9.5% of SIDS infants were found to be cyanotic or pale during sleep at least once (80). These events occurred one to three weeks before death while none of the surviving infants presented similar manifestations, particularly surviving co-twins did not show such symptoms, despite sleeping in the same rooms and being cared for in similar ways (80). Therefore, the investigators hypothesized that these symptoms may attribute to apnea or bradycardia during sleep (80).

Apnea may be a risk factor for SIDS if it takes the form of an apparent life-threatening event (ALTE) and ALTEs may result from a wide variety of definable processes with possible causes, such as sepsis, epilepsy and aspiration (81). It seems reasonable to infer that an infant with defective autonomic control is at an increased risk of SIDS and might suffer ALTEs when exposed to particular environmental stresses (17). However, infants who had experienced these events make up only a small percentage of SIDS victims (<7%) (82). Although infants have been monitored in homes for many years, there is no evidence that morbidity or mortality has been reduced (17).

2.4.2 Cardiovascular theories

It is difficult to determine the exact percentage of deaths that have been caused by cardiac abnormalities. However, conditions such as a prolonged QT interval have accounted for approximately 2% of cases in some studies (83). Many research findings suggest that defective cardiac conduction may be implicated in some SIDS deaths with the possible terminal event being arrhythmia rather than apnea (17). However, the data are contradictory. A number of physiologic studies demonstrated apparent prolonged QT interval in infants who later died of SIDS or in the relatives of SIDS infants while some have shown normal QT intervals in SIDS infants (17). More recent work by Schwartz and colleagues showed prolonged QT intervals in certain SIDS infants, suggesting that some infants may indeed be at the increased risk of lethal arrhythmias (84). But the role of clinical screening for this defect remains uncertain (85).

Problems arising in attempting to prove a cardiac cause of SIDS include lack of antemortem ECG tracings in the majority of infants who died of SIDS, the relative insensitivity of the routine light microscopy in assessing central cardiac control pathways, and the difficulty in relating mechanisms of death to morphologic findings (17).

2.4.3 Central and peripheral nervous system theories

Central and peripheral nervous system dysfunction is thought to be the basis for a number of cardiorespiratory abnormalities observed in infants who have subsequently died of SIDS (86). Unfortunately, the current understanding of the complexities of neurophysiologic mechanisms is far from complete, and in some cases even knowledge of neuroanatomic pathways and connections is lacking (17). In spite of the inconsistencies in the literature, it is quite plausible that the neural maturational

imbalance in certain infants, combined with a general arousal deficit, makes them susceptible to cardiorespiratory dysfunction (17). Brainstem gliosis was speculated to be a reaction to previous ischemic damage and involved chronic hypoventilation, however the etiology and significance of brainstem gliosis in SIDS infants is uncertain (87). It has also been hypothesized that neuronal changes may contribute to SIDS or episodes of ALTEs, e.g. an increased number of dendritic spines in brainstem reticular neurons due to a maturational delay in neuronal function which may lead to the possibility of subsequent effects on the control of cardiorespiratory function, the reduced numbers of neurons in the hypoglossal nucleus which may contribute to upper airway obstruction by impairing normal tongue movements, and an increased neuronal degeneration or hypoplasia of the arcuate nucleus which may be another cause of disturbing central respiratory control (17).

Moreover, other theories have been proposed, including: firstly, an apparent delay in the central nervous system myelination might be associated with a developmental disorder in SIDS infants; secondly, an increased brain endorphin level may cause respiratory depression and bradycardia in infants at risk; thirdly, the abnormalities within the arcuate nucleus of the ventral medulla may finally result in the failure of an infant to rouse or respond to airway obstruction or asphyxial rebreathing; and fourthly, deranged vagal function could cause respiratory abnormalities due to hypoventilation (87). In addition, the hypothesis that the sleep states may increase susceptibility to sudden death was supported by a reduced arousal response to partial nasal obstruction in siblings of SIDS during their quiet sleep and a decreased waking time during the early morning in infants who had subsequently died of SIDS (17). However, these specific defects are

based on inconsistent findings and may have been attributed to the non-specific effects of hypoxia (20).

2.4.4 Gastrointestinal theories

The reflux of gastric contents into the upper aerodigestive tract, especially during the active sleep has been hypothesized as a cause of SIDS with a variety of different mechanisms proposed, including: acid stomach contents stimulating peripheral esophageal receptors might cause a vagally mediated fatal apnea or bradycardia; the reflux of cow's milk protein into the airways may result in a fatal anaphylaxis; or the acid damage to type II pneumocytes may compromise the surfactant production and result in alveolar collapse (17).

Cases of death due to a large amount of the gastric material being aspirated into the lungs are quite rare in infants (75,88). In the study of 196 infants and children under the age of three years, only three had the significant filling of the airways with gastric contents and three of them had been sleeping face down, with the face in a pool of vomitus in at least one case (75). In another study of 38 infants who died of SIDS, only eight had histological changes of the reflux (88). Thus, some researchers think that in the majority of cases, reflux and apnea may be independent manifestations of a more generalized developmental delay and may have a purely coincidental relationship to each other (17).

2.4.5 Microbiological theories

A variety of viruses and bacteria have been proposed as the possible agents responsible for SIDS, including respiratory syncytial virus (RSV), cytomegalovirus (CMV), and Bordetella pertussis. However, no any single infectious agent has been

isolated consistently in SIDS cases, and there is little evidence of a significant ongoing sepsis in SIDS victims (89). The occurrences of apnea in the hospitalized infants with RSV and a higher rate of CMV infection in SIDS infants added weight to the association of the virus with SIDS, however, they were not consistent with the finding that the infants dying with SIDS had a similar viral load to the neighboring age-matched controls or the controls taken from the general autopsy population (17). In addition, toxin-producing bacteria, such as clostridia, Escherichia coli, and Staphylococci were reported in SIDS infants in some studies while some other reports failed to substantiate these associations or raised the possibility of a coincidental association (17).

The significant increase of SIDS rate during a pertussis epidemic in Norway intrigued researchers as to whether a slight infection was a trigger for SIDS (90). Recently, Heininger and colleagues proposed that Bordetella pertussis is important in SIDS because they found that most of the positive cases were classified as SIDS in their study (91). However their explanation of the contribution of B pertussis to SIDS seemed difficult to justify when the bacteria are found in the same percentage of SIDS cases and the controls (44). Therefore, some researchers considered that the problem might not be the infection itself but the way SIDS cases respond to the infection (44).

Although SIDS infants and controls appear microbiologically similar, it is still possible that mild infections may contribute to lethal episodes in infants who are not fully equipped to deal with additional stresses (17). It appears unlikely that a bacterial toxin or virus in isolation could account for the majority of SIDS cases given the apparently heterogeneous nature of SIDS. However, the possibility remains that a synergistic and

additive activity among several bacterial or viral strains, compounded by the environmental factors and other risk factors, contributes to infant deaths (92).

2.4.6 Miscellaneous theories

Immunologic theories were considered due to the high incidence of SIDS in premature infants with lower immunoglobulin levels and allergic responses to a wide variety of substances (17). However, there is no evidence of increased antemortem infections in infants who died of SIDS and research shows that serum complement and cell-mediated immunity are usually normal in SIDS infants (93). A deficiency of medium-chain acylcoenzyme A dehydrogenase (MCAD) which could result in hypoglycemia has been identified as an inborn error of metabolism (94), however, there is no evidence of a significant hypoglycemia in SIDS infants (95). Furthermore, studies have not demonstrated the elevated levels of electrolytes, abnormal levels of cortisol and growth hormone, deficiencies of trace metals and various vitamins, elevated lead concentrations, and the exposure to toxic trihydride gases produced by the chemicals within mattresses in SIDS victims (17).

2.5 Triple-risk Model and Multifactorial Concept

Traditional studies usually focus on seeking out a single potential cause to be responsible for all cases of SIDS. Although a great deal of research has investigated a single cause of SIDS, such as a cardiac, respiratory or neurological disorder, it now appears that this 'syndrome' is most likely a heterogeneous entity, with not all the previous proposed causes playing significant roles (18).

SIDS appears the common endpoint for a variety of mechanisms that represent a complicated mix of predisposing factors, environmental stresses, and underlying

vulnerabilities. Different factors possibly affect infants in particular ways, so that the population of SIDS infants are quite heterogeneous, being composed of subgroups with unique predispositions and characteristics (18).

Although SIDS is diagnosed on the basis of the exclusion of the known causes of death, there are common features in most cases that have led to the notion of a triple-risk model, or "fatal triangle", for the understanding of SIDS (19). This model was proposed in 1993 to integrate the complex individual susceptibilities with developmental stages and environmental factors. The fatal triangle implies "SIDS only occurs if three conditions occur simultaneously: a vulnerable developmental stage of the central nerve system and the immune system, predisposing factors including a certain genetic pattern, and trigger events, such as a sleeping position, maternal smoking, or infection." (19).

However, the triple-risk model has recently been challenged by Guntheroth and colleagues. They supported Bergman's and Raring's concept which stated "SIDS was more likely to be of multifactorial causation with interactions of various risk factors with variable probabilities." (20). This concept was thought "less restrictive in keeping on the large number of the demonstrated risk factors with varying prevalence". Therefore, the current view is that SIDS is a multifactorial disorder influenced by developmental, environmental, and biological risk factors (44).

Based on the above mentioned theories, it would now seem appropriate for researchers to concentrate on identifying the characteristics of particular subgroups of SIDS infants with the aim of modifying specific features in infants at risk. Instead of the traditional 'single cause' research, the current approaches concentrate on developing an overall understanding of the complexities of infant physiological and pathologic

responses to a variety of intrinsic and extrinsic factors (18). Each additional factor that is identified may, therefore, hold clues to the further understanding of the mechanisms of sudden infant deaths, with the potential for preventing death for more, but undoubtedly not all, vulnerable infants.

2.6 SIDS in Twins

The rate of twinning in the United States in recent years has risen sharply from 18.9 per 1000 births in 1980 to 26.8 per 1000 births in 1997, a relative increase of 42% (4). This increase has been largely attributed to the introduction of assisted reproduction techniques, increased use of ovulation-inducing drugs, and delayed childbearing (4).

Compared with singletons, twins experience perinatal mortality rates 4 to 10 times higher (26), which were mainly attributed to the higher incidence of prematurity and lower birth weight (24,26). Twins have a 2- to 4-fold increased risk for SIDS compared with singletons (8,23-25). However, some studies found that the risk of SIDS did not appear to be higher for the twin population of live births than for the singletons after adjusting birth weight and some maternal factors, and consequently speculated that the increased frequency of SIDS among twins might be related to the higher prevalence of low birth weight and prematurity in the twin population (5,61).

It has been found that the occurrence of both twins dying of SIDS is uncommon, that the occurrence of both twins dying on the same day is extremely uncommon, and that the risk of a second twin dying of SIDS given that a first twin has already done so is unlikely higher than the risk of a temporally unrelated sibling dying of SIDS (5). Thus it was speculated that environmental factors may play a larger role in SIDS deaths among twins than hereditary factors, and that attention to the same precautions for SIDS prevention

among infants of single pregnancies, such as infant supine sleep position, is appropriate for the infants of twin pregnancies.

Moreover, a twin pair, consisting of one SIDS victim and one surviving co-twin, provides a situation with similar socioeconomic status and parental factors. This avoids differences in parental and environmental conditions in SIDS research (33).

2.7 Unique Characteristics of Twins with SIDS and Non-SIDS

Compared with singletons, twins have three unique characteristics: birth weight discordance, birth order within a pair, and sex combinations.

2.7.1 Birth weight discordance

Birth weight discordance, typically defined as a percentage difference in birth weight, is a fairly common occurrence among twins: approximately 25% of twin deliveries were affected by the discordance of at least 15%, with nearly 5% experiencing severe discordance (30% or more) (27,30,96). Therefore it is an important factor in the management of twin pregnancies.

A clinically important threshold that correlates to perinatal morbidity and mortality has not been well established. This uncertainty is partly due to conflicting data on the associated adverse perinatal outcomes (27,28). More recent studies concluded that twin birth weight discordance from more than 15% to 30% was strongly associated with perinatal death and with postnatal morbidity (30,97).

Birth weight discordance is an important contributor to twin fetal death. The divergent growth could result from intrauterine growth restriction or twin-twin transfusion syndrome, both of which carry serious implications for fetal outcomes (27,28).

Unlike fetal death, the significance of birth weight discordance as a major contributor to neonatal mortality among twins is not fully understood. Some studies didn't find a significant risk of neonatal death with the discordance and argued that the actual birth weight of each twin within the pair, rather than the difference between the twins, is the most important determinant of outcomes (97,98). However, other studies showed a clearly higher risk for neonatal mortality among discordant twins when compared with nondiscordant twins (28-30,99). In addition, it was observed that the frequencies of small-for-gestational-age infants, the admission to the neonatal intensive care unit, and the respiratory distress increased significantly as the intrapair birth weight difference increased (27,100). Furthermore, it was found that even after neonatal survival, those infants have an increased risk for long-term morbidity, including cardiomyopathy and periventricular leukomalacia (101).

Birth weight discordance is associated with obstetric interventions that appear to increase the delivery of preterm twins and correlated to the concomitant morbidity due to respiratory distress (27). Moreover, fetal malformations are related to the discordance and contribute significantly to neonatal death (27). These results suggest that the severe twin discordance increases the risk of fetal death and neonatal morbidity due to prematurity (27). Patterson and Woods concluded that prematurity could pose a greater threat to twins than birth weight discordance based on the analysis of 194 twin pairs (98). On the other hand, some studies demonstrated that intrapair birth weight discordance remained an important risk factor even after accounting for the higher rate of preterm birth, and concluded an important point related to prematurity that the increased risk of mortality

with the increased discordance was not necessarily attributable to preterm birth (27,29,99).

Twin birth weight discordance is probably a heterogeneous condition which has several different mechanisms, such as disorders of the placenta, chronic twin-twin transfusion, congenital anomalies and possibly cigarette smoking (30,99). Among them, the disorder of placental blood flow appears to be the most common cause of birth weight discordance, and cigarette smoking is known to affect placental function (99). This is supported by a twin study in that the decreased placental weight and increased umbilical cord abnormalities were observed with the severe discordance (102).

Previous studies found that birth weight discordance tended to be larger among twin pairs in which one or both twins died of SIDS than those in which both twins survived (5,23). If the birth weights of twins within a pair were significantly different, it was observed that usually the smaller twin died of SIDS (23,33). SIDS infants were also reported to be smaller and lighter than their surviving co-twins, possibly because of some fetal growth retardation (33). However, these studies did not establish a clinically important threshold correlating birth weight discordance to SIDS.

2.7.2 Birth order within twin pairs

Several studies showed that, compared with first-born twins, those delivered second carried increased risks of perinatal mortality (24,31). Moreover, second-born twins were more vulnerable to labor and delivery complications than first-born twins (32).

Thus, several hypotheses have been proposed to explain the increased mortality in second-born twins compared with first-born twins, including: "1) risk of oxygen deficiency in the second-born twin due to premature separation of the placenta after the

delivery of the first twins; 2) reduced placental circulation; 3) increased interval between delivery of the two fetuses, and therefore, increased oxygen deficiency; 4) a tendency of macerated fetuses to be delivered after the birth of a liveborn twin; and 5) more frequent breech delivery among second-born twins" (103).

Sheay and colleagues recently found that second-born twins had slightly higher rates of low and very low birth weight compared with first-born twins, and also higher rates of the factors related to complications of delivery: breech presentation, cesarean delivery, and fetal distress (103). In addition, they observed that the increased risk of perinatal death in second-born twins with RR 1.37 (1.32-1.42) was chiefly driven by an increase in the number of stillborn twins delivered second with RR 2.46 (2.29-2.63) (103). On the other hand, they reported that the risk of neonatal mortality or postneonatal mortality was similar between first- and second-born twins, with RR 0.99 (0.95-1.04) and RR 1.02 (0.93-1.13), respectively (103). Sheay's study confirmed an earlier report that second-born twins were considerably more likely to have the growth restriction than first-born twins (96). Another study also demonstrated that second-born twins had three to six times the risk of being the smaller infants when there was at least 25% discordance within twin pairs (104).

The previous studies reported that the rate of SIDS for the first delivered twins was only 3 per 1000 live births but rose to 7 per1000 live births for the second (9,24,34). However, Kahn's study found that SIDS victims tended to be first born even though this difference was not statistically significant (33). Therefore, studies of the birth order within twin pairs as a risk factor for SIDS have produced inconsistent results.

2.7.3 Sex combinations

Little is known about twin morbidity and mortality with respect to zygosity. Since the biology of monozygotic (MZ) and dizygotic (DZ) twin pregnancies is profoundly different, it is often expected that twin pregnancies of different zygosity experience different risks for various complications and birth outcomes (105). It is known that the risk of mortality is higher in MZ pregnancies where twins are sharing a placenta (106). However, zygosity is not known from the birth certificate data. As a result, the Weinberg rule is usually used to convert the results of different sex (DS) versus same sex (SS) twins to those of DZ versus MZ, based on the assumption that there are the same numbers of DZ twins in SS as in DS twins (105). Among three types of twin pairs, SS includes Male-Male (M-M) and Female-Female (F-F) while DS refers to Male-Female (M-F) or Female-Male (F-M).

Previous studies have demonstrated that male twins had 20% to 30% higher infant mortality rates than female twins and SS twins had an increased risk of mortality than DS twins (24). A retrospective cohort study found that the RR 1.1 (0.9-1.2) of complications of pregnancies comparing DZ to MZ twins was slightly higher than RR 1.0 (1.0-1.1) comparing DS to SS twins (105). Another cohort study reported that the fetal sex and sex concordance were associated with preterm, with the highest preterm birth rate in MM, intermediate rate in FF and the lowest rate in FM/MF twin pairs (107).

Since the risk of SIDS is higher in males than in females, the assessment of the relationship between sex combinations and SIDS might be biased towards M-M > M-F/F-M > F-F (8). However, inverse results have been observed in a large-scale twin study which reported that FF, MF, and MM accounted for 41.3%, 31.0% and 27.6%,

respectively, of the twin pairs with at least one SIDS death, while their corresponding proportions were 34.6%, 30.5%, and 34.9% of the twin pairs with two surviving twins (5). In addition, another one study reported RR 1.5 (0.4-5.1) of SIDS comparing DS to SS in first-born twins and 0.2 (0.1-1.7) in second-born twins (105).

2.8 Recommended Interventions to Decrease SIDS

The purpose of recommending the interventions is to reduce the incidence of SIDS, with minimal adverse effects. Although the specific cause of SIDS remains unknown, we do have some knowledge of certain risk factors from observational data. While researchers continue to search for the physiologic or anatomic abnormalities responsible for SIDS deaths, the national and local education campaigns, based on the research of the leading risk factors for SIDS, have been effective in reducing the risk for and rates of SIDS (53). For example, in Canada, the following key messages are being recommended to the society based on the latest research (38): "1) Put your baby on his or her back to sleep; 2) Make sure no one smokes around your baby; 3) Avoid putting too many clothes and covers on your baby...". The dramatic decline in the rates of SIDS following these campaigns is a major achievement for epidemiology (108).

3. METHODOLOGY

3.1 Study Design

This is a retrospective cohort study based on a large twin registry data in the United States for the period of 1995-1997. The scheme of the study methodology is presented in Chart-1 and the details of the methodology are described in the following sections.

3.2 Material

3.2.1 Twins data

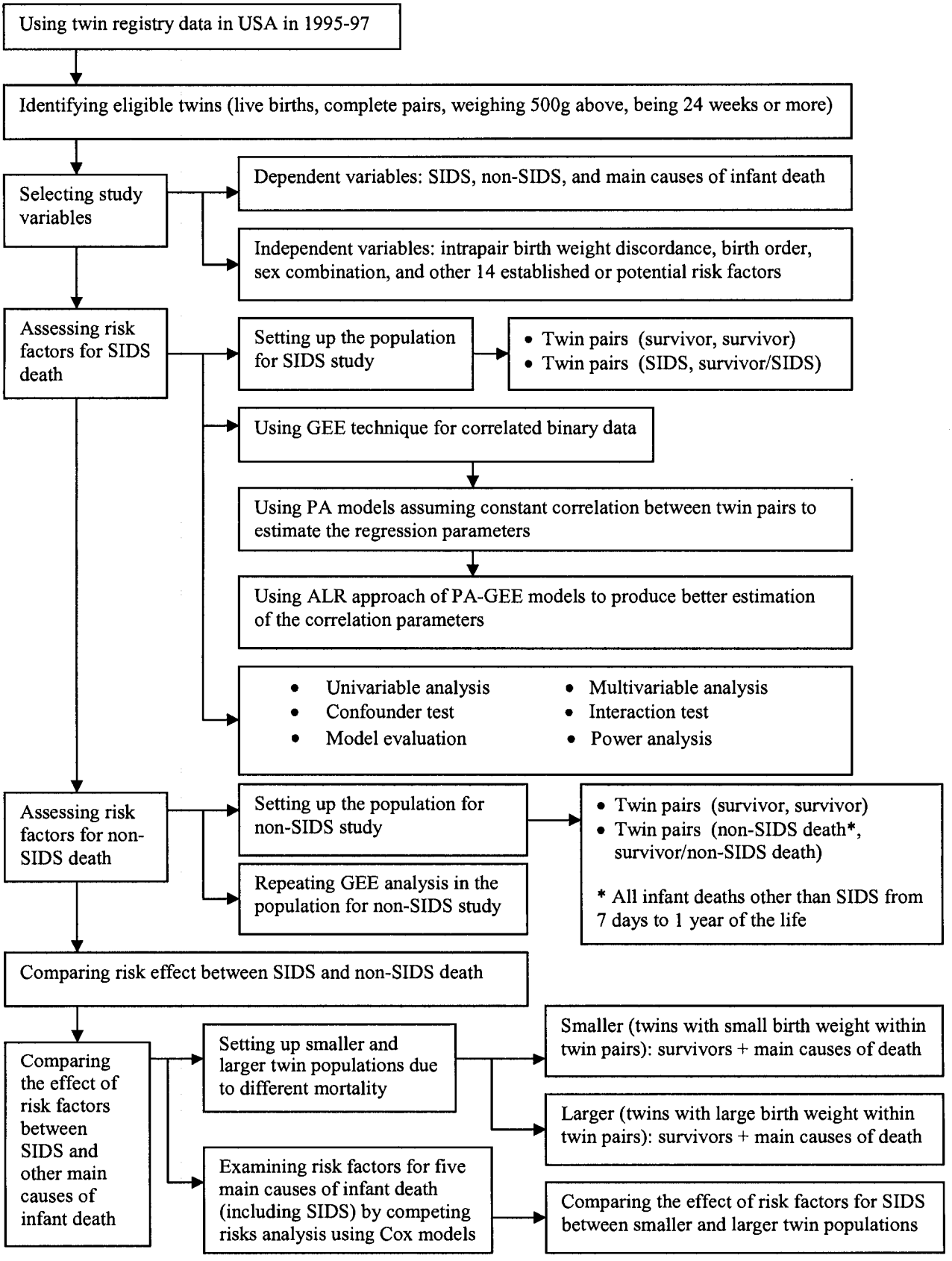
The Centers for Disease Control and Prevention's Matched Multiple Birth File 1995-1997 was used for the study (67). An example of the observations and variables in the data set is showed in Table-2, in which each row represents an individual twin and each column represents a variable for each individual twin.

Table 2 - Observations and variables in the study data set

Observation Numbers (for every individual twin)	**Variables**								
	V1 Live birth	V2 **ID#** (for every twin pair)	V3 Birth weight (grams)	V4 Birth order within a pair	V5 Sex	V6 Age of mother	V7 ICD code	V8 Age at death (days)	Vn ...
1	Live birth	**1**	2480	First-born	Female	32	.	.	
2	Live birth	**1**	2550	Second-born	Female	32	.	.	
3	Live birth	**2**	3129	First-born	Male	21	.	.	
4	Live birth	**2**	2765	Second-born	Male	21	798.0	118	
5	Live birth	**3**	2340	First-born	Male	39	.	.	
6	Live birth	**3**	2320	Second-born	Female	39	.	.	
...									

As the basis of this data file, the 1997 period linked national birth/infant death data set was created taking advantage of two existing data sources: State linked files for the identification of linked birth and infant death certificates, and National Center for Health Statistics (NCHS) natality and mortality computerized statistical files (67). The latter one includes statistical data from birth and death certificates provided by States under the Vital Statistics Cooperative Program (VSCP). The data have been coded according to

Chart 1 - Scheme of the study methodology



uniform coding specifications, have passed rigid quality control standards, and have been edited and reviewed before being the basis for official U.S. birth and death statistics (67).

Since all States have adopted laws requiring the registration of births and deaths, more than 99 percent of the births and deaths occurring in the United States are registered (67). In statistical tabulations, the United States refers only to the aggregate of the 50 States (including New York City) and the District of Columbia (67).

The U.S. Standard Certificate of Live Birth and the U.S. Standard Certificate of Death are used as the principal means to attain uniformity in the contents of documents when collecting information on births and deaths, respectively. They could be modified by each State for the particular needs. However the certificates of most States conform closely in content and arrangement to the standards. The certificates have been revised periodically by the national vital statistics agency through abroad consultation. The revision procedure has ensured careful evaluation of each item in terms of its current and future usefulness for legal, medical and health, demographic, and research purposes. New items would be added when necessary, and old items would be modified to ensure better reporting or, in some cases, dropped when their usefulness appeared to be limited (67).

There is verification at the State level before the data are sent to NCHS. In the VSCP, States are required to have an error rate of less than 2.0 percent for each item for 3 consecutive data months during the initial qualifying period (67). Once a State is qualified, NCHS monitors the quality of data received. The quality control was achieved in NCHS through independent verification of a sample of records for some States as well as comparing the State data with data from previous years. Each sample record is independently coded by NCHS staff and compared to the State code assignments.

Differences between NCHS and State are adjudicated to ascertain the source of the error and need for corrective action (67). The demographic coding for 100 percent of the certificates was independently verified and the estimated average outgoing error rate for all demographic items was 0.25 percent in 1995 (67). In addition, editing procedures ensure that records with inconsistent or impossible codes are modified. Further, the certifier or a State health officer confirms conditions specified on a list of infrequent or rare causes of death and statistical clerks verify all subsequent operations in tabulating and in preparing tables during the computer processing (67).

In the United States, all States routinely link infant death certificates to their corresponding birth certificates for legal and statistical purposes. When the birth and death of an infant occur in different States, copies of the records are exchanged by the State of death and State of birth in order to keep a link. After the initial linkage in national files, NCHS returns computer lists of unlinked infant death certificates to the States where the death occurred for follow up linking. After incorporating state additions and corrections, a final national linked file is produced. Most States link a high percentage of infant deaths, thus the national overall percent linked for infant deaths is 97.9% in 1997 period linked birth/infant death data set (67).

Based on above, this multiple births database includes sociodemographic information about the infants and mothers, obstetric history of mothers, complications of the index pregnancy, as well as labor and neonatal outcomes. For infant deaths, the age at death and cause of death were also recorded. Twin pairs were labeled with a unique identifier allowing the first and second members of a pair to be linked together. Twin pairs were identified by matching on plurality (twins, triplet, quadruplet, etc), state and county of

occurrence of delivery, mother's date of birth, date of last menstrual period, number of prenatal visits, level of education of the mother, weight gain during pregnancy, and date of delivery (67)

This matched multiple births data file, with a total of 301,626 individual live twin births and 398 SIDS deaths, permitted a more in-depth analysis of the characteristics of SIDS among twin births.

3.2.2 Study populations

Since SIDS only occurs in live births, all fetal deaths were excluded in the analysis. In order to focus on SIDS among twins, incomplete twin pairs (i.e. only one twin is eligible within the twin pair) were also excluded. In addition, live births weighing less than 500g or being less than 24 weeks' gestational age were excluded because non-SIDS infant mortality rate is virtually 100% in this group (109). In addition, excluding this group could avoid "errors in gestational age estimation and to minimize interstate differences in reporting live births that were at borderline of viability" (15). In other words, only live-born twins within matched complete twin pairs, weighing greater than 500g and being 24 weeks' gestational age or more were eligible for this study. Based on this selection, various study populations were created for the following analyses to achieve different research objectives.

3.3 Variables of Interest

3.3.1 Dependent variables

The primary outcome of the study is SIDS, which was identified by the ICD-9 code 798.0 and occurred in a postperinatal period (7-364 days of life), as the previous research studied (5,109).

Cause-of-death statistics in the data set are based on the underlying cause of death, a simple and one-dimensional statistic, to identify the initiating cause of death. The underlying cause is selected from an array of conditions reported in the medical certification section on the death certificate (67). The certifiers translate the conditions into medical codes through use of the classification structure and the selection and modification rules contained in the ICD-9, thus the reliability and accuracy of cause-of-death highly rely on the ability of the certifiers to make the proper diagnosis and their care when recording this information on the death certificate (67). NCHS has employed computerized coding of the underlying cause on the death certificate to eliminate intercoder variation by consistently applying the same criteria in computer (67).

There is no well-defined program to systematically assess the quality of medical certifications reported on death certificates or to measure the error effects on the levels and trends of cause-of-death statistics (67). However, the proportion of death certificates coded to the symptoms, signs, and ill-defined conditions (ICD-9: 780-799, including SIDS 798.0) can be used as one index of the quality of reporting causes of death, because this proportion indicates the care and consideration given to the certification by the medical certifier (67). The percent of deaths assigned to this category in NCHS data set has declined slightly from 1.5 percent in 1987 to 1.2 percent in 1995 (67). In addition, using NCHS quality control procedures, the average outgoing error rate for underlying cause data in 1995 was estimated at 2.8 percent for the 41 states sending electronic files and 3.6 percent for the remaining 9 states (67). The improvement of reporting "the quality index" from 1987 to 1995 and the low error rates for underlying cause data in 1995 make us confident in using this coding as reliable.

In order to investigate specific risk factors for SIDS, the effects of risk factors were compared between SIDS and non-SIDS deaths at the same lifetime. Correspondingly, non-SIDS infant death in the first part GEE analysis of this study was defined as any death of an infant during 7-364 days of life other than SIDS. On the other hand, since some main causes of infant death such as congenital anomalies and immaturity could occur during 0-6 days of life, as competing risks of SIDS, specific main causes of infant death were extended to 0-364 days of life in the second part survival analysis to compare risk factors for each individual main cause of infant death including SIDS.

3.3.2 Independent variables

In this study, total 17 independent variables of interest were identified, including 3 unique characteristics of twins as primary exposure variables, 10 previously established risk factors as confounders, and 4 clinically relevant factors as potential confounders.

3.3.2.1 Primary exposure variables

Birth weight discordance(BWD): This is a new variable created by, within a twin pair, subtracting the birth weight of the smaller twin from that of the larger twin and dividing the difference by the birth weight of the larger twin (28,29). Since there is no established clinical threshold correlating birth weight discordance to postperinatal morbidity and mortality (27,28,30,97), the continuous variable birth weight discordance cannot be categorized by the clinically meaningful cut-offs. If we treat this variable as continuous, the regression coefficients will predict outcome changes for 1% birth weight discordance and this is not clinically meaningful. As a result, the percent difference of birth weight was categorized into quintiles, i.e. categorizing this continuous variable into 5 groups (q1 to q5), each of which contains 20% of the data, and producing 4 cut-offs of

the birth weight discordance percentage (20th, 40th, 60th, and 80th percentile) (110). For example, the upper limit value is 5% of birth weight discordance in q1 group, which means that 20% the observations (birth weight discordance percentage) is less than 5%. Among the 5 groups, q1 was used as the reference category in the analysis.

Birth order within twin pairs: This variable indicates whether the twin was the first- or second-born. The group of the first-born twins was the reference in the analysis.

Sex combinations: This is a new variable created by classifying the gender combinations in each twin pair as M-M, F-F, and M-F/F-M. The group of F-F was used as the reference in the analysis.

3.3.2.2 Established confounding variables

Based on the assessment of the risk factors for SIDS in previous large-scale studies (5,9,11,25,51), the following established risk factors were included in the analysis as confounders. Keeping consistent with those previous studies (5,9,11,25,51) and consulting clinical experts, these variables were categorized into different groups as described below.

Maternal age: very young (<20 years), young (20-24 years), medium (25-29 years), and old (>=30 years); *race of mother*: black, other races and white; *education of mother*: before high school (0-11 years), high school graduation (12 years), college (13-15 years), and university (>=16 years); *marital status of mother*: unmarried or married; *prenatal care*: no prenatal care, late prenatal care (started in the second or third trimester), and normal prenatal care (started in the first trimester); *tobacco use during pregnancy*: yes or no; *gestational age*: very preterm (24-31 weeks), preterm (32-36 weeks), and

term/postterm (>=37 weeks); *sex of infant*: male or female; and *5 minute APGAR score*: abnormal (<7) or normal (>=7).

Fetal growth: This variable was measured by birth weight-for-gestational-age Z-score and was calculated by the following formula (111):

Z = (observed birth weight – mean birth weight) / SD

where mean birth weight and standard deviation refer to sex- and gestational age-specific birth weight of this study population, i.e. they were based on sex-specific births at the observed gestational age in completed weeks. Fetal growth was further categorized into small-for-gestational-age (SGA, Z-score <10^{th} percentile), large-for-gestational-age (LGA, Z-score >90^{th} percentile), and appropriate-for-gestational-age (AGA, Z-score 10-90^{th} percentile) (62,111).

The last categorical level of each variable above was used as reference in the analysis.

3.3.2.3 Potential confounding variables

Based on previous studies (14,15,51) and clinical experts' opinions, the following variables related to clinical practice were added as potential confounders.

Mode of delivery: Two modes were involved, cesarean delivery and vaginal delivery. The former included the primary and repeat cesarean delivery and the latter included the vaginal birth even after a previous cesarean delivery.

Medical risk factors: Based on the reported information (67) on anemia, cardiac disease, acute or chronic lung disease, diabetes, genital herpes, hemoglobinopathy, chronic hypertension, pregnancy-associated hypertension, eclampsia, renal disease, and RH sensitization, this variable was coded as "factor reported = Yes" if any one or more of the above diseases were reported, "factor reported = No" if none of the above diseases

were reported, or "Unknown" if "factor not on certificate" or "factor not classifiable" was reported for any of the diseases.

Obstetric complications: Similarly, based on the reported information on hydramnios, incompetent cervix, uterine bleeding, moderate/heavy meconium, abruptio placenta, placenta previa, and cord prolapse, this variable was coded as "Yes", "No" or "Unknown" for the obstetric complications mentioned.

Abnormal conditions of the newborn: Similarly, based on the reported information on hyaline membrane disease, meconium aspiration syndrome, 30 minutes or more assisted ventilation, and seizures, this variable was coded as "Yes", "No", or "Unknown" for the abnormal conditions mentioned.

3.4 Statistical Analysis

3.4.1 GEE analysis for the risk factors of SIDS

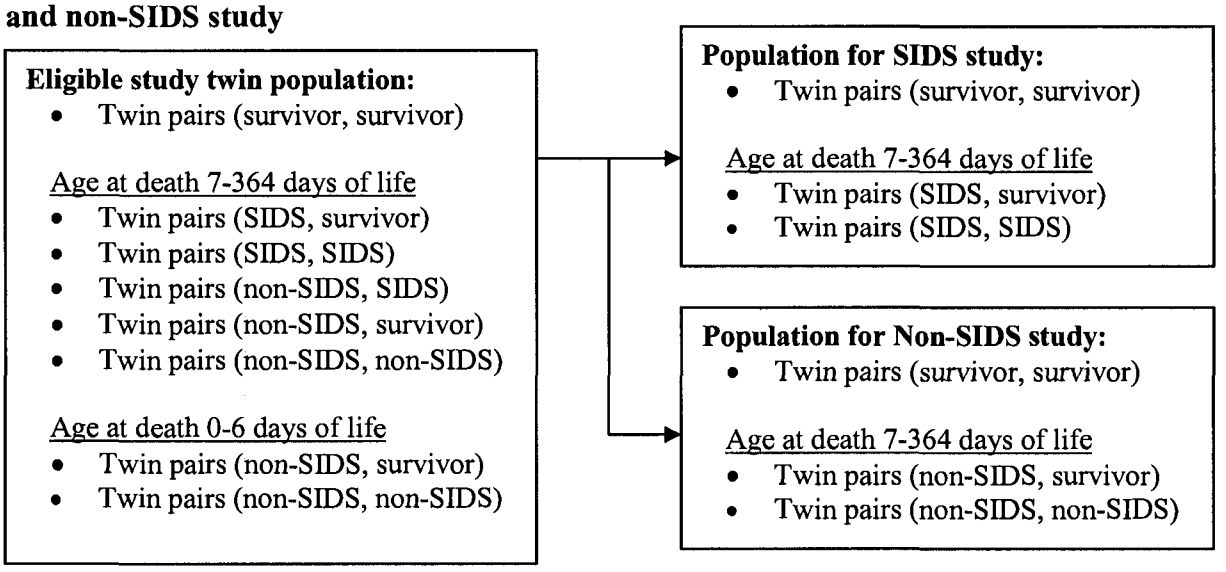
The first goal of generalized estimating equations (GEE) analysis was to examine the relationship between SIDS deaths and three unique characteristics of twins: birth weight discordances, birth order within twin pairs and sex combinations, before and after adjusting for various potential confounding factors.

The second goal was to determine which risk factors are specific for SIDS rather than postperinatal deaths in general, i.e., comparing effects of various risk factors for SIDS and non-SIDS deaths. Consequently, the same analysis method used for SIDS was repeated for non-SIDS infant deaths and then odds ratios of the risk factors were compared between the two populations.

3.4.1.1 Populations for SIDS and non-SIDS study

Chart-2 shows the composition of eligible study twins in the populations for SIDS and non-SIDS study. Among the eligible study twin population, the population for SIDS study was selected by excluding all infant deaths other than SIDS by the end of their first life year as well as individual surviving twins within the incomplete twin pairs caused by the non-SIDS exclusion. Generally speaking, the population for SIDS study was made up of two types of twin pairs: most twin pairs with two surviving twins and a few twin pairs with at least one twin died of SIDS.

Chart 2 - Composition of eligible study twin population and populations for SIDS and non-SIDS study



To compare with SIDS, a postperinatal death (7-364 days of life), the population for non-SIDS study was selected from the same eligible study twin population by excluding all SIDS deaths and non-SIDS deaths within 0-6 days of life as well as individual surviving twins within the incomplete twin pairs caused by these exclusions. Similarly, the population for non-SIDS study also included two types of twin pairs: most twin pairs

with two surviving twins and a few twin pairs with at least one twin suffering various infant deaths at 7-364 days of their life other than SIDS.

Apparently, the most twin pairs with two surviving twins are same between the two populations for SIDS and non-SIDS study while a few twin pairs with various causes of infant death are different. Because of the large overall sample sizes and relatively small event numbers of these two populations, the populations for SIDS and non-SIDS study should be highly similar and the results of GEE analysis based on them should be comparable.

3.4.1.2 Data description and rates of SIDS and non-SIDS

The distributions of maternal and infant characteristics in twins with SIDS were described by various potential risk factors. The overall rate of SIDS was calculated by dividing the number of SIDS deaths by the total number of twins in the population for SIDS study and was expressed as a rate per 1000 live births. Rates of SIDS were further calculated per 1000 live births in each stratum of various risk factors. The same methods were applied to calculate the distributions of those characteristics and rates of non-SIDS deaths in the population for non-SIDS study for comparison.

3.4.1.3 GEE method

In this analysis, present or absent SIDS was the outcome measurement for each individual twin within each twin pair. The investigation of SIDS in relation to total 17 potential or previous risk factors was conducted. Similarly, GEE analysis was repeated to investigate the same risk factors for non-SIDS deaths. The results of the risk effects were compared between SIDS and non-SIDS deaths.

- **Correlated binary data**

Each twin pair, as a cluster, has two individual twins who tend to be more like one another than any two singletons. This non-independence results in the study outcome, SIDS observations, of two individual twins within a pair being correlated, which is commonly referred to as the within-cluster correlation (112). Some of the covariates of the study are measured for each twin within a pair with unique values (e.g. birth weight and birth order) while some are measured for the pair as a whole with same values (e.g. mothers' variables). The former ones are referred to as cluster-specific covariates and the latter ones as cluster-level covariates (113).

Logistic regression is a conventional statistical method for analyzing binary response data. However, the fundamental lack of independence in SIDS observations within twin pairs violates the independence assumption upon which many likelihood and quasi-likelihood models are based (114). In other words, logistic regression models with likelihood function can not address within-cluster correlation. Ignoring this correlation would lead to unreliable variance estimates and statistically inefficient estimates of the regression parameters (115).

Liang and Zeger provided a practical method - generalized estimating equations (GEE) to handle correlated binary data (116), which has been applied in some twin studies and multiple birth data (15,29,112,117). Ananth and colleagues compared the ordinary logistic regression (OLR) models and GEE-based logistic regression models in the analysis of perinatal mortality in relation to different perinatal risk factors in the same twin population as that used in this study, and found that the variance estimates from OLR models for cluster-level covariates 7-71% smaller than those from GEE-based

models and more obvious underestimation for cluster-specific covariates. Based on that, they concluded that the implications of ignoring within-cluster correlation could be substantial (112).

In another multiple birth study to examine the association between birth order and binary health outcomes, Davidov and colleagues compared three methodological approaches available: GEE, conditional logistic regression (CLR), and mixed effects models (MEM), and concluded that GEE and MEM were preferable to CLR because of their flexibility and efficiency. Furthermore, their simulation results indicated that GEE was more powerful than MEM (117).

Therefore, logistic regression using GEE was chosen in our study to adjust the correlation between the binary outcomes, SIDS of twins, within twin pairs.

- **Exchangeable correlation and robust sandwich variance estimation**

Unlike the estimating equation in a likelihood-based model, GEE is obtained by generalizing another estimating equations that look like weighted versions of the likelihood equations, and the weights involve an approximation of the underlying covariance matrix of the correlated within-cluster observations (113). In most applications, exchangeable correlation, one of the correlation structures, is used as the working correlation in GEE while the correlation between clusters of outcomes is assumed to be constant (114).

The effects of extra correlation because of non-independent outcome observations are commonly taken into account by an empirical robust sandwich-type variance estimator to incorporate it into the estimation of the standard errors of the estimated coefficients (112,113,116). The outer pieces of the sandwich estimator are based on the observed

information matrix under the assumption of exchangeable correlation, and the middle of the sandwich is an information matrix that uses empirical residuals to estimate the within-cluster covariance matrix, i.e. the sums of the contributions in each cluster (113).

All GEE models consider an estimating equation in two parts: estimating the regression parameters and estimating the association parameters. The estimated coefficients and estimated standard errors of GEE models can be used to estimate odds ratios (114).

Here, each twin pair is a cluster and every individual twin is the subject within the cluster, i.e. the individual twin is the unit of analysis in this study. SAS GENMOD procedure was used to perform the GEE analysis and the "REPEATED" statement in the GENMOD procedure was used to fit a GEE model (118).

- **Population-averaged models**

There are two different models most frequently used to address the correlated data in GEE: A population-averaged (PA) model handling the within-cluster dependence by averaging effects over all clusters and a subject-specific (SS) model addressing the within-cluster dependence by introducing specific cluster-level random components. The difference between the parameters from PA and SS models is that a SS model fully parameterizes the distribution of the population while a PA model parameterizes only the marginal distribution of the population (115). As a result, the PA model is more useful to assess exposure effects in epidemiological studies through the outcome observations in larger groups while the SS model is more useful to provide inferences incorporating individual subject covariate values (113).

Since our study interest was the comparison of SIDS in a large twin population with and without various risk factors but not to estimate how the cessation of these risk factors decreased the chance of SIDS, PA models were selected for this analysis.

If the binary outcome Y_{ij} (coded 0/1) denoted SIDS for the jth twin ($1 \leq j \leq 2$) from the ith twin pair ($1 \leq i \leq K$), z_{ij} denoted a vector of cluster-specific covariates, and x_{ij} denoted a vector of cluster-level covariates, the probability of SIDS was as below which was assumed to follow a logistic regression structure:

$$\mu_{ij} = \Pr(Y_{ij} = 1 \mid z_{ij}, x_{ij})$$

Based on a marginal regression framework, the PA model was:

$$\log\left[\frac{\mu_{ij}}{1-\mu_{ij}}\right] = \alpha + \gamma z_{ij} + \beta x_i$$

where α, the intercept, was an estimate of the log-odds of the baseline risk of SIDS when z_{ij} and x_i were set to zero; γ and β, the marginal regression coefficients related to cluster-specific and cluster-level covariates, respectively, indicated difference in the average of SIDS across twin pairs (112). In this way, the probability of SIDS reflected the proportion of SIDS among twins with different risk factors in the whole population. This was without regard to a specific twin or mother.

- **Alternating logistic regression (ALR)**

Marginal PA-GEE models permit modeling of the relationship of the response with explanatory variables and provide efficient estimates of regression coefficients β for correlated binary data (119). However, when the association among responses is one of the research focuses, e.g. considering whether SIDS tends to aggregate in families after accounting for common environmental factors or the situation that both twins died of

SIDS or non-SIDS in some twin pairs, the estimates of correlation parameters α obtained by first-order estimating equations in PA-GEE models could be seriously inefficient (120). Hence second-order estimating equations are necessary to provide more efficient estimates for α (116,119).

ALR procedure combines the first-order GEE for estimating β with new logistic regression equations for estimating α as second-order estimating equations (119). This approach obtains the estimated correlation by fitting a logistic regression model to the pairwise odds ratios (121).

$$OddsRatio(y_{ij}, y_{ik}) = \frac{\Pr(y_{ij}=1, y_{ik}=1)\Pr(y_{ij}=0, y_{ik}=0)}{\Pr(y_{ij}=0, y_{ik}=1)\Pr(y_{ij}=1, y_{ik}=0)}$$

In other words, the log odds ratios are used in a logistic regression to estimate the correlation matrix (116). This algorithm iterates between a logistic regression using first-order GEE to estimate regression coefficients β and a logistic regression of each response on others from the same cluster using an appropriate offset to update the odds ratio parameters α (119,121). "LOGOR=", instead of "CORR=", can be used in the REPEATED statement in the SAS GENMOD procedure to specify correlations estimated by log odds ratios (121,122).

Since not only were we interested in the relationship of the SIDS with various risk factors but also considering the association between SIDS observations within each twin pair, ALR was used for this analysis, based on the above standard PA-GEE model, to produce better estimation of the association. The software packages were not available to select variables for fitting correlated data models like stepwise, therefore the purposeful selection was conducted using Wald tests with PA models in the following steps.

3.4.1.4 Univariable analysis

Each of 17 independent variables of interest was put into 17 ALR PA-GEE models containing single independent variable one by one. Before univariable analysis, a contingency table of SIDS (yes, no) versus the different levels of independent variables was done and checked in order to avoid a zero cell.

Since the SAS program provided Wald-type testing of coefficients after the model estimation using either the naïve or the modified sandwich estimate of variance, Wald test was chosen to evaluate the coefficient of individual independent variables (113)

The crude odds ratios with 95 percent confidence intervals of each independent variable were obtained using one of the levels as the reference group. The same way was applied in non-SIDS univariable analysis and the comparison of crude odds ratio of each variable was conducted between SIDS and non-SIDS deaths.

3.4.1.5 Multivariable analysis

After completion of the univariable analyses, any variable with p-value < 0.25 was considered as a candidate for the multivariable model along with all variables of known clinical importance (123). Since we were interested in all 17 independent variables as primary study variables, existing confounders or potential confounders, all of them were included in the multivariable model, regardless of their 'statistical significance', in order to completely control confounding as much as possible. Similar to the univariable analyses, the adjusted odds ratios with 95 percent confidence intervals of each independent variable were obtained using the same level as the reference group. The same criteria were applied in non-SIDS multivariable analysis and comparison of adjusted odds ratios was conducted between SIDS and non-SIDS deaths. Model

overfitting was considered by observing unrealistically large estimated coefficients and /or estimated standard errors.

3.4.1.6 Test of confounders

Confounder is a covariate that is associated with a primary independent variable, and also a risk factor for the outcome variable of interest, but not an intermediate step between the outcome and the primary independent variable. When the both associations are present then the relationship between the study risk factor and the outcome variable could be confounded (124).

To test whether the 10 established risk factors and 4 clinically potential risk factors were confounders of the 3 primary exposure variables in this study, the estimated coefficients of the 3 primary exposure variables from the model containing and not containing each of the 14 other variables were compared to check for the confounder status of these 14 variables. The change in coefficient estimate of the 3 primary exposure variables by more than 10% was thought to be a good indicator of confounding, i.e. [(coefficient of each of 3 primary exposure variables without the potential confounder – coefficient of the same exposure variable with the potential confounder) / coefficient of the same exposure variable with the potential confounder] > 10% (125).

3.4.1.7 Interaction test

Effect modification occurs when the direction or magnitude of an association between the study exposure and the outcome varies at different levels of a third factor (124). Effect modifier here is a risk factor that interacts with one of three primary exposure variables. When the interaction term was both clinically meaningful and statistically

significant after added to the model, that risk factor, a covariate, was considered an effect modifier of the corresponding primary exposure variable.

In this study, to test interactions between each of 3 primary exposure variables and any of the covariates with a strong effect on SIDS, all of these interactions were included in the multivariable GEE model one by one and their Wald statistics examined the statistical significance. Only statistically significant interactions were included in the final multivariable GEE model.

3.4.1.8 Model evaluation

It is a challenge as to how to assess the adequacy of the fitted GEE models because the residuals within cluster are correlated. Although several goodness of fit (GOF) statistics have been proposed, there is no sufficient comparison and evaluation of these methods (126).

Hardin and Hilbe cataloged and introduced techniques for assessing PA-GEE model adequacy and proposed that a complete assessment should use several of these techniques (127). Evans and Li recently evaluated and compared several GOF statistics for logistic GEE models, and found that the performance of each GOF statistics varied under various scenarios. Similarly, they also suggested researchers to alternatively use GOF statistics to compliment each other but not to rely on a single one. In addition, Evans and Li indicated that these statistics actually evaluated the evidence of 'lack of fit' and consequently that a non-significant GOF test didn't provide sufficient evidence of model fit. On the other hand, researchers should ensure that the fitted models were biologically supported (126).

Based on the real situation above and considering our limitations of accessing to the software packages which support these tests as well as to analysts for programming,

Deviance and Pearson Chi-Square shown in the SAS output were used as measures to assess PA-GEE models fit here. Models were judged to be adequate if the value/DF of deviance was close to zero as well as the value/DF of Pearson Chi-Square was close to 1.

3.4.1.9 Power analysis

If non-significant results (p>0.05) were obtained in this study, a retrospective power calculation would be performed. As an "after the fact" power analysis, it would provide information on the power of this study based on detectable effect difference with real involved sample size (128). If the study power was enough, the non-significant study results could be interpreted more clinically.

Since ALR and GEE were similar to logistic regression analysis, power analysis in logistic regression was applied in this study. Therefore, the formula of simple size calculation in a multivariable logistic regression model was used to obtain retrospective study power based on original sample size in this study (113).

$$n = \frac{(1+2P_0)}{1-\rho^2} \times \frac{\left(z_{1-\alpha/2}\sqrt{\frac{1}{1-\pi}+\frac{1}{\pi}} + z_{1-\theta}\sqrt{\frac{1}{1-\pi}+\frac{1}{\pi e^{\beta_1^*}}} \right)^2}{P_0\beta_1^{*2}}$$

where $\pi = P(X = 0)$ denoted the fraction of subjects in the study expected to have x=0 (unexposed); ρ^2 was the squared multiple correlation of the covariate of interest and the remaining p-1 covariates in the model; P_0 was the estimated probability of the outcome with all covariates equal to zero.

$$P_0 = \frac{e^{\alpha}}{1+e^{\alpha}}$$

For this kind of power analysis, the number of events per covariate was a key element in assessing adequate data to fit a particular model. The rule of 10 required that

the minimum observed frequency was 10 in the contingency table of outcome by covariate to avoid problems of over estimation and under estimation of variances as well as the poor coverage of Wald-based confidence intervals and Wald tests of coefficients. The number of events might determine the performance of model-based estimates more than the total simple size here (113).

3.4.2 Competing risks analysis of SIDS

Although previous studies have demonstrated that SIDS and non-SIDS infant deaths share some important risk factors, some associations differ. Consideration of similarities and differences between associations of risk factors with SIDS and other main causes of infant death could help clarify disease mechanisms and elucidate the impact of potential interventions on these infant deaths.

To compare explicitly the relative risks of SIDS and other main causes of infant death, i.e. SIDS's competing events, associated with various risk factors, competing risks analysis was conducted using survival models based on the various causes of infant death and age at death recorded in the data set.

3.4.2.1 Main causes of infant death by functional groups

Using coded underlying cause of death to compare the characteristics of cause-specific infant mortality is sometimes difficult because there are often a number of potential causes for an infant death or certain diagnostic codes do not make clinical sense (36). International Collaborative Effort (ICE) recommended a system to group underlying causes of infant death, coded from the ICD-9, following a functional classification on main causes of infant death (36). The common features in each functional group indicate the needs for prevention and treatment (36).

To compare risk effects between SIDS and other main causes of infant death, the underlying causes of infant death coded in ICD-9 were grouped into eight functional categories according to ICE functional classification (36). The eight groups consisted of congenital anomalies, asphyxia related conditions, immaturity related conditions, infections, sudden infant death, deaths due to external causes, specific conditions other than the above, and remaining causes comprised by 'other and unclassifiable' diagnoses.

In order to focus our study interest on SIDS and main causes of infant death, the last three functional groups, death due to external causes, other specific conditions, and remaining causes, were ignored in this analysis due to their heterogeneity and lack of specificity.

3.4.2.2 Smaller and larger twin populations

The eligible study twins here were obtained by deleting infant deaths with external causes, other specific conditions and remaining causes as well as incomplete twin pairs from the study twin population used in GEE analysis. In other words, infant deaths with congenital anomalies, asphyxia, immaturity, infections, sudden infant death as well as survival twins in complete twin pairs were used in this competing risks analysis.

Because of the higher infant mortality risk in twins with smaller birth weight (28,29) and the technical limitations to handle cluster data in survival analysis, the competing risks analysis was conducted separately on the two twin populations: twins with smaller birth weight and twins with larger birth weight. Therefore, the twin pairs with equal birth weights were excluded and then two individual twins within each of eligible twin pairs were divided into two study groups by their different birth weights.

As a result, any two individual twins are independent of each other within either smaller or larger twin population, in terms of the occurrence of the outcome. The unit of analysis is still an individual twin, and two populations have the same number of total twins but different numbers of infant death.

3.4.2.3 Incidence rates of main causes of infant death in smaller and larger twins

The incidence rates of five main causes of infant death, including SIDS, were calculated separately in smaller twin population. Each rate was obtained by dividing the number of infant death due to a single cause among smaller twins by the total number of the smaller twin population and was expressed as a rate per 1000 live births. Similar calculations were applied in the larger twin population.

3.4.2.4 Method of competing risks analysis

In competing risks analysis, the occurrence of one type of event removes the individual from the risk of the other event types (129). This method permits an unbiased analysis of competing events by fitting cause-specific models separately for each type of events, using cumulative incidence function and treating any subject who experiences an event but does not experience the event of interest as censored (130,131). However, the assumption should be made that censoring must be noninformative, i.e. subjects who are at high risk of one event type are no more likely to experience other types of events, accounting for observed risk factors (129). Cox proportional hazards models can be fitted for the effects of covariates across event types, and log-log survivor functions for each type of events can be used to estimate whether the type-specific hazard functions are same for all event types (129).

In this analysis, the infant deaths were classified into five types according to causes. Since each dead twin was given only one primary cause of death in the original data set (67), it was reasonable to follow the assumption that one individual twin who died of one of five main causes of death was no longer at the risk of dying of the other four. A separate cause-specific hazard was estimated for each cause of infant death as follows (129):

$$h_{ij}(t) = \lim_{\Delta t \to 0} \frac{\Pr\{t \le T_i < t + \Delta t, J_i = j | T_i \ge t\}}{\Delta t}, j = 1,...,5$$

where T_i denoted the time of death for twin i; J_i denoted the cause of infant death that occurred to twin i; $H_{ij}(t)$ was defined as the hazard for the cause of death j at time t for twin i. The overall hazard of infant death was just the sum of all the cause-specific hazards:

$$h_i(t) = \sum_j h_{ij}(t).$$

In addition, log-log survivor functions, *log [-log S(t)]*, were estimated using PROC LIFETEST to provide graphic examination of proportionality for each of the five causes of death. If the hazards were proportional, the log-log survivor functions should be parallel (129).

Within this competing risks framework, Cox models were fitted with PROC PHREG to estimate the covariate effects on the cause-specific hazard function for SIDS and other four main causes of death of interest. The dependent variable was an infant's reported age at death measured in days, the multiple event types of interest were five main causes of infant death in the five functional groups, and the covariates were the 17 risk factors investigated in GEE analysis.

$$\log h_{ij}(t) = \alpha_j(t) + \beta_j x_i(t), j = 1,...,5$$

where $x_i(t)$ was a vector of covariates varying with time, β_j indicated that the effects of the covariates different from the causes of death, and $\alpha_j(t)$ allowed the dependence of the hazard on time to vary across the causes of infant death (129).

There were five single Cox models for the five main causes of infant death to be estimated. Each of them focused on one cause of death by treating others as censoring. Thus, the coefficients, indicating the effect of the covariates, were compared across different causes of infant death. Likelihood-ratio chi-square statistic was used to test whether the differences of the coefficients across different causes of death were merely the result of the random variation based on –2 x log-likelihood reported in PROC PHREG output (129).

3.4.2.5 Comparison of log survivor curves by main causes of infant death

Since different causes of infant death have different distribution of age-at-death, a graph about various causes of infant death versus age-at-death should be helpful to understand the difference among these main causes of death. Although graphs based on the survivor function are certainly useful, we are more interested in the comparison of the hazard function of the five main causes of death in this study. Log survivor functions, $-\log \hat{S}(t)$, often referred as the cumulative hazard function, could provide information about whether the hazard is constant, increasing, or decreasing with time by observing the shape of the curves, i.e. an upward log survivor function curve is the evidence for an increasing hazard with time while a downward curve suggests a decreasing hazard (129). Hence, five log survivor curves for the five main causes of infant death were compared.

3.4.2.6 Risk factors with main causes of infant death in smaller and larger twins

Competing risks survival analysis was conducted separately in smaller twins and larger twins. All reported hazard ratios and their 95 percent confidence intervals were tabulated for comparing the associations between different risk factors and different main causes of death.

3.5 Missing Values

It was expected that there might be missing values in such a large national data set. Two steps were used to deal with this issue in this study.

- Observing whether the pattern of the missing values was random, by comparing the frequencies and coefficients of all levels of various variables before and after deleting missing values.
- Deleting missing values if they occurred in less than 5% of the subjects while keeping the missing values in the analysis if they occurred in more than 5% of the subjects as a separate category.

4. RESULTS

4.1 Eligible Study Twin Population

There are 308,013 individual twins with 398 SIDS cases in the original database. Among them, 14,335 individual twins were excluded because of 6,387 fetal deaths, 3,547 twins within incomplete pairs, 7,127 twins with gestational age less than 24 weeks, and 5,774 twins with birth weight less than 500g. Some excluded twins had more than one ineligible factor. Corresponding to these ineligible twins, their 2,306 co-twins within the incomplete twins were excluded. Therefore, 291,372 eligible twins with 392 SIDS were kept in the data set. (Please refer to Appendix A-1 for details.)

As proposed, subjects with missing values more than 5% for each study factor of interest were retained in the main analysis. As a result, 273,130 eligible study twins with 362 SIDS were available for the following analysis. (Please refer to Appendix A-2 for details.)

4.2 GEE Analysis for the Risk Factors of SIDS

4.2.1 Data sets

4.2.1.1 Data set for SIDS study

After excluding the twins with all infant deaths other than SIDS and their consequently co-twins within the incomplete pairs from the above eligible study twins, the data set for SIDS study consisted of 359 twins with SIDS and 266,627 surviving twins. In this data set, there were 133,136 twin pairs with two surviving twins to account for 99.73% of the population for SIDS study and 2 twin pairs within each of which two twins died of SIDS. (Please refer to Appendix A-3 for details.)

4.2.1.2 Data set for non-SIDS study

Similarly, after excluding the twins with age at death less than 7 days and the twins with SIDS as well as their consequently co-twins within the incomplete pairs from the same eligible study twin population, the data set for non-SIDS study consisted of 1,607 twins with deaths other than SIDS and 26,7671 surviving twins. In this data set, there were 133,136 twin pairs with two surviving twins to account for 98.88% of the population for non-SIDS study and 104 twin pairs within each of which two twins died of various non-SIDS at 7-364 days of their life. (Please refer to Appendix A-3 for details.)

As a result, 99.73% of the population for SIDS study and 98.88% of the population for non-SIDS study are the same surviving twins within 133,136 complete twin pairs.

4.2.2 Rates of SIDS and non-SIDS deaths

From Table-3, the distributions of maternal and infant characteristics of surviving twins were nearly same in the data sets for SIDS and non-SIDS study. Compared with those in their corresponding surviving twins, the higher proportions of MM combination, very young (<20 years) and young maternal age (20-24 years), black mothers, mothers' education lower than college, unmarried status of mothers, no or late prenatal care, tobacco use during pregnancy, very pre-term (24-31 weeks), male twins, twins with SGA, abnormal 5 minute APGAR scores, reported obstetric complications, and reported abnormal conditions of the newborns were observed in both twins with SIDS and twins with non-SIDS deaths. On the other hand, twins with SIDS had higher proportions in small birth weight discordance (q2: 3.2-6.9%), first-born twins, vaginal delivery, and reported medical risk factors of mothers, while twins with non-SIDS deaths had higher proportions in large birth weight discordance (q5: 17.7-84.6%), second-born twins, and

cesarean delivery. In addition, the proportions of very pre-term, abnormal 5 minute APGAR score and abnormal conditions of the newborns in twins with non-SIDS deaths were much higher than those in twins with SIDS.

SIDS death rate of twins within the completed pairs was 1.3 per 1000 live births while non-SIDS overall death rate was 6 per 1000 live births. In Figure-1, comparing the SIDS death rates in different status of each of the three primary exposure factors, the highest ones for each factor were 1.6, 1.4, and 1.7 per 1000 live births in small birth weight discordance (q2: 3.2-6.9%), first-born twins, and MM combination, respectively. Discrepantly, the non-SIDS death rates for each main study factor were high to 9.3, 6.5, and 7 in large birth weight discordance (q5: 17.7-84.6%), second-born twins and MM combination.

For other existing and potential risk factors showed in Figure-2, the highest SIDS death rates were 3.7 per 1000 live births in infants born to mothers who smoked during pregnancy, 3.7 per 1000 live births in infants born to mothers without prenatal care, and 3.1 per 1000 live births in infants of young mothers (<25 years). Following them, SIDS rate was 2.7 per 1000 live births in black mothers and mothers' education before high school and 2.6 per 1000 live births in unmarried status of mothers or infants with small-for-gestational-age. Non-SIDS death rates were always higher than SIDS rates in different status of each risk factor, and the trend was similar to that of SIDS, except for the extremely high rates, 38.2, 50.8 and 30.6 per 1000 live births in very pre-term (24-31 weeks) infants, infants with abnormal 5-minute APGAR score, and reported abnormal conditions of newborns, respectively.

Table 3 – Percentage distribution of maternal and infant characteristics in twins with SIDS and non-SIDS deaths by various risk factors, 1995-97 USA matched multiple birth file (continue)

Variables	Twins with SIDS		Twins with Non-SIDS	
	SIDS deaths (%) (n=359)	Survival (%) (n=266,627)	Non-SIDS deaths (%) (n=1,607)	Survival (%) (n=267,671)
Quintile of percentage of BWD				
q5 (17.7-84.6%)	20.61	19.69	30.80	19.75
q4 (11.3-17.7%)	20.61	20.06	17.05	20.05
q3 (6.9-11.3%)	17.55	20.07	17.11	20.06
q2 (3.2-6.9%)	24.23	20.07	16.12	20.05
q1 (0-3.2%)	16.99	20.01	18.92	20.09
Birth order within twin pairs				
First	46.80	44.63	40.88	44.65
Second	44.29	44.63	48.91	44.61
Not stated	8.91	10.74	10.21	10.74
Sex combination				
MM	42.34	33.37	39.39	33.39
FM / MF	31.20	33.18	27.38	33.16
FF	26.46	33.45	33.23	33.45
Maternal age (Years)				
<20	16.16	6.90	14.31	6.92
20-24	43.45	18.73	26.45	18.74
25-29	20.33	27.39	26.14	27.39
>=30	20.06	46.98	33.11	46.94
Maternal race				
White	63.23	79.92	67.39	79.87
Black	32.87	16.41	28.06	16.45
Others	3.90	3.67	4.54	3.68
Maternal education (Years)				
Before high school (0-11)	32.87	16.11	24.95	16.13
High school graduation (12)	40.39	31.58	35.97	31.58
College (13-15)	21.45	23.48	20.04	23.47
University (>=16)	5.29	28.83	19.04	28.81
Marital status of mother				
Married	47.63	73.15	58.43	73.10
Unmarried	52.37	26.85	41.57	26.90
Month of prenatal care began				
First trimester	74.65	85.85	79.34	85.83
2nd-3rd trimester	22.84	13.24	17.98	13.25
No care	2.51	0.91	2.68	0.92

Table 3 – Percentage distribution of maternal and infant characteristics in twins with SIDS and non-SIDS deaths by various risk factors, 1995-97 USA matched multiple birth file

Variables	Twins with SIDS		Twins with Non-SIDS	
	SIDS deaths (%) (n=359)	Survival (%) (n=266,627)	Non-SIDS deaths (%) (n=1,607)	Survival (%) (n=267,671)
Tobacco use during pregnancy				
Yes	27.02	9.69	14.13	9.69
No	55.99	70.92	67.95	70.92
Unknown	16.99	19.39	17.92	19.39
Gestation (Weeks)				
Very preterm (24-31)	12.26	8.05	54.82	8.28
Preterm (32-36)	52.09	43.60	27.38	43.51
Term & postterm (>=37)	35.65	48.35	17.80	48.21
Sex				
Male	58.77	49.96	54.45	49.96
Female	41.23	50.04	45.55	50.04
Z-score of birth weight for gestation				
SGA (<10th percentile)	18.66	9.76	20.54	9.77
LGA (>90th percentile)	4.74	10.16	3.80	10.14
AGA (10th-90th percentile)	76.60	80.08	75.67	80.10
Five minute APGAR score				
<7	2.51	2.09	19.10	2.14
>=7	77.72	77.19	57.13	77.12
Unknown	19.78	20.72	23.77	20.74
Method of delivery				
C-section	50.97	54.24	61.29	54.29
Vaginal	49.03	45.76	38.71	45.71
Medical risk factors of mother				
Reported	20.89	17.07	15.56	17.05
Not reported	70.19	74.02	74.11	74.03
Unknown	8.91	8.91	10.33	8.92
Obstetric complications				
Reported	9.47	6.18	12.69	6.21
Not reported	81.89	85.40	78.28	85.37
Unknown	8.64	8.42	9.02	8.42
Abnormal conditions of the newborns				
Reported	6.13	5.42	29.00	5.51
Not reported	91.64	89.56	66.21	89.46
Unknown	2.23	5.02	4.79	5.03

Figure-1: Comparison of death rates between SIDS and Non-SIDS across the three primary exposure variables

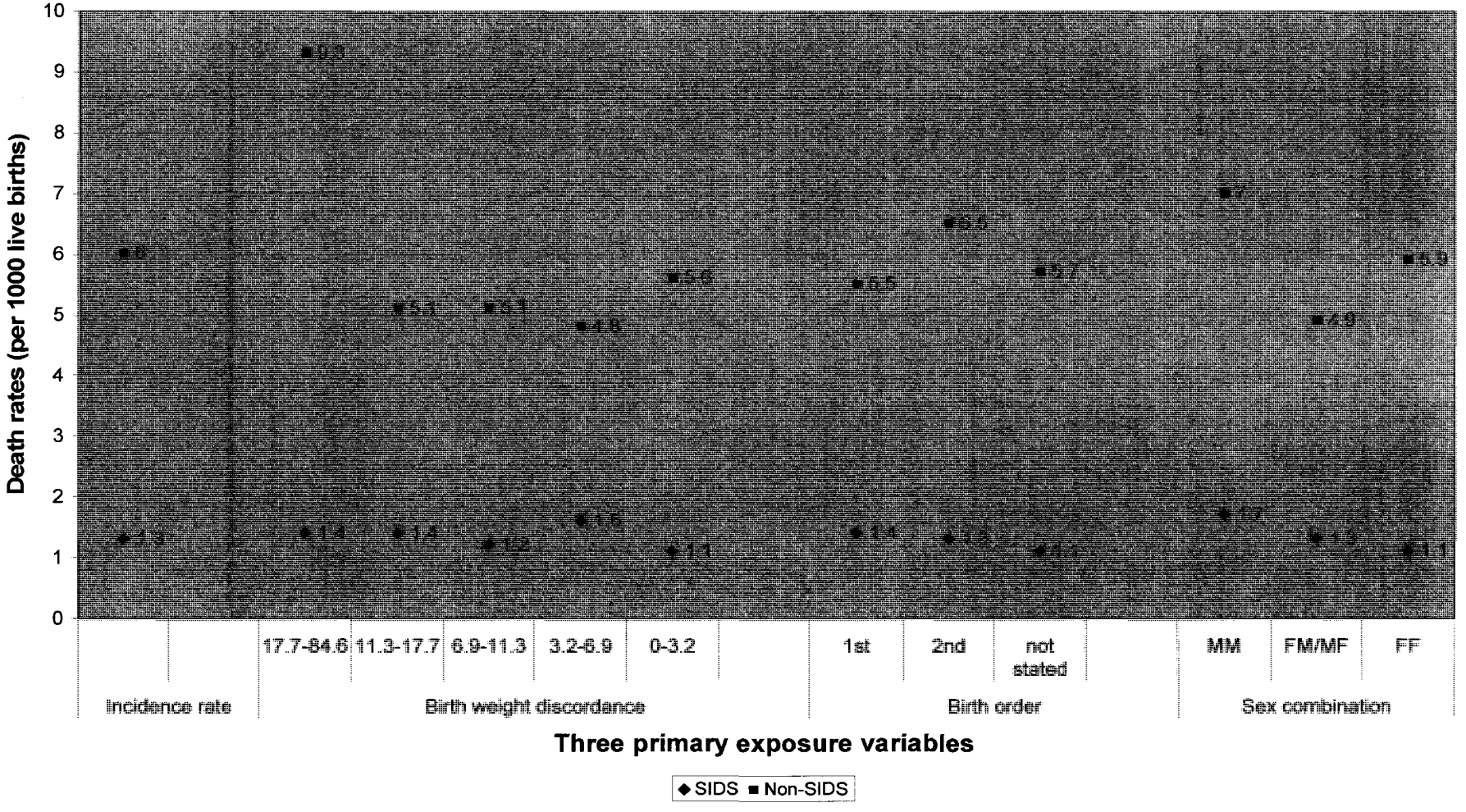
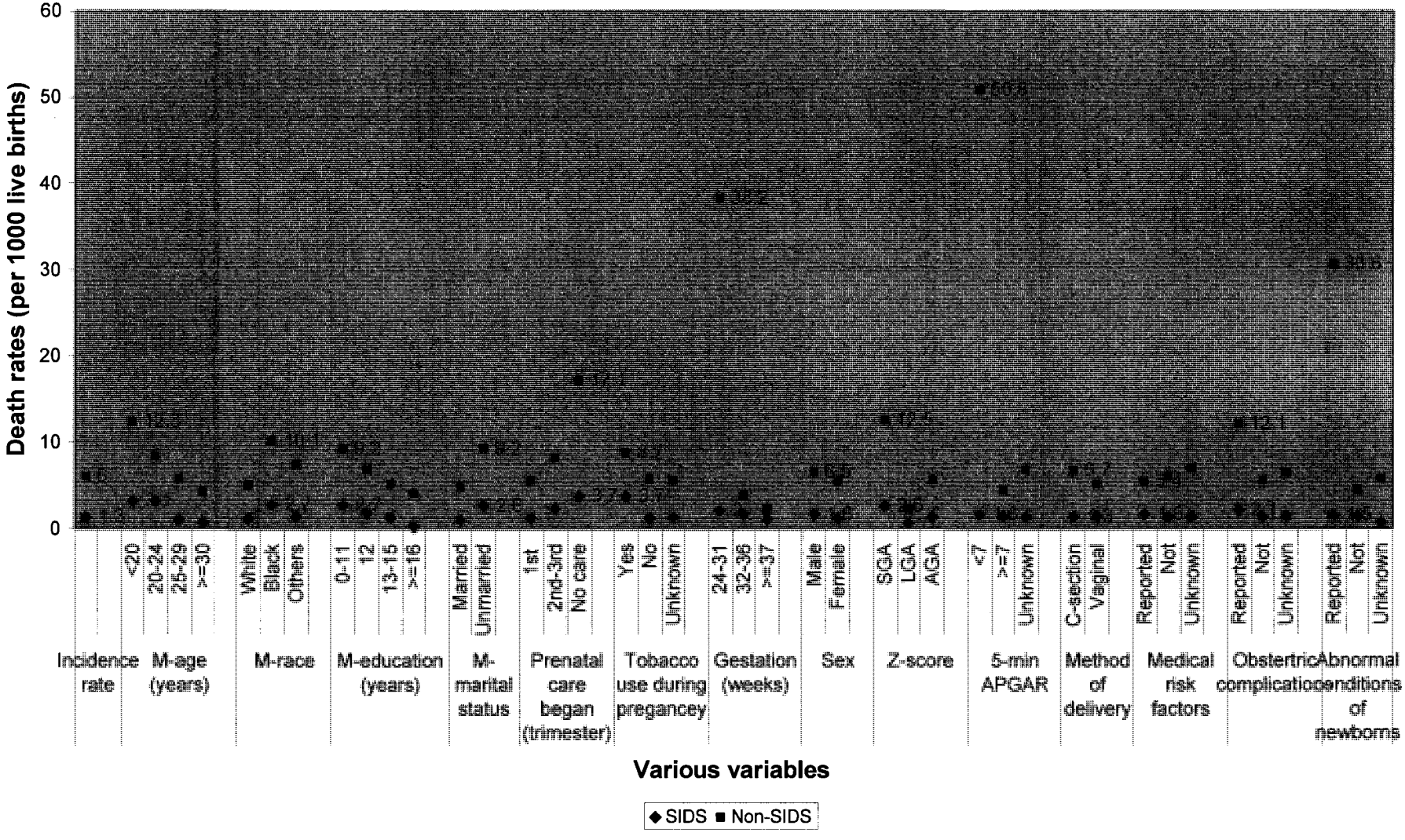


Figure-2: Comparison of death rates between SIDS and non-SIDS across the various variables other than three primary exposure variables



4.2.3 Risk factors of SIDS

The associations between different risk factors and SIDS were evaluated by GEE analysis and compared with the associations between the same risk factors and non-SIDS.

4.2.3.1 Crude and adjusted odds ratios (ORs)

Table-4 shows the crude and adjusted ORs of three primary risk factors and other factors through univariable and multivariable GEE analyses. In the univariable analysis, the associations were positive between SIDS and q2 of percentage of birth weight discordance (BWD) (3.2-6.9%), MM combination, younger maternal age, black mothers, lower education, unmarried status of mothers, no and late prenatal care, tobacco use during pregnancy, very pre-term and pre-term twins, male twins, small z-scores of birth weight-for-gestational-age (SGA), and reported obstetric complications. However, after adjusting for existing and potential confounders, MM combination, unmarried status, no and late prenatal care, and male twins were not associated with SIDS any more.

4.2.3.2 Confounders

Among 17 independent factors, the 14 existing and potential risk factors were checked whether they were confounders of the three primary exposure variables.

Among these 14 factors, maternal age and z-score of birth weight-for-gestational-age were the confounders for the three primary exposure variables; mother's race and gestation confounded the association between birth weight discordance and SIDS; mother's education, tobacco use during the pregnancy and abnormal conditions of newborn were confounders of birth order; mother race, tobacco use, and sex were confounders of sex combination. The rest of factors, i.e. marital status, prenatal care, 5-minute APGAR score, method of delivery, medical risk factors, and obstetric

Table 4 - Comparison of odds ratios and 95 percent confidence intervals for SIDS and non-SIDS deaths in relation to various risk factors, 1995-97 USA matched multiple birth file (continue)

Variable	Univariable analysis		Multivariable analysis	
	OR[+] for SIDS	OR[+] for Non-SIDS	OR[*] for SIDS	OR[*] for Non-SIDS
Quintile of BWD%				
q5 (17.7-84.6%)	1.24 (0.88, 1.74)	1.66 (1.44, 1.91)	1.15 (0.81, 1.63)	1.31 (1.11, 1.53)
q4 (11.3-17.7%)	1.22 (0.87, 1.71)	0.90 (0.77, 1.06)	1.21 (0.86, 1.70)	0.96 (0.80, 1.15)
q3 (6.9-11.3%)	1.03 (0.73, 1.47)	0.91 (0.77, 1.07)	1.05 (0.74, 1.49)	0.93 (0.78, 1.11)
q2 (3.2-6.9%)	1.43 (1.03, 1.99)	0.85 (0.72, 1.01)	1.45 (1.04, 2.02)	0.87 (0.72, 1.04)
q1 (0-3.2%)	1	1	1	1
Birth order within twin pairs				
First	1	1	1	1
Second	0.95 (0.76, 1.17)	1.20 (1.08, 1.33)	0.94 (0.76, 1.17)	1.14 (1.03, 1.26)
Not stated	0.79 (0.54, 1.16)	1.04 (0.87, 1.23)	0.83 (0.57, 1.23)	1.12 (0.93, 1.35)
Sex combination				
MM	1.60 (1.24, 2.08)	1.19 (1.06, 1.33)	1.43 (0.91, 2.25)	0.86 (0.69, 1.08)
FM / MF	1.19 (0.90, 1.56)	0.83 (0.73, 0.94)	1.19 (0.85, 1.66)	0.80 (0.67, 0.95)
FF	1	1	1	1
Maternal age (Years)				
<20	5.48 (3.88, 7.75)	2.93 (2.51, 3.42)	2.68 (1.81, 3.98)	1.62 (1.32, 1.98)
20-24	5.43 (4.10, 7.19)	2.00 (1.76, 2.27)	3.22 (2.38, 4.36)	1.43 (1.23, 1.66)
25-29	1.74 (1.26, 2.41)	1.35 (1.19, 1.54)	1.40 (1.00, 1.94)	1.20 (1.04, 1.37)
>=30	1	1	1	1
Maternal race				
White	1	1	1	1
Black	2.53 (2.02, 3.17)	2.02 (1.81, 2.26)	1.71 (1.32, 2.21)	1.33 (1.16, 1.52)
Others	1.34 (0.78, 2.30)	1.46 (1.15, 1.86)	1.49 (0.86, 2.57)	1.36 (1.04, 1.76)
Maternal education (Years)				
Before high school (0-11)	11.11 (6.84, 18.05)	2.34 (2.02, 2.72)	3.64 (2.14, 6.20)	1.14 (0.94, 1.39)
High school graduation (12)	6.97 (4.32, 11.25)	1.72 (1.50, 1.98)	3.09 (1.88, 5.08)	1.12 (0.95, 1.32)
College (13-15)	4.98 (3.01, 8.22)	1.29 (1.10, 1.51)	2.95 (1.77, 4.92)	1.00 (0.84, 1.18)
University (>=16)	1	1	1	1
Marital status of mother				
Married	1	1	1	1
Unmarried	2.99 (2.43, 3.69)	1.93 (1.75, 2.14)	1.14 (0.87, 1.49)	1.06 (0.93, 1.21)
Month of prenatal care began				
First trimester	1	1	1	1
2nd-3rd trimester	1.98 (1.55, 2.55)	1.47 (1.29, 1.67)	1.16 (0.90, 1.51)	1.19 (1.03, 1.39)
No care	3.15 (1.62, 6.12)	3.13 (2.31, 4.26)	1.40 (0.71, 2.74)	1.12 (0.80, 1.57)

Table 4 - Comparison of odds ratios and 95 percent confidence intervals for SIDS and non-SIDS deaths in relation to various risk factors, 1995-97 USA matched multiple birth file

Variable	Univariable analysis		Multivariable analysis	
	OR+ for SIDS	OR+ for Non-SIDS	OR* for SIDS	OR* for Non-SIDS
Tobacco use during pregnancy				
Yes	3.53 (2.76, 4.51)	1.52 (1.32, 1.76)	2.64 (2.02, 3.44)	1.26 (1.07, 1.48)
No	1	1	1	1
Unknown	1.11 (0.83, 1.48)	0.96 (0.85, 1.10)	1.29 (0.88, 1.90)	0.76 (0.61, 0.96)
Gestation (Weeks)				
Very preterm (24-31)	2.06 (1.47, 2.91)	17.94 (15.69, 20.51)	1.87 (1.30, 2.68)	11.79 (9.98, 13.93)
Preterm (32-36)	1.62 (1.29, 2.03)	1.70 (1.47, 1.98)	1.60 (1.27, 2.01)	1.59 (1.36, 1.86)
Term & postterm (>=37)	1	1	1	1
Sex				
Male	1.43 (1.15, 1.76)	1.20 (1.08, 1.32)	1.12 (0.77, 1.63)	1.26 (1.04, 1.52)
Female	1	1	1	1
Z-score of birth weight for gestation				
SGA (<10th percentile)	1.99 (1.52, 2.60)	2.23 (1.97, 2.52)	1.63 (1.23, 2.15)	2.52 (2.20, 2.88)
LGA (>90th percentile)	0.49 (0.30, 0.79)	0.40 (0.31, 0.51)	0.56 (0.34, 0.91)	0.48 (0.36, 0.63)
AGA (10th - 90th percentile)	1	1	1	1
Five minute APGAR score				
<7	1.18 (0.61, 2.31)	12.04 (10.55, 13.74)	0.79 (0.40, 1.56)	3.13 (2.67, 3.67)
>=7	1	1	1	1
Unknown	0.95 (0.73, 1.23)	1.55 (1.37, 1.74)	0.89 (0.58, 1.35)	2.10 (1.66, 2.66)
Method of delivery				
C-section	0.88 (0.71, 1.08)	1.33 (1.21, 1.47)	0.90 (0.73, 1.12)	1.02 (0.91, 1.14)
Vaginal	1	1	1	1
Medical risk factors of mother				
Reported	1.29 (1.00, 1.67)	0.91 (0.79, 1.04)	1.29 (0.99, 1.69)	0.85 (0.73, 0.98)
Not reported	1	1	1	1
Unknown	1.05 (0.73, 1.52)	1.16 (0.98, 1.36)	0.99 (0.54, 1.81)	0.96 (0.71, 1.30)
Obstetric complications				
Reported	1.60 (1.12, 2.28)	2.23 (1.92, 2.59)	1.54 (1.07, 2.21)	1.09 (0.92, 1.29)
Not reported	1	1	1	1
Unknown	1.07 (0.74, 1.55)	1.17 (0.98, 1.39)	1.23 (0.62, 2.42)	0.69 (0.49, 0.97)
Abnormal conditions of the newborns				
Reported	1.10 (0.72, 1.70)	7.11 (6.37, 7.94)	0.75 (0.48, 1.18)	2.11 (1.83, 2.43)
Not reported	1	1	1	1
Unknown	0.43 (0.22, 0.87)	1.29 (1.02, 1.62)	0.47 (0.23, 0.96)	1.15 (0.89, 1.47)

OR+: Crude odds ratio OR*: Adjusted odds ratio

complications, were not confounders of any one of the three primary exposure factors.

4.2.3.3 Interactions

None of the interactions between each of the three primary exposure variables and three covariates with the strongest effects on SIDS (mother's education, maternal age, and tobacco use during the pregnancy) were both statistically and clinically significant, after bringing them one by one into the multivariable GEE model.

4.2.3.4 Model evaluation

Deviance and Pearson Chi-Square were used for model evaluation. The ranges of the values of deviance/DF and the Pearson Chi-Square/DF were 0.0205-0.0189 and 0.9803-1.000, respectively, in the models of univariable and multivariable GEE analysis for SIDS study; and similar results were for non-SIDS study. Therefore the models were considered adequate. (Please refer to Appendix B for details.)

4.2.3.5 Power analysis

Since the largest quintile of percentage of birth weight difference (q5: 17.7-84.6%), second birth order within twin pairs, and MM sex combination were not associated with SIDS, a retrospective power calculation was performed by these three variables based on the detectable effect difference with the real involved sample size in this study. ρ^2 the squared multiple correlation was assigned different values as 0.1, 0.5 and 0.9 in the calculation. From Table-5, most calculated study powers reached 90% or more.

4.2.4 Risk factors of non-SIDS

Same GEE method was applied to investigate the 17 independent variables for non-SIDS. From Table-4, the significant crude and adjusted ORs were observed in the largest quintile of percentage of birth weight difference (q5: 17.7-84.6%), second birth order,

Table 5 – Study power analysis

Variable	Study power	ρ^2	$\alpha(P_0)$	$z_{1-\alpha/2}$	β_1	n (Sample size)	No. of Exposure	π (Unexposure /sample size)
q5 of percentage of BWD	95.6%	0.1	-9.2676	1.96	0.1412	266,986	52,564	0.8
	96.2%	0.5						
	97.1%	0.9						
Second birth order	96.3%	0.1			-0.0625		119,161	0.55
	96.6%	0.5						
	97.0%	0.9						
MM	88.9%	0.1			0.3579		89,130	0.67
	92.5%	0.5						
	96.2%	0.9						

younger maternal age, black and other race of mother, late prenatal care began, tobacco use during pregnancy, preterm, male twins, smaller z-score of birth weight for gestational age (SGA), abnormal 5-minute APGAR score, and reported abnormal conditions of the newborns, while those in FM/MF sex combination and larger z-score of birth weight for gestational age (LGA) were significant inversely. Among them, very preterm had an extremely high adjusted OR 11.79 (95% CI: 9.98, 13.93). On the other hand, the adjusted ORs were not significant in MM twins, low maternal education, unmarried marital status of mother, C-section, and obstetric complications, even though these variables had significant crude ORs.

4.2.5 Comparison of risk factors between SIDS and non-SIDS

The comparison of the risk effects of 17 independent variables between SIDS and non-SIDS is showed in Figure-3. The larger birth weight difference, second-born order,

Figure 3 - Comparison of significant adjusted odds ratios between SIDS and non-SIDS (continue)

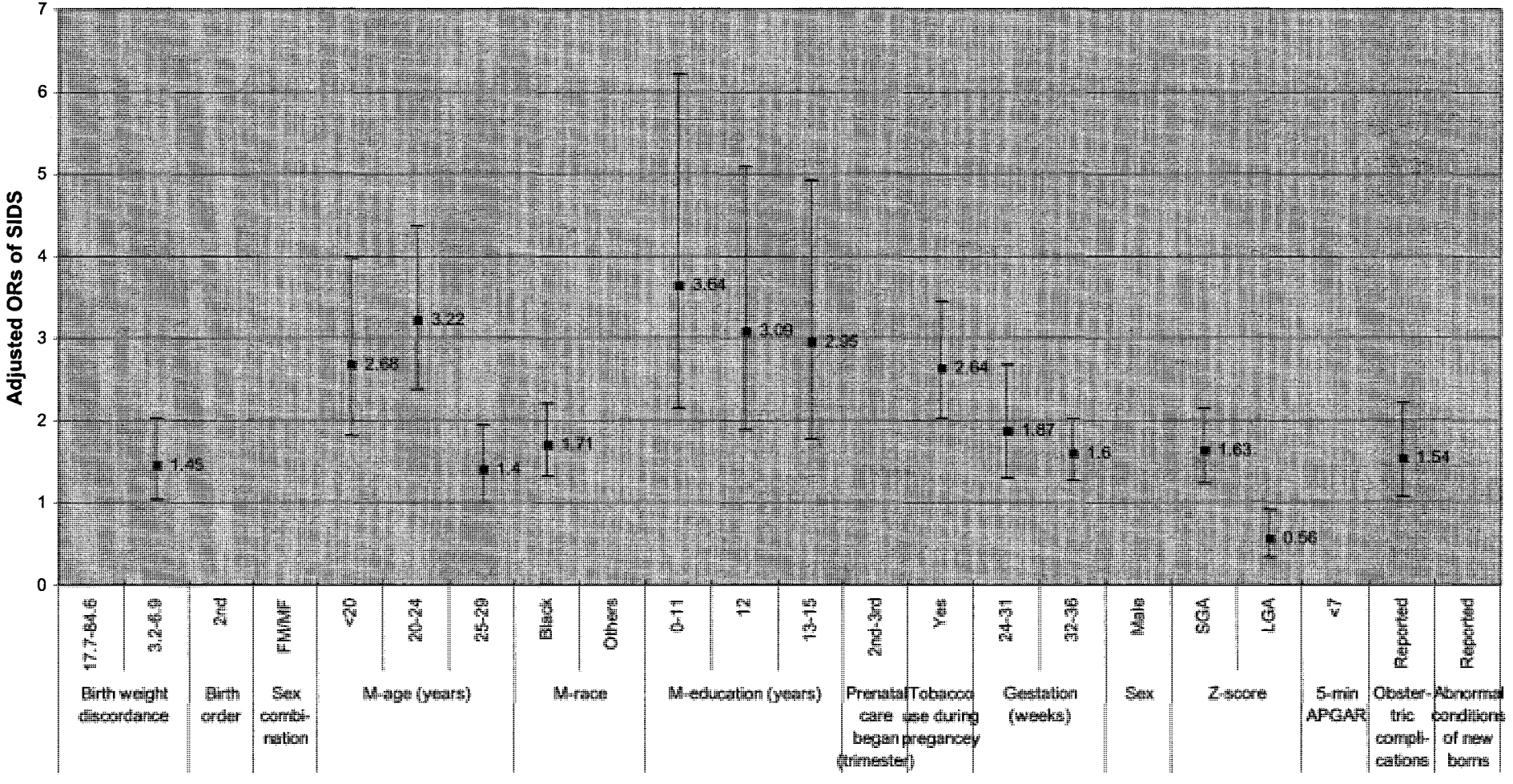
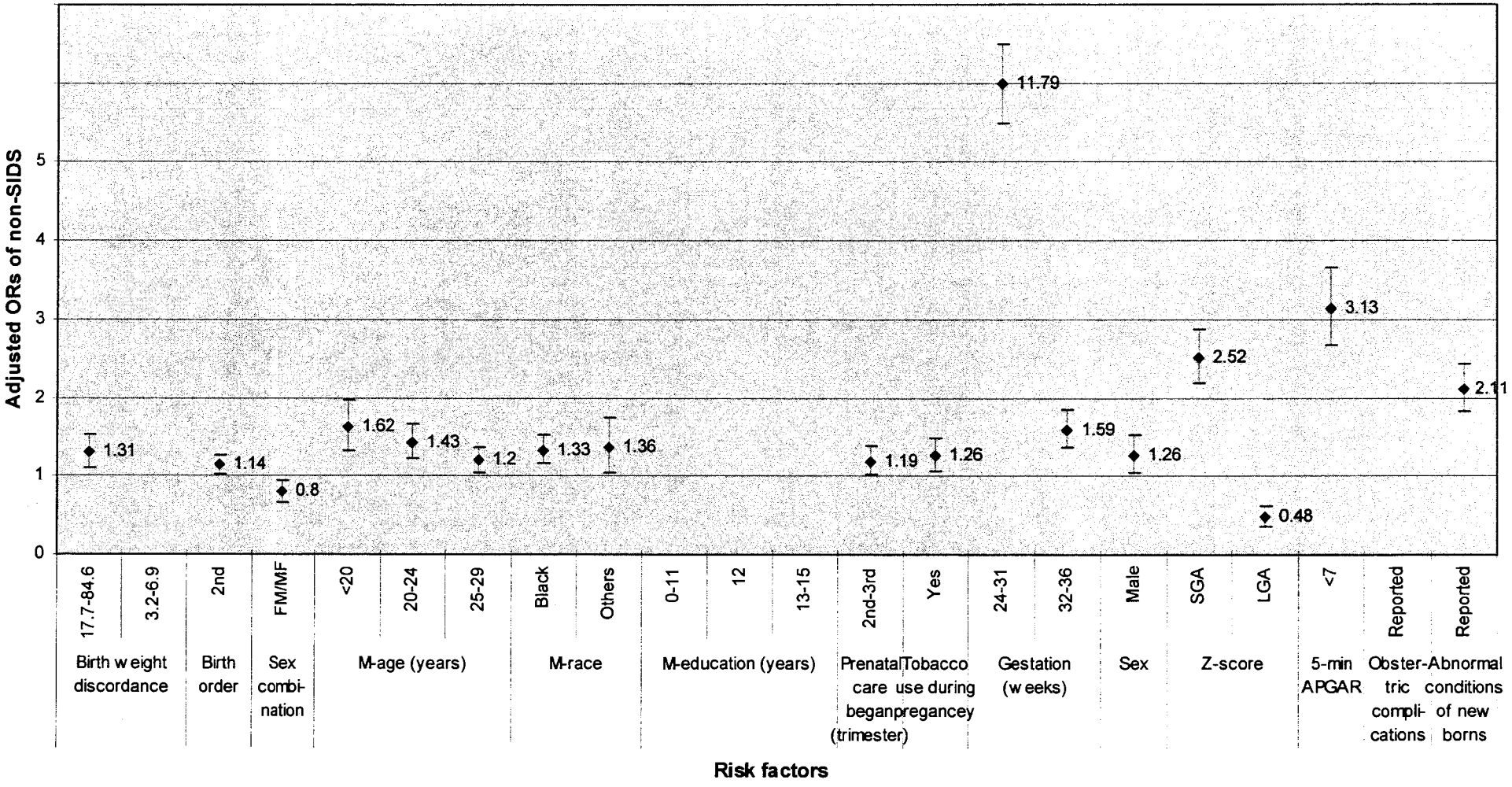


Figure 3 - Comparison of significant adjusted odds ratios between SIDS and non-SIDS



FM/MF sex combination, male twins, late prenatal care, abnormal 5-minute APGAR score, and abnormal conditions of newborns were associated with non-SIDS but not SIDS. On the contrary, low maternal education and obstetric complications were associated with SIDS but not non-SIDS. In addition, the adjusted ORs of younger maternal age and tobacco use during pregnancy had higher ORs in SIDS than those in non-SIDS while the ORs of very preterm gestation and smaller Z-score were lower in SIDS than in non-SIDS. Black maternal race was weakly associated with both SIDS and non-SIDS.

4.3 Competing Risks by Survival Analysis

4.3.1 Smaller and larger twin data sets

Among 273,130 eligible study twins, 3,839 twins died of various causes. 2,749 dead twins with the main causes of infant death (congenital anomalies, asphyxia, immaturity, infections, and SIDS) as well as 268,363 surviving twins kept in the complete twin pairs were used in the following analyses. On the other hand, 1,098 dead twins with external causes, specific conditions other than above five main causes, and remaining causes with other and unclassifiable diagnoses, as well as their 920 co-twins were excluded.

In order to split the included twins into two independent populations, smaller and larger twin population, by the unequal birth weight, the 10,878 twins with equal birth weight within twin pairs were excluded. Consequently, 260,234 individual twins containing 2,575 infant deaths were included in the competing risks analysis through dividing them into smaller and larger twin data sets. Each population has 130,117 twins but with 1,531 and 1,044 infant deaths in smaller and larger twin population, respectively. (Please refer to Appendix A-4 for details.)

4.3.2 Main causes of infant death by functional groups

As main causes of infant death, congenital anomalies, asphyxia related conditions, immaturity related conditions, and infections are the competing events of SIDS. The distribution of these infant deaths and death rates by the five individual causes are shown in Table-6.

From Table-6, the overall infant death rate of the smaller twins was higher than that of the larger twins. The death rates in order from the highest to the lowest were congenital anomalies, immaturity, SIDS, infections and asphyxia in the smaller twins while immaturity, congenital anomalies, SIDS, asphyxia and infections in the larger twins. The death rates of SIDS were close as the third highest ones between the two twin populations.

Table 6 - Distribution of infant death and death rates by five main causes of infant death in smaller and larger twins

Cause of death	Smaller twins		Larger twins	
	Event number	Death rate (%)	Event number	Death rate (%)
Total twins	130,117		130,117	
All infant deaths	1,531	1.18	1,044	0.80
Congenital anomalies	646	0.50	271	0.21
Asphyxia	63	0.05	60	0.05
Immaturity	548	0.42	499	0.38
Infections	81	0.06	49	0.04
SIDS	193	0.15	165	0.13

4.3.3 Comparison of log survivor curves

In Figure-4, the cumulative hazard of the five main causes of infant death in the smaller twins are represented by five log survivor curves in different colors: congenital anomalies in green, asphyxia in black, immaturity in gold, infections in blue, and SIDS in

Figure-4: Log survivor plot for five main causes of infant death in smaller twins

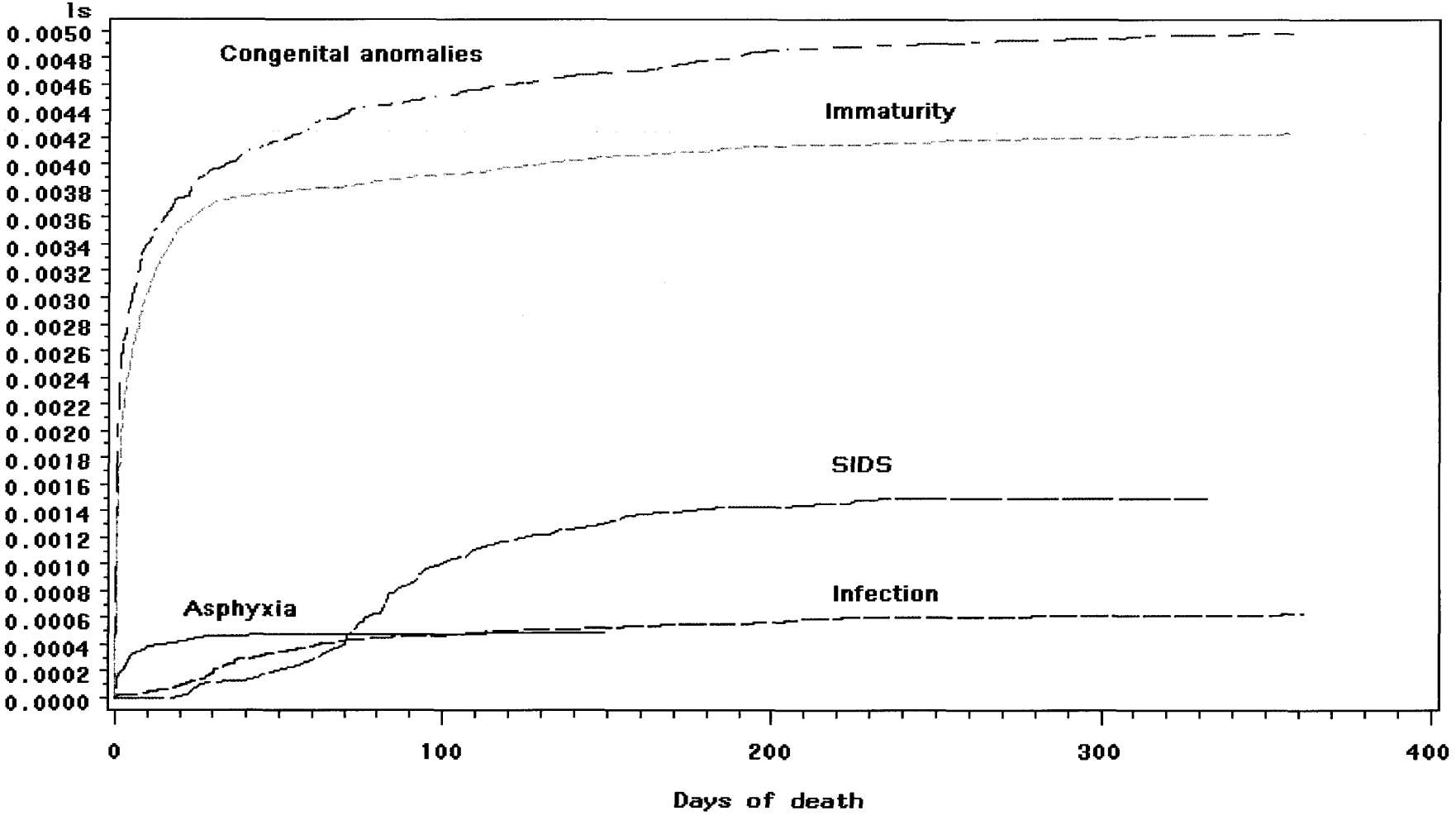
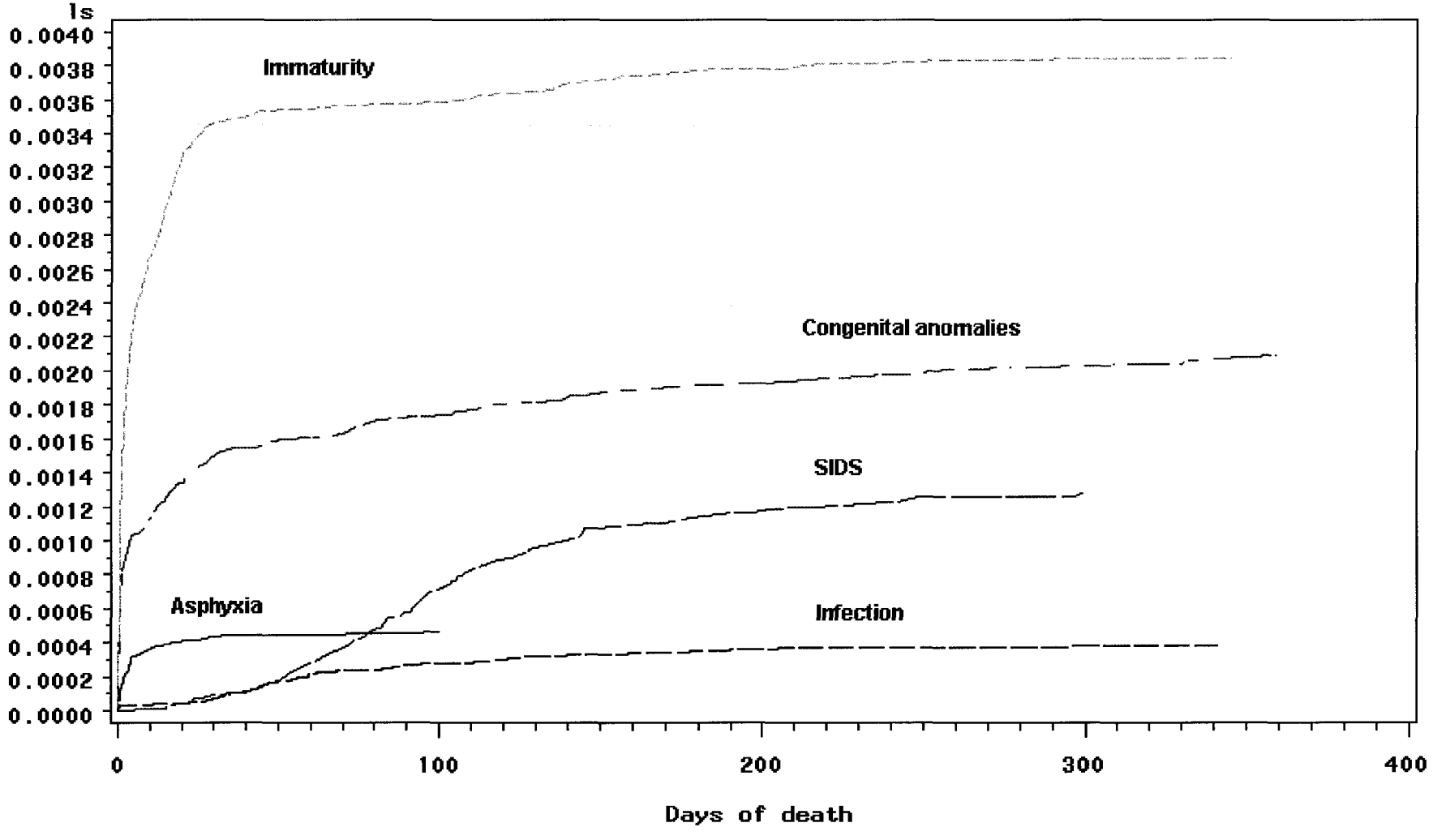


Figure-5: Log survivor plot for five main causes of infant death in larger twins



red. The five curves showed that the hazard of each type of infant death was not constant. The order of the cumulative risk from highest to lowest was congenital anomalies, immaturity, asphyxia, infection, and SIDS before the 70th day while the order changed to SIDS, infection, and asphyxia from the third to fifth highest after the first 70 days. The curves for congenital anomalies, immaturity, and asphyxia rose steeply in the first 10 days, continued increasing gradually to the highest and then kept flat in the rest of the year. On the contrary in the first 10 days, the hazards for SIDS and infections were almost close to zero. Since then, both curves gradually rose and the curve for infections was little higher than that for SIDS till they crossed at the 70th day. After that, the hazard for SIDS increased at a higher rate than that for infection, exceeded that for asphyxia, rose till the 180th day, and kept flat from the 180th day to the 330th day. The curve for infections tended to be flat in the rest of the year.

Similar situation is shown in Figure-5 for the five main causes of infant death in the larger twins. Besides the lower hazard for congenital anomalies versus the higher hazard for immaturity, the differences were that the curve for SIDS was virtually indistinguishable from that for infections during the first 50 days, then increased till the 180th day, and exceeded the curve for asphyxia around the 75th day, while the curve for infections kept flat after the 70th days.

Comparing two plots, the shapes of the curves for each cause of infant death were highly similar between the two twin populations, but the smaller twins had a higher hazard than the larger twins for each cause, especially for congenital anomalies. (The combined plot is not shown here.)

4.3.4 Competing risks for main causes of infant death

4.3.4.1 Competing risks in smaller twins

Gestational age and Z-score of birth weight for gestation were associated to all five main causes of infant death, whereas maternal age and tobacco use during pregnancy were only related to SIDS, and maternal education was related to both SIDS and infections. Most of the rest of 17 factors were associated to congenital anomalies and immaturity but not SIDS.

From Table-7, for each five-year increase in the maternal age, the hazard of SIDS went down by an estimated 39%. Twins whose mothers used tobacco during pregnancy were 2.35 times as likely as those whose mothers didn't use tobacco to suffer SIDS. In addition, one-year increase in the maternal education yielded 8% decrease in the risk of SIDS as well as 11% decrease in infections. For one-week increase in the gestational age, the hazard of SIDS went down by 8% while the hazard of immaturity, infections, asphyxia, and congenital anomalies went down by 47%, 32%, 20% and 14%, respectively. Similarly, one unit increase of Z-score of birth weight for gestation yielded 28%, 82%, 63%, 39%, and 42% decrease in the risk of above causes of infant death in the same order.

In addition, one-percent increase in birth weight difference was associated with 22% increase in the risk of infant death due to congenital anomalies and FM/MF twins only had about 74% of the hazard for congenital anomalies compared with FF twins.

Twins with abnormal 5-minute APGAR score were 36.77, 16.18, and 2.57 times as likely as those with normal APGAR score to die of asphyxia, congenital anomalies, and immaturity, respectively. Twins of black mothers were 2.58 times as likely as those of

white mothers to die of infections while the hazards of death due to congenital anomalies and immaturity for the twins of black mothers were only about 73% and 72% of the hazards for those with white mothers. Furthermore, twins of unmarried mothers and male twins were associated with congenital anomalies, and reported obstetric complications were related to not only congenital anomalies but also immaturity. (Please refer to Appendix C-1 for details.)

4.3.4.2 Competing risks in larger twins

Similarly, gestational age and Z-score of birth weight for gestation were associated to the five main causes of infant death, whereas maternal age and tobacco use during pregnancy were only related to SIDS, and maternal education was marginally related to SIDS. Most of the rest of the factors were associated to congenital anomalies and immaturity but not SIDS. In addition, MM sex combination and black mother race were also associated with SIDS in larger twins.

From Table-8, the twins with MM sex combination were 2.52 times as likely as those with FF combination to suffer from SIDS. For each five-year increase in the maternal age and one-year increase in the maternal education, the hazard of SIDS went down by an estimated 29% and 6%, respectively. Twins whose mothers used tobacco during pregnancy were 3.35 times as likely as those whose mothers didn't smoked cigarettes to suffer from SIDS. The twins of black mothers were 2.37 times as likely as those of white mothers to die of SIDS while the hazard of death from immaturity for the twins of black mothers were only about 77% of the hazard for those of white mothers. For one-week increase in the gestational age, the hazard of SIDS went down by 8% while the hazards of immaturity, infections, congenital anomalies, and asphyxia went down by 44%, 29%,

Table 7 - Comparison of significant adjusted hazard ratios and 95 percent confidence intervals in smaller twins for five main causes of infant death in relation to various risk factors, 1995-97 USA matched multiple birth file

Variable	Adjusted hazard ratios and 95% confidence intervals in smaller twins				
	SIDS	Congenital anomalies	Asphyxia	Immaturity	Infections
Maternal age (5 years)	0.61 (0.53, 0.71)				
Tobacco use during pregnancy	2.35 (1.64, 3.37)				
Maternal education (1 year)	0.92 (0.86, 0.98)				0.89 (0.81, 0.97)
Male sex	0.59 (0.36, 0.96)	0.65 (0.48, 0.88)			
Reported abnormal conditions of newborns	0.47 (0.23, 0.94)				1.91 (1.15, 3.17)
Gestation (1 Week)	0.92 (0.88, 0.96)	0.86 (0.84, 0.88)	0.80 (0.75, 0.86)	0.53 (0.51, 0.55)	0.68 (0.64, 0.73)
Z-score	0.72 (0.61, 0.86)	0.58 (0.53, 0.64)	0.61 (0.43, 0.86)	0.18 (0.16, 0.21)	0.37 (0.27, 0.50)
FM/MF sex combination		0.74 (0.58, 0.95)			
Unmarried status of mother		1.36 (1.10, 1.68)			
Reported medical risk factors of mother		0.70 (0.55, 0.88)			
Birth weight discordance (%)		1.22 (1.18, 1.26)		0.91 (0.87, 0.94)	
Reported obstetric complications		1.27 (1.02, 1.57)		1.28 (1.04, 1.59)	
Black maternal race		0.73 (0.57, 0.92)		0.72 (0.58, 0.89)	2.58 (1.54, 4.32)
Abnormal 5-minute APGAR score (<7)		16.18 (13.19, 19.84)	36.77 (16.89, 80.04)	2.57 (2.09, 3.14)	

Table 8 - Comparison of significant adjusted hazard ratios and 95 percent confidence intervals in larger twins for five main causes of infant death in relation to various risk factors, 1995-97 USA matched multiple birth file

Variable	Adjusted hazard ratios and 95% confidence intervals in larger twins				
	SIDS	Congenital anomalies	Asphyxia	Immaturity	Infections
MM sex combination	2.52 (1.26, 5.04)				
Maternal age (5 years)	0.71 (0.61, 0.83)				
Tobacco use during pregnancy	3.35 (2.31, 4.86)				
Maternal education (1 year)	0.94 (0.87, 1.00)				
Black maternal race	2.37 (1.65, 3.40)			0.77 (0.61, 0.97)	
Gestation (1 Week)	0.92 (0.88, 0.96)	0.88 (0.85, 0.91)	0.89 (0.83, 0.95)	0.56 (0.54, 0.58)	0.71 (0.66, 0.76)
Z-score	0.78 (0.66, 0.92)	0.78 (0.68, 0.89)		0.24 (0.21, 0.29)	0.42 (0.29, 0.60)
FM/MF sex combination		0.59 (0.35, 0.98)			
Late prenatal care			1.97 (1.03, 3.77)		
No prenatal care				1.63 (1.10, 2.42)	
C-section delivery		0.65 (0.50, 0.85)			
Reported medical risk factors of mother		0.66 (0.46, 0.95)			
Birth weight discordance (%)		1.10 (1.05, 1.16)		1.07 (1.02, 1.12)	
Reported abnormal conditions of newborns		1.78 (1.30, 2.45)	2.78 (1.51, 5.12)		
Abnormal 5-minute APGAR score (<7)		10.96 (7.95, 15.11)	54.93 (24.99, 120.71)	2.88 (2.33, 3.56)	

12% and 11%, respectively. One unit increase of Z-score of birth weight for gestation yielded 22%, 76%, 58%, and 22% drop in the risk of above causes of infant death, except for asphyxia.

Moreover, one-percent increase in birth weight difference was associated with 10% and 7% increase in the risk of infant death due to congenital anomalies and immaturity, respectively, and FM/MF twins had about 59% of the hazard for congenital anomalies compared with FF twins.

The twins with abnormal 5-minute APGAR score were 54.93, 10.96, and 2.88 times as likely as those with normal 5-minute APGAR score to die of asphyxia, congenital anomalies, and immaturity. The twins with abnormal conditions of the newborns were 2.78 and 1.78 times as likely as those without abnormal conditions to die of asphyxia and congenital anomalies. Furthermore, c-section delivery, no prenatal care and late prenatal care were associated with congenital anomalies, immaturity and asphyxia, respectively. (Please refer to Appendix C-2 for details.)

4.3.4.3 Comparison of competing risks between smaller and larger twins

The significant adjusted hazard ratios of the potential risk factors were compared for different causes of infant death between the smaller and larger twins.

From Figure-6, among the three twin characteristics, only MM sex combination was associated with SIDS in larger twins. The effects of birth weight discordance and FM/MF for congenital anomalies were consistent in both twin populations while the effect of birth weight discordance was opposite for immaturity in the two populations but very close to one.

From Figure-7, the effects of maternal age, maternal education and tobacco use during pregnancy in SIDS were consistent in both smaller and larger twins while black mother factor was only associated with SIDS in the larger twins. The effect of black mother for immaturity death was also consistent in both twin populations. Only in the smaller twins, unmarried status was associated with congenital anomalies and maternal education was associated with infections, while black mother was related to both causes of death. On the contrary, no prenatal care, and late prenatal care were related to immaturity and asphyxia respectively only in the larger twins.

Among infant physiological variables in Figure-8, effects of gestation and Z-score were consistent in the five causes of infant death in both twin populations. Male sex was related to SIDS and congenital anomalies only in smaller twins.

Figure-9 shows consistent associations between 5-minute APGAR score and congenital anomalies, asphyxia and immaturity in both smaller and larger twins. The effects were extremely high in asphyxia and congenital anomalies.

Figure-10 shows that the effects of other factors in different causes of infant death were inconsistent and weak in both smaller and larger twins.

4.3.4.4 Test proportionality

Log-log survivor curves for the five main causes of infant death shows that the curves of congenital anomalies, immaturity and asphyxia tended to be parallel in both smaller and larger twins. However, SIDS curve moved up to cross the curves of asphyxia and infections and closer to those of congenital anomalies and immaturity from the 20^{th} to 120^{th} day, suggesting nonproportionality in both twin populations. (Please refer to Appendix D for details.)

Figure-6: Significant adjusted hazard ratios for three twin characteristics in smaller and larger twins

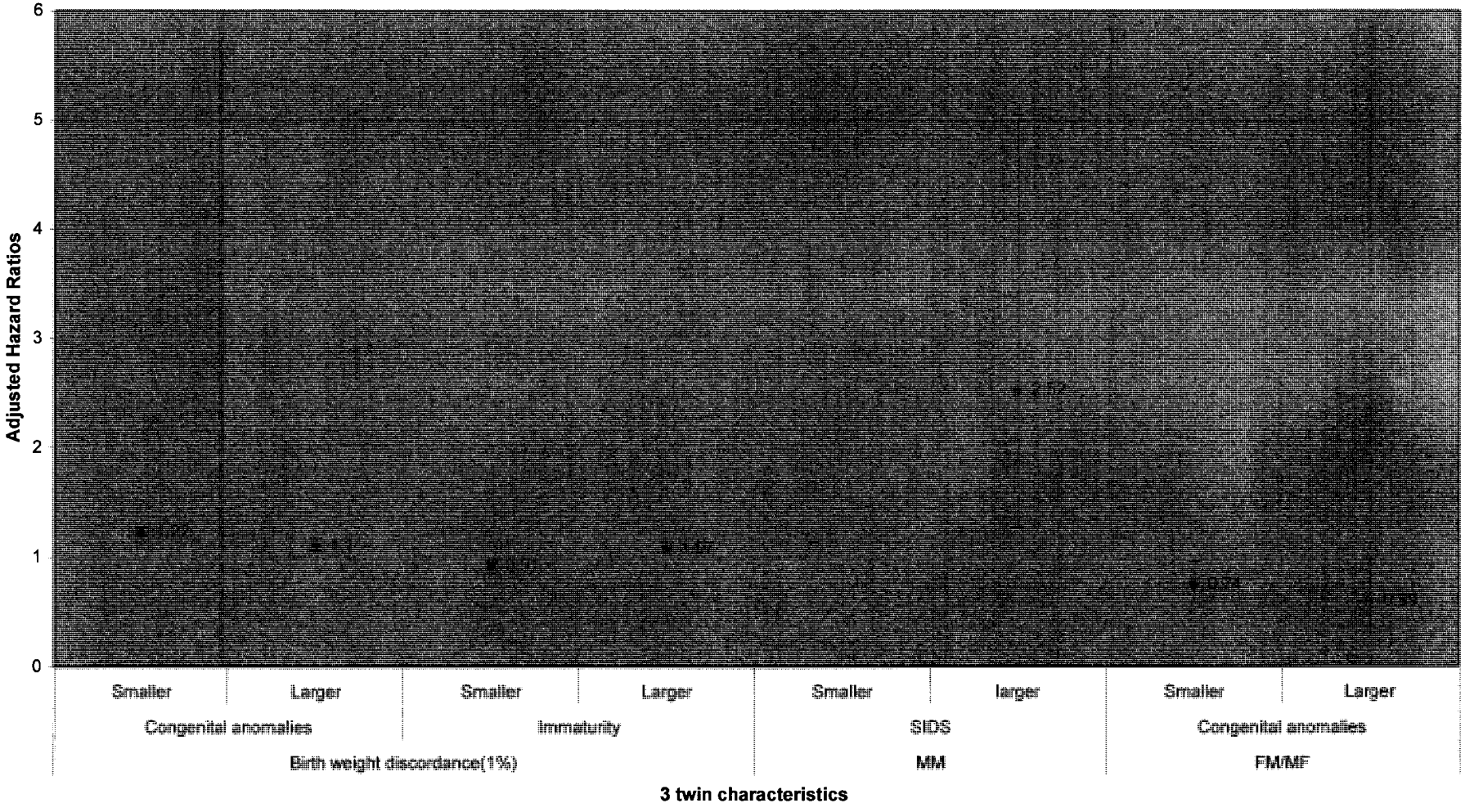


Figure-7: Significant adjusted hazard ratios for six maternal variables in smaller and larger twins

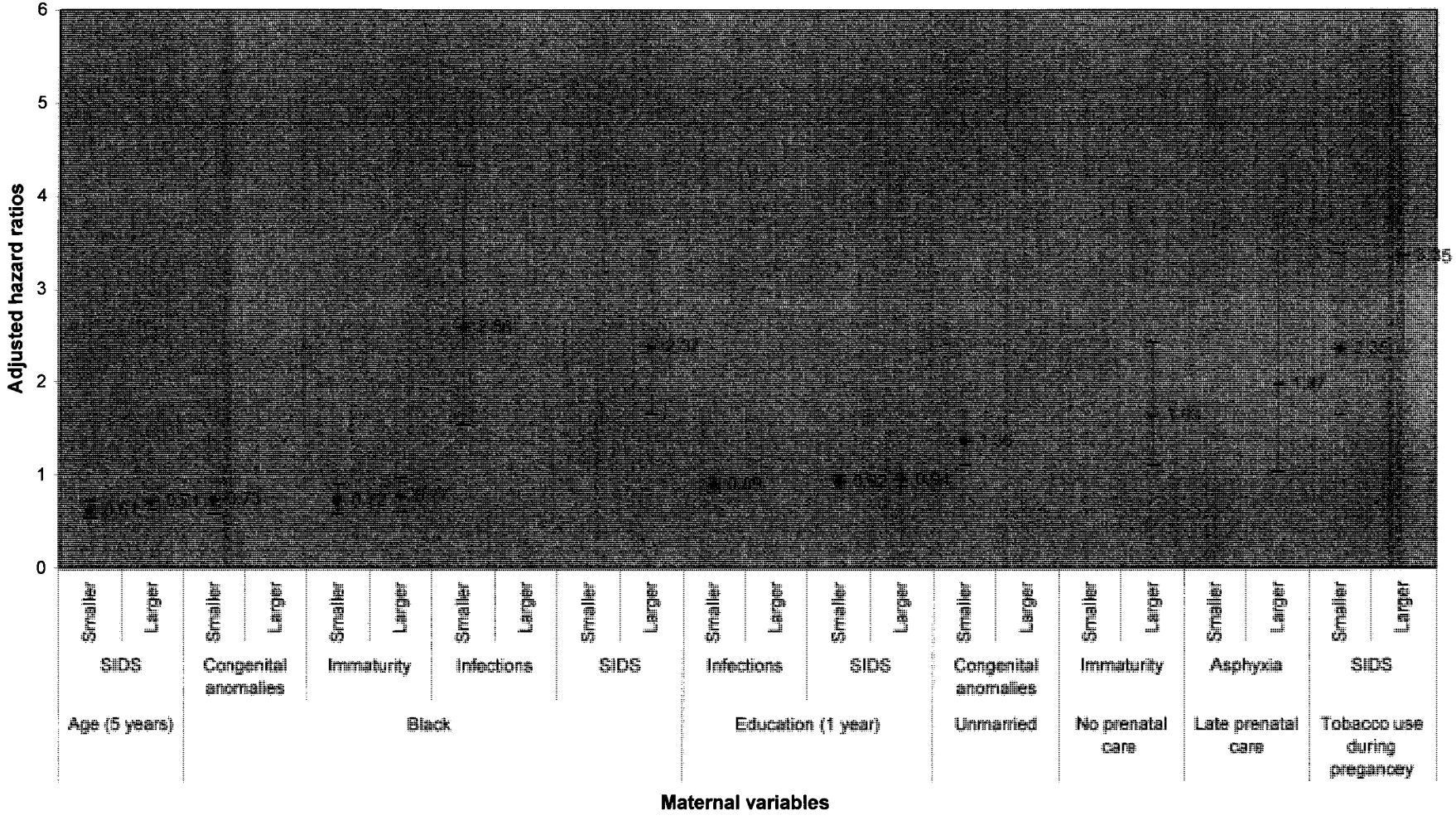


Figure-8: Significant adjusted hazard ratios for three infant physiological variables in smaller and larger twins

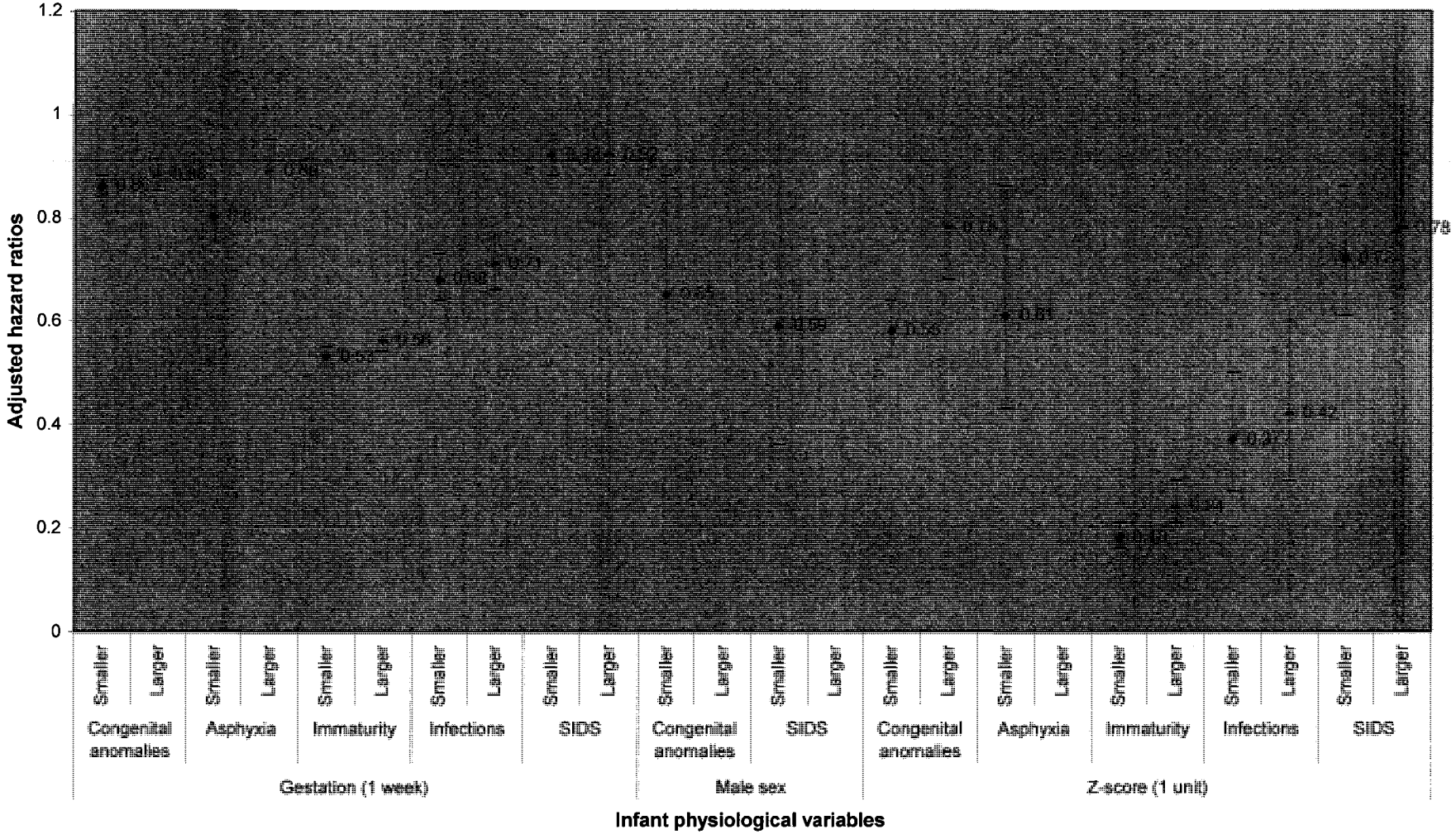


Figure-9: Significant adjusted hazard ratios for 5-minute APGAR score in smaller and larger twins

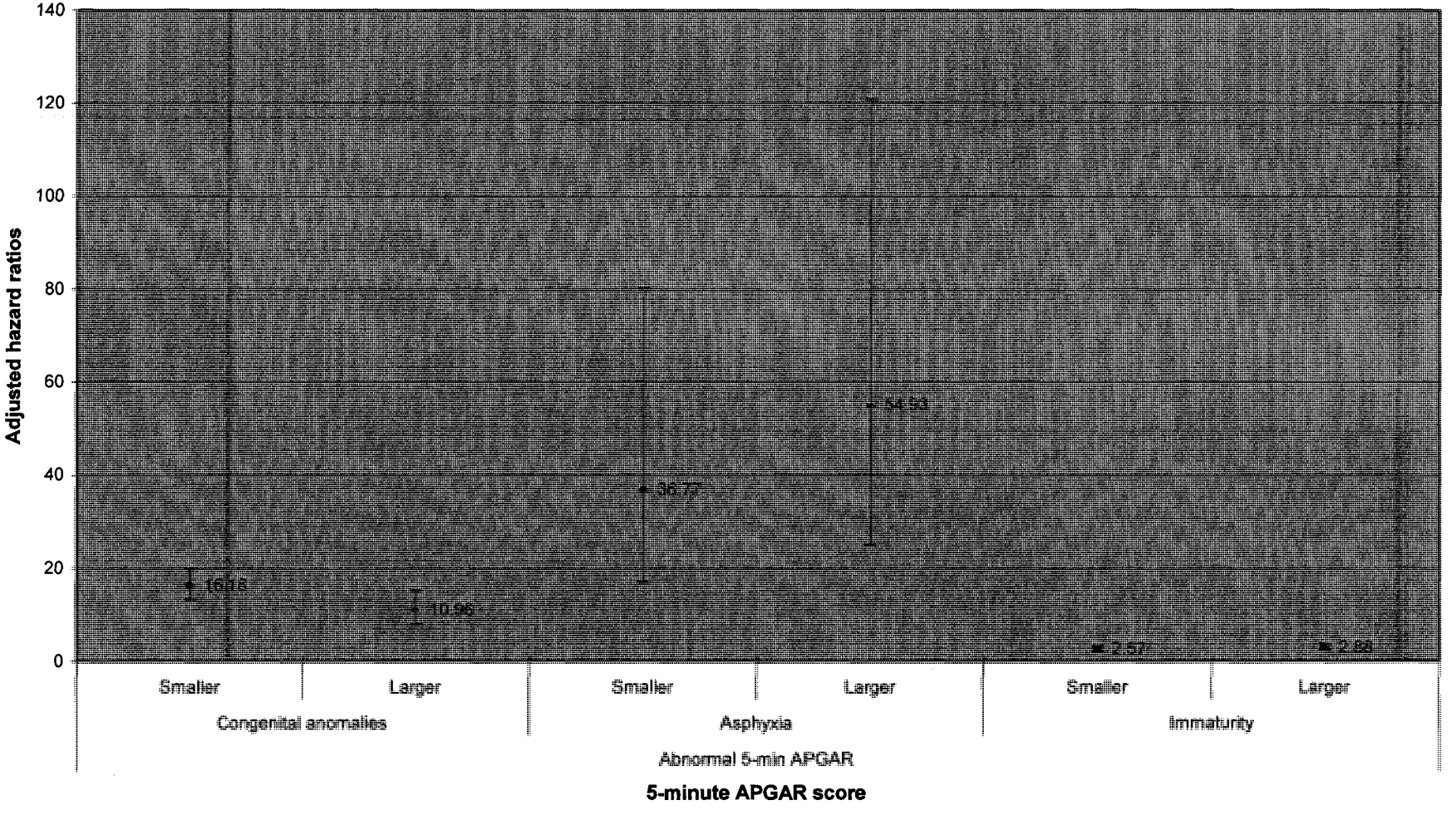
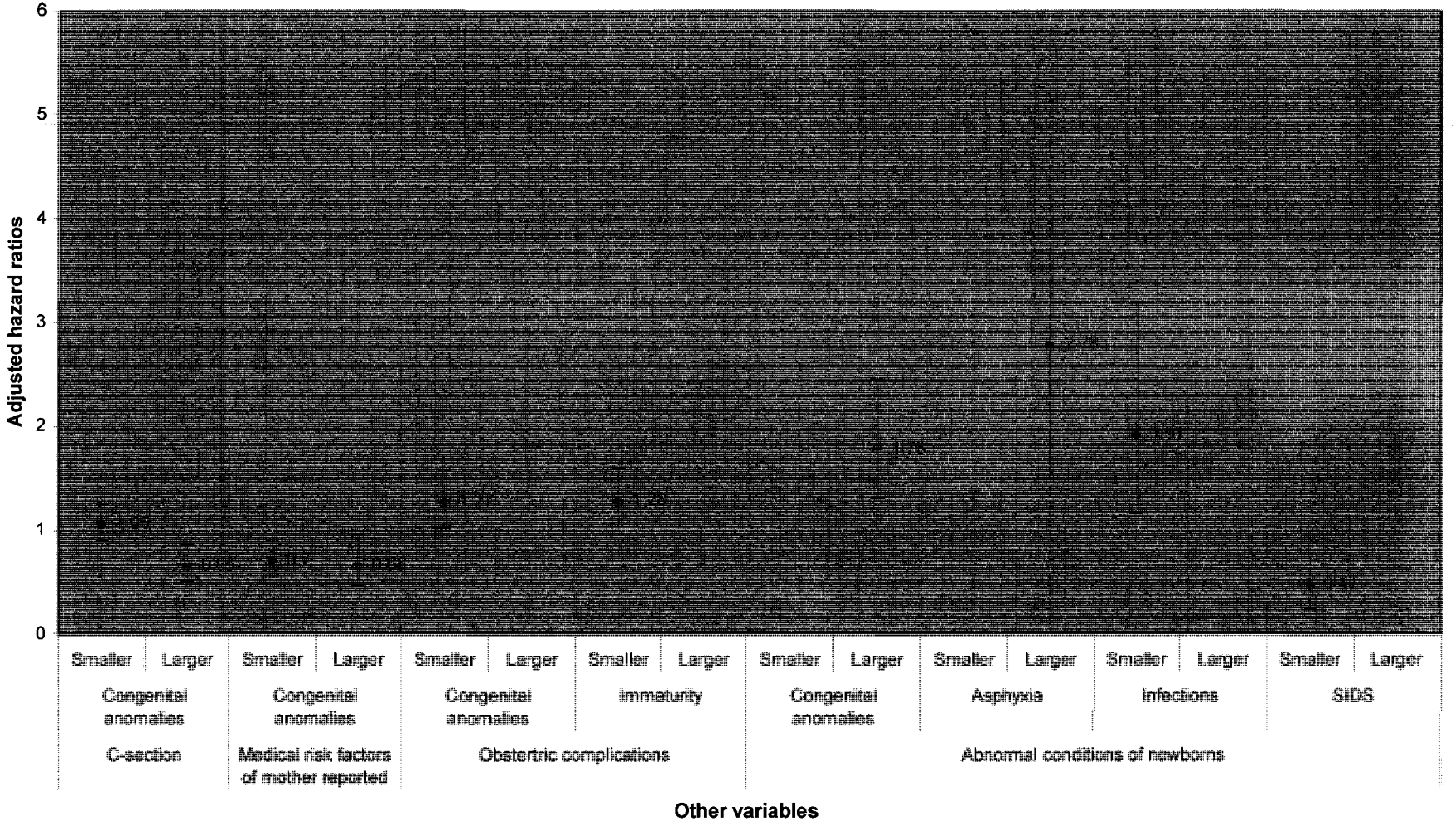


Figure-10: Significant adjusted hazard ratios for four other variables in smaller and larger twins



5. DISCUSSION

5.1 Summary of Key Findings and Implications

This retrospective cohort study using the matched live twin births in 1995-1997 in the United States demonstrated that larger birth weight discordance and second birth order within twin pairs were risk factors for non-SIDS infant deaths among twins, particularly for congenital anomalies and immaturity, and that MF sex combination was inversely associated with non-SIDS deaths. However, this study did not find that larger birth weight discordance and second birth order were associated with SIDS among twins. MM sex combination was associated with an increased risk of SIDS but this association was not statistically significant after adjustment for previously established risk factors in GEE analysis.

This study also found that low maternal education and obstetric complications were related only to SIDS risk but not to non-SIDS risk and that the risk effects of young maternal age and maternal smoking during pregnancy were stronger for SIDS than those for non-SIDS. In addition, lower gestational age and small-for-gestational-age were associated with all infant deaths, including SIDS, but stronger in non-SIDS risk.

The above results implicate that common biological factors (e.g., preterm births and fetal growth restriction) are risk factors for SIDS among twins, and the higher SIDS rate among twins is likely related to the common biological factors but not the unique twin factors including birth weight discordance, birth order within pairs, and sex combinations. Furthermore, socioeconomic factors, such as maternal education, maternal age, and maternal smoking, play a more important role in SIDS risk while biological factors play a more important role in non-SIDS risk.

The findings from GEE and competing risks analyses were generally consistent in this study while there were some differences on the effects of various risk factors for individual causes of infant death between the smaller and larger twins in competing risks analysis.

5.2 Interpretation of the Findings

5.2.1 SIDS death rate in twins

The overall SIDS incidence among twins was 1.3/1000 live births in this study, which is consistent with the finding of a report about SIDS in twins in 1993-1998 (25) and is nearly two times the overall SIDS incidence of 0.74/1000 live births in the United States in 1996 (132). SIDS incidence was 1.5/1000 live births in the smaller twins, higher than the 1.3/1000 live births in the larger twins, which was supported by previous studies (23,33). Similar to other twin studies (5,61), the increased risk of SIDS among twins, particularly among the smaller twins, might be related to the higher prevalence of low birth weight and prematurity (29).

5.2.2 Birth weight discordance with SIDS

To our surprise, one group of infants with smaller birth weight discordance (q2: 3.2-6.9 percentage of birth weight discordance) was significantly associated with SIDS after adjusting for gestational age and fetal growth as well as extensively controlling for the confounding effects of sociodemographics, pregnancy complications, and other important pregnancy-related factors in this study. However, with the increasing birth weight discordance, ORs became closer to one and not statistically significant. The lack of linear trend (by quintile) and multiple comparisons suggest that this finding of statistical significance could be a result of the play by chance. Therefore, this study does not

provide additional evidence to support the previous findings that large birth weight discordance among twin pairs was associated with an increased risk of SIDS (5,23). On the other hand, an obvious linear trend was observed in the associations with non-SIDS deaths as the percentage of birth weight discordance went up and a significant association was found in the group with the largest percentage of birth weight discordance (q5: >17.7%). This finding was consistent with previous studies (28,29,97).

Gestational age, birth weight-for-gestational-age and maternal age were found to confound the association between birth weight discordance and SIDS, and birth-weight-for-gestational-age was especially a strong confounder of birth weight discordance. This is supported by the results of other studies that the significance of the extent of birth weight discordance may be confounded by the birth weight of the smaller twin (28), that approximately two-thirds of highly discordant twins (e.g. 30% or more) were also small for gestational age (SGA) (96), and that the risk of neonatal mortality was significantly reduced after adjusting for fetal growth (29). Based on those results, some researchers have suggested that the birth weight relative to gestational age of the individual twin, rather than birth weight discordance is a more important contributor to neonatal mortality (97,98).

In competing risks analysis, birth weight discordance was not significantly associated with SIDS but significantly related to congenital anomalies in smaller and larger twins. This finding is consistent with two recent studies that birth weight discordance was associated with congenital malformation-related neonatal deaths in both smaller and larger twins (28) and there was little difference in mortality risk between highly discordant larger and smaller twins after adjustment for fetal growth (29). It was also

suggested that although smaller twins were more subject to growth restriction, they might not necessarily be more vulnerable to stresses outside of those associated with preterm birth and growth restriction in a highly discordant pregnancy (29).

Even though there have been several mechanisms about the risk effect of twin birth weight discordance such as disorders of the placenta and twin-twin transfusion, the critical birth weight discordance that differentiates normal variation from pathologic process has not been established (104).

5.2.3 Birth order with SIDS

This study failed to find that second-born twins had a higher risk for SIDS, even though this factor was moderately significantly associated with non-SIDS infant deaths. Second-born twins were weakly and inversely but not significantly associated with SIDS in this study. It is consistent with the observation of Kahn's study (33) but opposite to other studies (9,24,34). In addition, second birth order was not significantly related to any individual main causes of infant death in either smaller or larger twin populations in competing risks analysis. These results are supported by another study using the same twin data set (103) with the conclusion: similar risk of neonatal mortality and no difference in risk of postneonatal mortality between first- and second-born twins. In addition, that study noted that the increased risk of perinatal death in second-born twins was chiefly driven by an increase in the number of stillborn twins delivered second (103).

That study also found that birth weight-for-gestational-age moderately confounded the association between second birth order and SIDS. However, fetal growth (birth weight-for-gestational-age) curves between first- and second-born twins were almost identical (103).

The higher risk of perinatal death in second-born twins may have been due to the fact that second-born twins have more antepartum complications than first-born twins (133). Some researchers demonstrated that a second-born twin has three to six times the risk of being the smaller baby when there is at least 25% discordance between two twins (104). In addition, the contribution of congenital malformation and chromosomal abnormality to the risk of neonatal death could have accounted for a small portion of the differences in mortality between first- and second-born twins (103). In this study, abnormal conditions of the newborn were found to be a confounder of the birth order for SIDS, but there was no association between abnormal conditions of the newborn and SIDS in twins.

Another study (31) found that delivery-related complications could lead to an increased risk of perinatal death in second-born twins (excluding antepartum stillbirths) and reported that intrapartum anoxia caused 75% of perinatal deaths in second twins, most of which resulted from mechanical problems after vaginal delivery of first-born twins. However, methods of delivery, including C-section and vaginal, were observed to be neither a predictor to SIDS nor a confounder of the birth order in this study.

It should be noted that misclassification of birth order of the twins for different routes of delivery can occur. In other words, the birth order that was reported for a cesarean delivery would be different if the twin fetuses had been delivered vaginally (103). For example the presenting twin that would have delivered first vaginally may be delivered second because of surgical access. In addition, approximately 20% of twin birth order information was missing in this data set (29, 67). Thus, any inference about the likelihood that the second-born twins had a higher risk of infant deaths has to be taken with caution.

5.2.4 Sex combinations with SIDS

This study found that MM sex combination had a higher risk of SIDS before adjustment but was not statistically associated with SIDS after controlling for sex and other risk factors. Comparing with other main causes of infant death, SIDS was observed to be associated with MM only among the larger twins. MF/FM sex combination tended to have a higher risk of SIDS than FF among twins but the risk was weaker than that of MM. These results were consistent with (not fully demonstrated) a previous speculation MM > MF/FM > FF about the risk of SIDS (8). They also partially confirmed other previous studies that the occurrence of SIDS in monozygotic twins was not more than that in dizygotic twins, thus there was no significant genetic determination of SIDS (23, 134). On the other hand, in another twin study, Malloy and Freeman observed a high sex concordance rate with a female predominance among twin pregnancies in which all were growth retarded or small for gestational age and both twins died (5).

MF/FM sex combination was protectively related with non-SIDS infant deaths and individual main causes of infant death other than SIDS in this study. This result did not entirely support a previous study that the same male preponderance holds for all infant mortality (24) but was consistent with another related study that the highest preterm rate was found in MM twin pairs, intermediate rate in FF, and the lowest one in MF/FM twin pairs (107). The variation of findings could be related to the relatively small sample sizes of some studies and consequent unstable estimation of effects, or related to different research methods by which some studies focused on overall infant mortality, including SIDS, but not specific to SIDS.

5.2.5 Important infant factors with SIDS

Early preterm (24-31 weeks) and preterm (32-36 weeks) gestation as well as fetal growth restriction (SGA) were associated with both SIDS and non-SIDS infant deaths, including each individual main causes of infant death, in this study. Particularly, very preterm gestation was found extremely related to non-SIDS. These observations confirmed the conclusions of previous studies that SIDS was more common in premature and small-for-gestational-age infants (50,51). These findings suggest that suboptimal in utero environment is associated with increased risk of SIDS (65).

With advances in neonatal intensive care (increased use of prenatal steroids, surfactant, etc), it is more likely that smaller and sicker infants are surviving the first several months of life, but are at an increased risk later on. In a recent study (50), the interactive effects of prone sleep position and prematurity were found striking: nearly a 50-fold increased risk of SIDS compared with supine sleeping term infants. Pollack and Frohna (109) examined the risk of SIDS for extremely low birth weight infants (500-1000 g birth weight) and demonstrated that the importance of low birth weight for SIDS markedly increased over time.

Similarly, Malloy and Freeman (5) found that the increased risk of SIDS is a function of the increased prevalence of low-birth-weight infants in the twin population. Compared with twin pregnancies in which both twins survived, pregnancies in which one or both twins died of SIDS had lower birth weights, greater discordance in weights, and lower gestational ages in their study. In addition, early preterm (24-31 weeks) and preterm (32-36 weeks) births were associated with non-SIDS infant deaths, including each individual main cause of infant death. These results not only supported that these two important

variables are not specific in the association with SIDS but also demonstrated that accidental death increased in infants of low birth weight with many shared risk factors of SIDS (47).

5.2.6 Important maternal factors with SIDS

5.2.6.1 Maternal education

An important finding in this study was that the lower the maternal education the higher the risk of SIDS. There was, however, no association between maternal education and non-SIDS infant deaths. This result is consistent with Malloy and Freeman's report (5) that SIDS was more prevalent among twins' mothers with 12 years of education or less, but did not entirely support the Nordic epidemiological SIDS studies (52,70), in which maternal education was not significantly associated with SIDS after adjusting for some established main risk factors. This variation could be related to differences in study populations and study designs as well as the context of health care and social security in Nordic countries. However, the latter study demonstrated that maternal education was the variable most closely related to all of the other sociodemographic risks, i.e. the risk for SIDS in younger maternal age, higher birth order and maternal smoking was highest if the mother had a low level of education (52).

It is known that failure to complete high school is often confounded with young maternal age (14) and usually leads to lower socioeconomic conditions (52). In our study, we have been able to adjust maternal age.

5.2.6.2 Young maternal age

This study found that younger maternal age (<25 years) was associated with both SIDS and non-SIDS infant deaths and its risk for SIDS was around twice of that for non-

SIDS. This finding is consistent with most SIDS studies (14,51,52). However, except for SIDS, younger maternal age was not related to any other four main causes of infant death investigated in this study after adjusting for the confounding effects. The strong effect of maternal age was speculated to be due to a higher prevalence of other risk factors of SIDS, such as smoking and low socioeconomic status among young women (51,52). In addition, younger mothers are apt to be less alert to medical problems, which would affect SIDS and other postneonatal causes of mortality (47).

5.2.6.3 Tobacco use during pregnancy

Cigarette smoke exposure, particularly maternal smoking during pregnancy, is a well known risk factor for SIDS. Similar results were found in this study.

As with most epidemiological data, smoking was neither sensitive nor specific in relation to SIDS, e.g. Naeye (135) found that 59% of the mothers of SIDS victims smoked, compared to 48% of the mothers of the matched control. However, smoking is an important risk factor for SIDS that is amenable to intervention, e.g. people found that maternal smoking, as well as prone sleeping and not breast-feeding, were independent risk factors and that in total, three of them accounted for 79% of all SIDS deaths (47). As the prevalence of the prone sleeping position approaches zero, smoking may become the major risk factor for SIDS (58,59,65). Although causality has not been demonstrated conclusively, there is consistency across many studies and also biologic plausibility: infants exposed to cigarette smoke in utero have a higher arousal threshold than infants of non-smoking mothers (72). In addition, maternal smoking during pregnancy could account for most of the risk of SIDS through being associated with intra-uterine growth retardation (136).

A New Zealand study showed that, after attending a national SIDS public education program, 89% of mothers of infants in a population at a high risk for SIDS were aware that smoking increased the risk of SIDS, but the prevalence of smoking was not different from before the program (71). This highlights the difficulty for mothers to stop smoking once they have begun. It is understandable that one of the reasons of mothers smoking during pregnancy may be that they are under stress or uncomfortable with their social situations, i.e. maternal smoking may be a surrogate marker for many factors associated with a low socioeconomic status (52).

5.2.6.4 Socioeconomic backgrounds

While SIDS strikes infants from all socioeconomic backgrounds, research has consistently shown that lower socioeconomic status, variously measured by higher density of persons within the home, larger families, lower household income, unemployment, lower maternal education, single maternal marital status, or young maternal age, and black mothers, is associated with a higher risk for SIDS (53). Despite the decline in SIDS across all social and racial groups following educational risk reducing campaigns, recent trends indicate that there are now even greater social and racial disparities (65).

It was found that the social problems were additive in the effect on SIDS risk; one-third of high risk infants were in families with multiple social problems compared with only 9% of controls (137). The influence of low socioeconomic status is not simple, e.g. it was reported in New Zealand to be associated with low room temperatures and with less bedding insulation, both of which should have a favorable effect relative to overheating (138). Families where SIDS deaths tend to occur now have been termed

"chaotic" due to significant social problems, including substandard housing, domestic violence, unemployment, and illicit drug use (139). Depressed, anxious or distressed mothers may be less aware of the infant's needs and less able to cope with a given situation, e.g. overlooking respiratory infections which may trigger SIDS (52).

The social status of a family may affect not only the risk of their infant dying of SIDS, but the probability of that diagnosis being made by a physician (140). A pattern of SIDS reporting in Florida was found to vary inversely with maternal education, prenatal care, and maternal race (47). Moreover, deaths in infants of lower socioeconomic status were found to be more frequently attributed to SIDS than warranted in the same study. This makes the assessment of infant death difficult, as childcare may have been suboptimal and relevant information may be unobtainable, resulting in the cause of death being left as undetermined (17).

Obviously, lower socioeconomic status is highly related to lower maternal education, young maternal age, and maternal smoking which are the three strongest predictors in our study. As part of the factors related to socioeconomic status, black race of the mother was weakly associated with both SIDS and non-SIDS while unmarried status of mothers, as well as late or no prenatal care, were not significantly related to SIDS and non-SIDS after adjustment of confounding variables in our study.

5.2.7 Other risk factors with SIDS

Among the other factors, only obstetric complications, such as uterine bleeding, abruption placenta and cord prolapse, were weakly associated with SIDS but not significantly related to non-SIDS after adjustment other risk factors. This finding is supported by a recent nested case-control study which reported that placenta previa,

abruption placentae, and premature repture of membranes increased the risk of SIDS (15). Placental abnormalities might predispose to SIDS with maternal smoking and preterm birth through resulting in fetal hypoxia and then subtle neurological damage (15).

The rest of the factors were not associated with SIDS after adjusting for important confounders. These results are consistent with previous studies and demonstrated that the risk factors of SIDS are closely associated with each other (14,63).

5.2.8 SIDS and other main causes of infant death

In this analysis, through the comparison of five main causes of infant death by days of death, SIDS, infections and congenital anomalies are the main causes of death in infants after the first month of birth while congenital anomalies, immaturity, and asphyxia are the main causes of death during the first month, particularly in the first week of birth. From the second to the fourth months of age, SIDS was the only cause of infant death greatly increased. Therefore, SIDS was confirmed by this analysis to be the leading cause of postneonatal death and should be mainly differentiated from infections and congenital anomalies.

In terms of reducing risk, except for gestational age and birth weight-for-gestational age z-score related to all five main causes of death, lower maternal education, young maternal age, and tobacco use during pregnancy were only associated with SIDS. Other biological factors, such as increased birth weight discordance and abnormal five minute APGAR score were related to congenital anomalies, immaturity and asphyxia but not SIDS and infections. As a result, preventing SIDS should focus more on the above three social factors beyond the general prevention from all infant deaths.

5.2.9 Comparison between smaller and larger twins

Stratification by birth weight within twin pairs in the competing risks analysis showed that the leading cause of infant death was congenital anomalies in the smaller twins and immaturity in the larger twins. In terms of SIDS, the striking difference between them was MM sex combination and black maternal race to be risk factors among larger twins.

5.3 Strengths of Methodology

5.3.1 Large administrative data set

As this data file contains information on all twin births in the country over a 3-year period, it is the largest matched multiple data file in the United States, and therefore provides a large sample size with adequate power for detecting differences in mortality risk (29). Selection bias and recall bias were not a problem in this retrospective cohort study, since the data were recorded prospectively for this analysis. In addition, the strength of the use of vital statistics data lying in the broad spectrum of the US population is to provide more accurate estimate of the prevalence of rare events, such as SIDS (5).

The linkage between natality and mortality records provides rich demographic and clinical information as well as flexibility in choosing relevant variables among nearly 200 variables, controlling major confounding factors and evaluating interactions between risk factors. Moreover, birth weight is reliably recorded on these data resulting in accurate estimates of discordance (29). Vital records data on maternal race, age, marital status, and education also appear to be reasonably accurate (67).

5.3.2 Comparison of general association

Many studies found that the some factors affect all infant mortality. This important epidemiological fact suggests that many predictors of SIDS, no matter what level of

significance they achieve statistically, may simply be predictors of the general vulnerability of an infant to any disease (47). In order to identify the risk factors relatively specific to SIDS, this study compared analysis results between SIDS and non-SIDS deaths, then clarified that three unique twin characteristics were not associated with SIDS even though they were related to non-SIDS. In addition, this comparison confirmed the relatively specific risk effects of low maternal education, young maternal age and tobacco use during pregnancy as well as obstetric complications for SIDS. These findings supported that SIDS among twins, as postperinatal deaths, was still more related to social factors which could be modified to improve infant- related environment. In addition, competing risks analysis helped to differentiate the risk effects of these potential and established risk factors between SIDS and the other four main causes of infant death. Finally, in terms of main study factors, the results from GEE and competing risks analyses were qualitatively consistent.

5.3.3 Study controls

Despite intensive efforts, attempts to identify risk factors in infants who eventually died of SIDS have yielded little clinically relevant information (8,33). A major difficulty encountered while studying infants at risk for SIDS has been the definition of appropriate control groups (51). A twin pair, consisting of one SIDS victim and one surviving co-twin, provides similar uterine environment, socioeconomic status and parental factors, even though some studies also investigated the histories of twin pairs in each of which an infant died of SIDS to avoid differences in parental and environmental conditions (33). Fortunately, only two pairs of twins suffered simultaneous sudden infant death syndrome among 359 SIDS victims in this study. It is reasonable in this study to assume that SIDS

twins and their surviving co-twins shared the same family and bedding, and were usually placed in the same sleeping position, which reduced the potential for confounding.

5.3.4 SIDS – postperinatal death or postneonatal death

Previously, many researchers studied SIDS as postneonatal death (≧28 days). However, in the United States, neonatal SIDS (<28 days) amounted to 7% to 8% of all SIDS cases (141). In Europe, the percentage of sudden unexplained deaths during the first three weeks of life increased from 1% of all SIDS cases in the period between 1984 and 1989, to 7% after 1990 (7). From a medical point of view, neonatal SIDS occurs and it would be preferable to include these deaths in analysis (47). However, perinatal death has been excluded from SIDS statistics since 1956 to avoid confusion with disorders of intrauterine disease or complications of parturition (47). Considering this progress of SIDS research, postperinatal SIDS was analyzed in this study.

5.3.5 Quality of the study

How a study is designed, conducted and analyzed is a critical issue before applying the study findings. The quality of this study was assessed using Newcastle-Ottawa quality assessment scale for cohort studies with the maximum of nine stars (142). Since this study is a retrospective cohort study based on a large national data file, both exposed and non-exposed cohorts are truly from all over the United States and the related exposures are systematically recorded in a national database. This analysis controlled for most established risk factors as well as potentially clinical risk factors as confounders. The outcome was identified through ICD-9 codes on database records and all study twins completed one year follow-up except for the death cases. However, this is a retrospective mortality cohort study with various infant deaths as outcomes. In addition, several

important confounders were not available due to the lack of relevant information in the data set. Based on above, the overall score is seven stars.

5.4 Limitations

5.4.1 Key variables

It is possible for any large database to miss some relevant variables. This data set prevented us from investigating some important variables, such as sleeping positions, soft-bedding, and family income as well as zygosity, because they were not reported on infant birth or death certificates. Although the analysis did not take into account sleeping positions for the outcomes examined, most of the risk factors for SIDS were also predictors for the prone sleep position (2,50). All these factors had been controlled for in our study. Furthermore, maternal education could be frequently used as an index of socioeconomic status and various types of sex combinations, SS (MM and FF) and DS (MF or FM) could be used to estimate MZ and DZ.

It is known that multiple logistic regression analysis does control for potential confounders to a substantial extent, perhaps not always completely, and that people can never be fully able to consider all possible confounders in the analyses (65). However, the general consistency of findings across this study and previous ones for many of the risk factors strengthens the overall validity of the findings from this study.

5.4.2 Non-sampling errors

Although the number of deaths reported for an area represents complete counts of such events, they may be subject to coding errors in the registration process (67). As a result, residual confounding is possible. These tend to attenuate the observed effects. However, more than 98% of the multiple sets (including twin pairs) were matched by

prespecified criteria about mothers and babies as well as pregnancy and delivery in this data set (67). Besides, coding errors were likely to be random if any (107), particularly after the data set had passed a rigorous quality control process (67). In addition, we only used completed twin pairs matched according to above criteria. All of these indicated minimal non-sampling errors in this study.

5.4.3 Accuracy of information

A limitation of the study using vital statistics data is that it can not be guaranteed that the causes of death have been accurately ascribed, except for coding errors. In an attempt to be more critical in the definition of SIDS, only cases in which an autopsy was performed are used. Nonetheless, it can not be assured that all the deaths reported as caused by SIDS have death scene investigations and reviews of the medical records as a means of attaining a most correct ascertainment of SIDS (5,45). Only four states (California, Minnesota, Missouri, and New Mexico) had detailed written protocols for a SIDS scene investigation at that time (67). Although assigning a cause of death based on ICD coding might be subject to errors (103), SIDS should not be overlooked by mistakes as a rare event, particularly with its unique ICD code.

The accuracy and completeness of gestational age based on the mother's last menstrual period (LMP) might also be subject to errors because the gestational age estimation was derived from the dates of infant birth and the LMP in this data file. However this measure has been demonstrated to be the most accurate method available on a population-wide basis (28).

5.4.4 Event number

SIDS is a rare event in infant deaths. Even though comparing with other SIDS studies, this study could have the biggest SIDS event number among twins based on a large national data file. However, the limited number of SIDS events was still a problem when fitting logistic regression models, especially when large amount of independent variables were entered into the models. In order to avoid zero frequency cells in contingency tables (113), the analysis had to reduce the number of potential confounding factors and collapse categories of confounding variables. Even though it inevitably resulted in loss of some information, the extensive review of previous studies as well as clinical expert opinions ensured that the selection and categorization of included variables were methodologically and biologically meaningful in this study.

5.4.5 Missing values

Similar to other studies based on a large national data set, this study had 10-20% missing values in the variables of twin birth order, tobacco use during pregnancy, five minute APGAR score, and abnormal conditions of newborns as well as less than 5% missing values in some other variables. However, there were no big and special changes observed in the frequencies and coefficients of all levels of various variables before and after deleting 5% missing values. The comparison results indicated the random missing in this study.

5.5 Conclusion and Future Work

This study found that lower maternal education, younger maternal age, and tobacco use during pregnancy were the strongest risk factors of SIDS among twins after the "back-to-sleep" campaigns in the United States, while the potential predisposed factors, birth

weight discordance, birth order within twin pairs and sex combinations were not associated with SIDS but related to non-SIDS mortalities. This finding demonstrates that social factors are more important for SIDS, while biological factors are more important for non-SIDS deaths. In addition, common biological factors which apply to both singletons and twins such as preterm birth and fetal growth restriction are important risk factors for SIDS among twins however the biological factors that are unique to twins are not.

The study findings suggest that in order to reduce the risk of SIDS among twins, as the similar efforts for the singletons or all infants, targeted efforts to promote educational interventions will be needed for the mothers with lower education, of a young age, and/or who smoke during pregnancy. In addition, extra attention should be paid to premature or growth restricted infants in SIDS prevention.

SIDS is a complex and multifactorial disorder. Epidemiologic research provides a comprehensive view of the risk factors for SIDS with which the theories of underlying physiologic defects or other putative causes should conform. Therefore, the future epidemiologic research should continue playing a vital role in investigating the interactions between the environmental trigger events and the development of fetus and infants as well as the cause of SIDS behind them.

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APPENDICES

Appendix A-1: Eligible paired twins from Matched Multiple Birth File 1995-1997

Appendix A-2: Eligible study twins after deleting 5 percentage of missing values

Appendix A-3: Data sets for SIDS and non-SIDS study in GEE analysis

Appendix A-4: Data sets of twins with smaller and larger birth weights

Appendix B: Model evaluation of GEE analysis

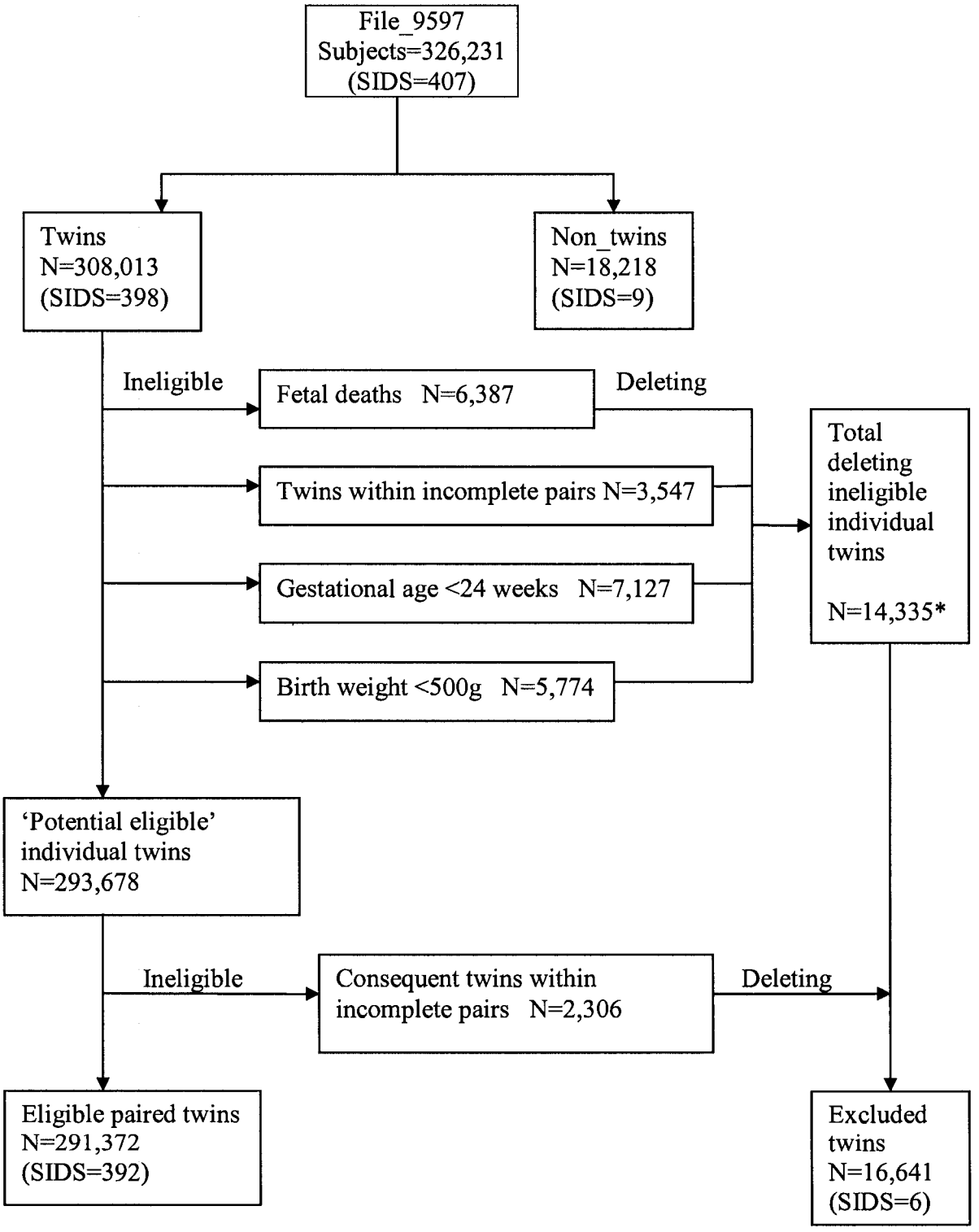
Appendix C-1: Adjusted hazard ratios and 95 percent confidence intervals in smaller twins for five main causes of infant death

Appendix C-2: Adjusted hazard ratios and 95 percent confidence intervals in larger twins for five main causes of infant death

Appendix D-1: Log-log survivor plot for five main causes of infant death in smaller twins

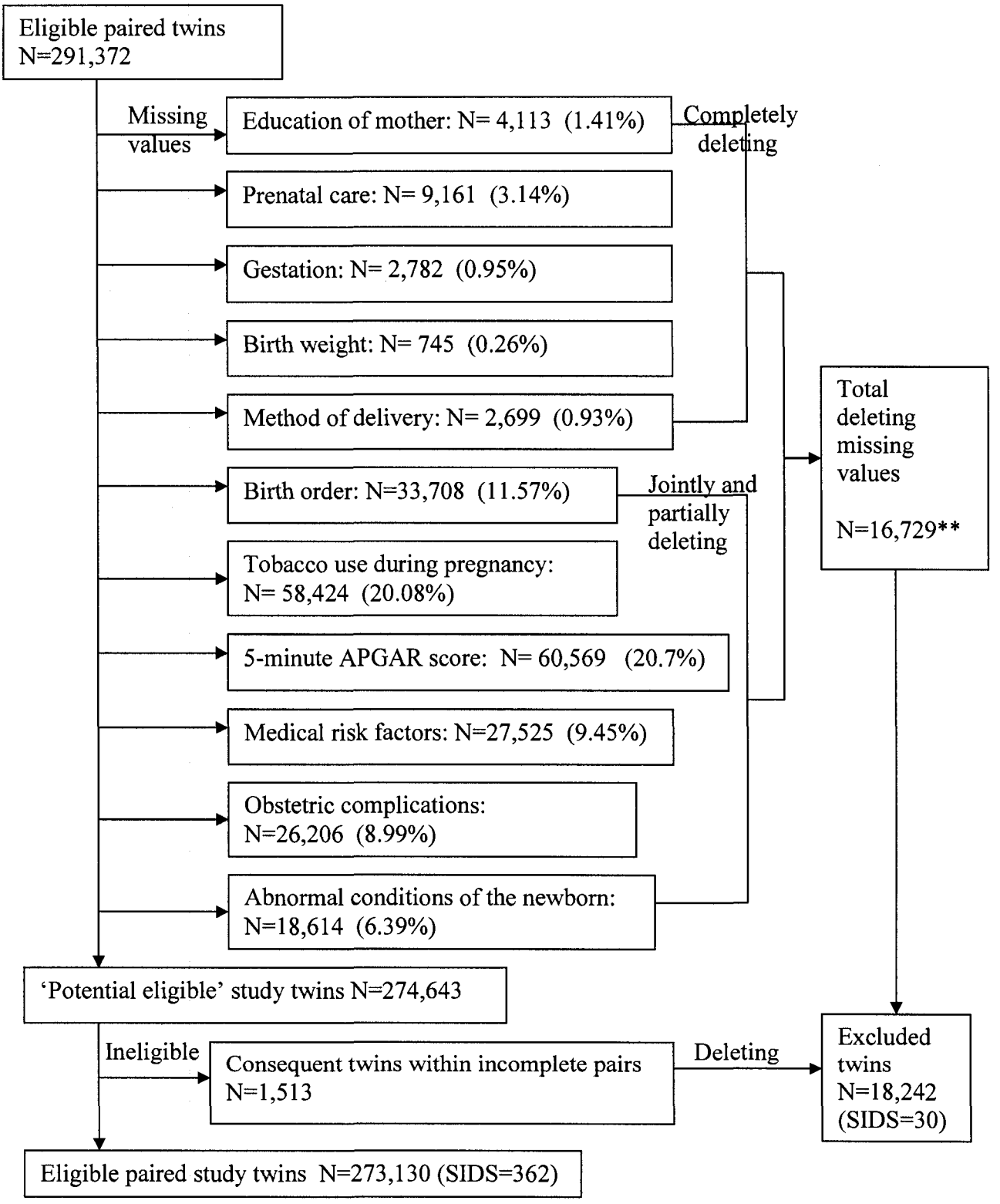
Appendix D-2: Log-log survivor plot for five main causes of infant death in larger twins

Appendix A-1: Eligible paired twins from Matched Multiple Birth File 1995-1997



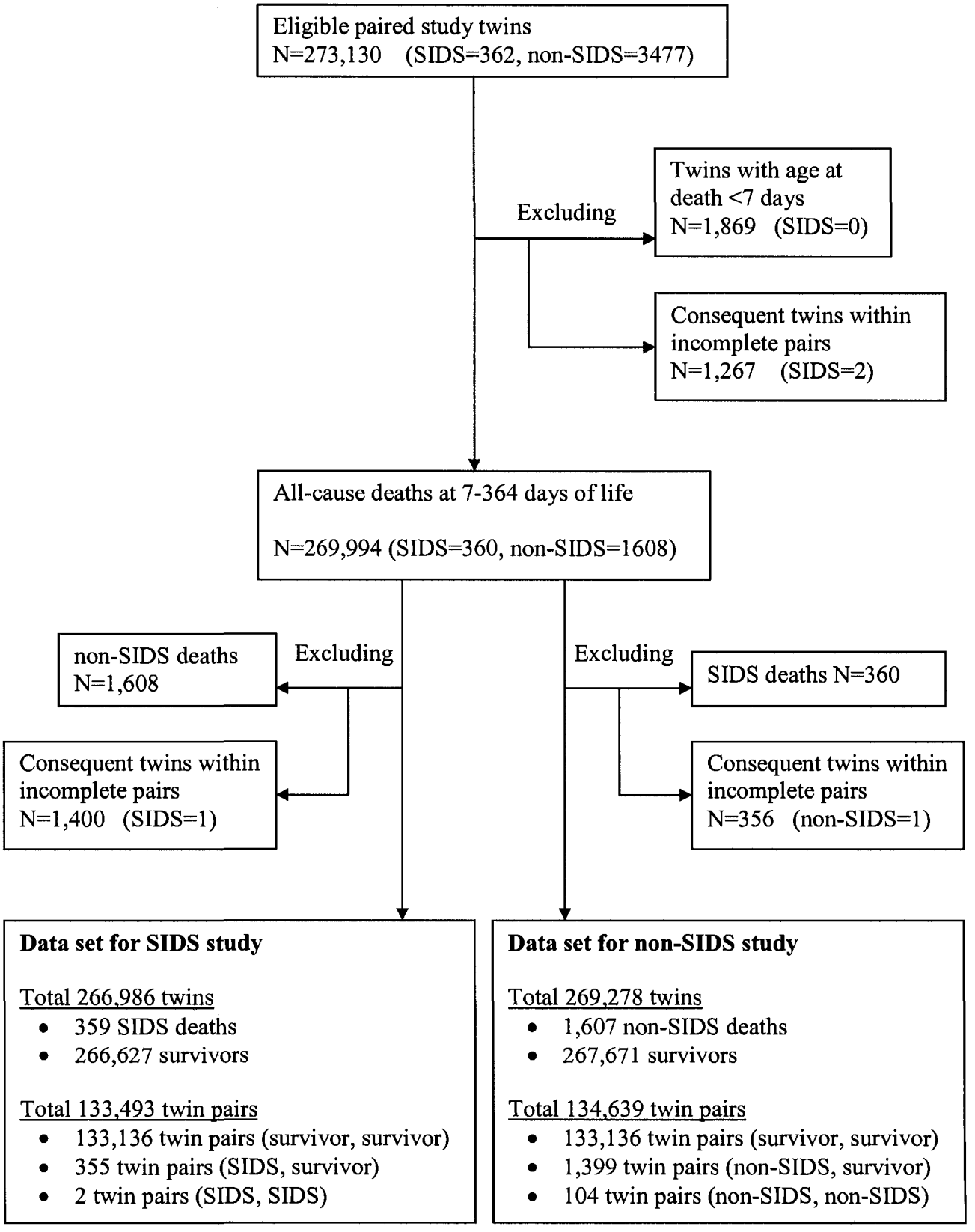
Note*: Some twins had more than one ineligible factor.

Appendix A-2: Eligible study twins after deleting 5 percentage of missing values

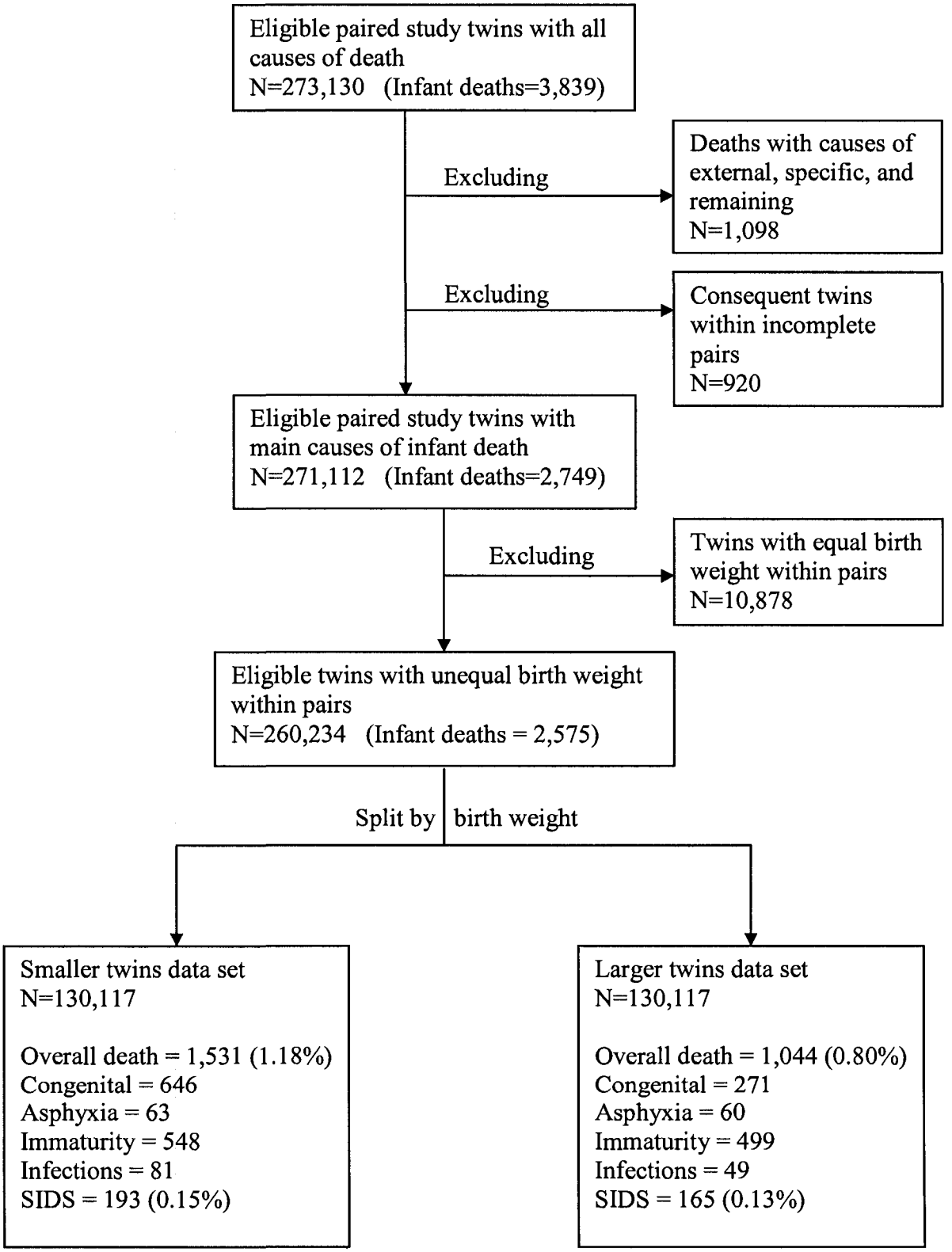


Note**: Some twins had more than one risk factor with missing values.

Appendix A-3: Data sets for SIDS and non-SIDS study in GEE analysis



Appendix A-4: Data sets of twins with smaller and larger birth weights



Appendix B: Model evaluation of GEE analysis

GEE Models		Deviance	Pearson Chi-Square	GEE Models	Deviance	Pearson Chi-Square
ID-SIDS	Variables	(value of DF)	(value of DF)	ID-Non-SIDS	(value of DF)	(value of DF)
Multivariable analysis				Multivariable analysis		
SMM-1	17 variables	0.0189	0.9803	NSMM-1	0.0607	0.9427
Univariable analysis				Univariable analysis		
SUM-1	bwdpq	0.0204	1	NSUM-1	0.0726	1
SUM-2	order	0.0205	1	NSUM-2	0.0730	1
SUM-3	sexcb	0.0204	1	NSUM-3	0.0729	1
SUM-4	agem	0.0197	1	NSUM-4	0.0722	1
SUM-5	racem	0.0202	1	NSUM-5	0.0725	1
SUM-6	edu	0.0199	1	NSUM-6	0.0725	1
SUM-7	marit	0.0201	1	NSUM-7	0.0724	1
SUM-8	caremth	0.0203	1	NSUM-8	0.0728	1
SUM-9	tobac	0.0201	1	NSUM-9	0.0729	1
SUM-10	gest	0.0204	1	NSUM-10	0.0644	1
SUM-11	sex	0.0204	1	NSUM-11	0.0730	1
SUM-12	zbga	0.0203	1	NSUM-12	0.0722	1
SUM-13	apgar	0.0205	1	NSUM-13	0.0697	1
SUM-14	deliv	0.0205	1	NSUM-14	0.0729	1
SUM-15	riskfn	0.0205	1	NSUM-15	0.0730	1
SUM-16	obstecn	0.0204	1	NSUM-16	0.0727	1
SUM-17	abnorch	0.0204	1	NSUM-17	0.0697	1

Appendix C-1: Adjusted hazard ratios and 95 percent confidence intervals in smaller twins for five main causes of infant death in relation to various risk factors, 1995-97 USA matched multiple birth file

Variable	Adjusted hazard ratios and 95% confidence intervals				
	Congenital anomalies	Asphyxia	Immaturity	Infections	SIDS
Number of deaths	646	63	548	81	193
Percentage of birth weight discordance (%)	1.22 (1.18, 1.26)	1.05 (0.93, 1.17)	0.91 (0.87, 0.94)	0.95 (0.85, 1.05)	1.02 (0.95, 1.11)
Birth order within pairs					
First	1	1	1	1	1
Second	0.98 (0.83, 1.16)	0.82 (0.49, 1.37)	0.96 (0.80, 1.14)	1.24 (0.79, 1.20)	0.84 (0.63, 1.13)
Not stated	1.16 (0.88, 1.51)	0.39 (0.12, 1.29)	1.21 (0.90, 1.62)	0.44 (0.13, 1.46)	0.70 (0.40, 1.22)
Sex combination					
MM	0.70 (0.49, 1.00)	0.53 (0.16, 1.74)	0.94 (0.64, 1.40)	0.90 (0.32, 2.55)	0.76 (0.42, 1.40)
FM / MF	0.74 (0.58, 0.95)	0.59 (0.27, 1.27)	0.86 (0.66, 1.13)	0.72 (0.36, 1.46)	1.04 (0.68, 1.61)
FF	1	1	1	1	1
Maternal age (5 years)	0.98 (0.91, 1.05)	0.97 (0.77, 1.22)	0.96 (0.89, 1.04)	0.89 (0.73, 1.09)	0.61 (0.53, 0.71)
Maternal race					
White	1	1	1	1	1
Black	0.73 (0.57, 0.92)	0.84 (0.43, 1.66)	0.72 (0.58, 0.89)	2.58 (1.54, 4.32)	1.28 (0.90, 1.83)
Others	0.88 (0.60, 1.31)	0.75 (0.18, 3.11)	0.69 (0.42, 1.13)	1.31 (0.40, 4.26)	1.26 (0.59, 2.71)

Variable	Congenital anomalies	Asphyxia	Immaturity	Infections	SIDS
Maternal education (1 year)	1.01 (0.98, 1.04)	0.96 (0.87, 1.06)	1.02 (0.98, 1.06)	0.89 (0.81, 0.97)	0.92 (0.86, 0.98)
Marital status of mother					
Married	1	1	1	1	1
Unmarried	1.36 (1.10, 1.68)	1.44 (0.76, 2.76)	0.96 (0.77, 1.18)	0.87 (0.50, 1.49)	0.91 (0.65, 1.28)
Prenatal care initiation					
First trimester	1	1	1	1	1
2nd-3rd trimester	1.12 (0.89, 1.42)	1.73 (0.90, 3.33)	1.22 (0.95, 1.56)	1.15 (0.66, 2.01)	1.13 (0.79, 1.62)
No care	0.65 (0.31, 1.39)	1.95 (0.57, 6.72)	1.32 (0.87, 2.01)	0.34 (0.05, 2.47)	1.18 (0.43, 3.25)
Tobacco use during pregnancy					
Yes	0.81 (0.61, 1.09)	0.99 (0.45, 2.17)	0.81 (0.60, 1.08)	0.79 (0.37, 1.70)	2.35 (1.64, 3.37)
No	1	1	1	1	1
Unknown	0.83 (0.63, 1.10)	0.51 (0.18, 1.41)	0.62 (0.45, 0.85)	0.89 (0.38, 2.13)	1.62 (1.00, 2.63)
Gestation (1 Week)	0.86 (0.84, 0.88)	0.80 (0.75, 0.86)	0.53 (0.51, 0.55)	0.68 (0.64, 0.73)	0.92 (0.88, 0.96)
Sex					
Male	0.65 (0.48, 0.88)	0.73 (0.26, 2.06)	0.74 (0.53, 1.04)	0.72 (0.29, 1.79)	0.59 (0.36, 0.96)
Female	1	1	1	1	1
Z-score of birth weight for-gestational-age	0.58 (0.53, 0.64)	0.61 (0.43, 0.86)	0.18 (0.16, 0.21)	0.37 (0.27, 0.50)	0.72 (0.61, 0.86)

Variable	Congenital anomalies	Asphyxia	Immaturity	Infections	SIDS
5-minute APGAR score					
<7	16.18 (13.19, 19.84)	36.77 (16.89, 80.04)	2.57 (2.09, 3.14)	1.38 (0.74, 2.56)	0.67 (0.27, 1.68)
>=7	1	1	1	1	1
Unknown	3.41 (2.49, 4.68)	10.64 (3.32, 34.10)	2.21 (1.58, 3.08)	1.92 (0.76, 4.87)	0.56 (0.32, 1.00)
Method of delivery					
C-section	1.05 (0.89, 1.24)	0.90 (0.53, 1.53)	1.13 (0.95, 1.34)	0.96 (0.61, 1.52)	0.98 (0.74, 1.31)
Vaginal	1	1	1	1	1
Medical risk factors of mother					
Reported	0.70 (0.55, 0.88)	0.55 (0.24, 1.30)	0.91 (0.70, 1.17)	1.13 (0.64, 2.02)	1.41 (1.00, 2.00)
Not reported	1	1	1	1	1
Unknown	0.91 (0.61, 1.38)	1.25 (0.39, 4.01)	0.93 (0.63, 1.39)	0.37 (0.09, 1.48)	0.91 (0.42, 1.94)
Obstetric complications					
Reported	1.27 (1.02, 1.57)	1.50 (0.81, 2.76)	1.28 (1.04, 1.59)	0.79 (0.39, 1.62)	1.34 (0.81, 2.22)
Not reported	1	1	1	1	1
Unknown	0.63 (0.39, 1.02)	0.22 (0.04, 1.11)	0.73 (0.45, 1.18)	0.97 (0.22, 4.27)	1.95 (0.83, 4.61)
Abnormal conditions of the newborns					
Reported	1.04 (0.84, 1.29)	1.21 (0.67, 2.19)	0.99 (0.82, 1.20)	1.91 (1.15, 3.17)	0.47 (0.23, 0.94)
Not reported	1	1	1	1	1
Unknown	1.30 (0.93, 1.83)	1.35 (0.40, 4.51)	1.03 (0.70, 1.51)	0.63 (0.15, 2.63)	0.61 (0.27, 1.41)

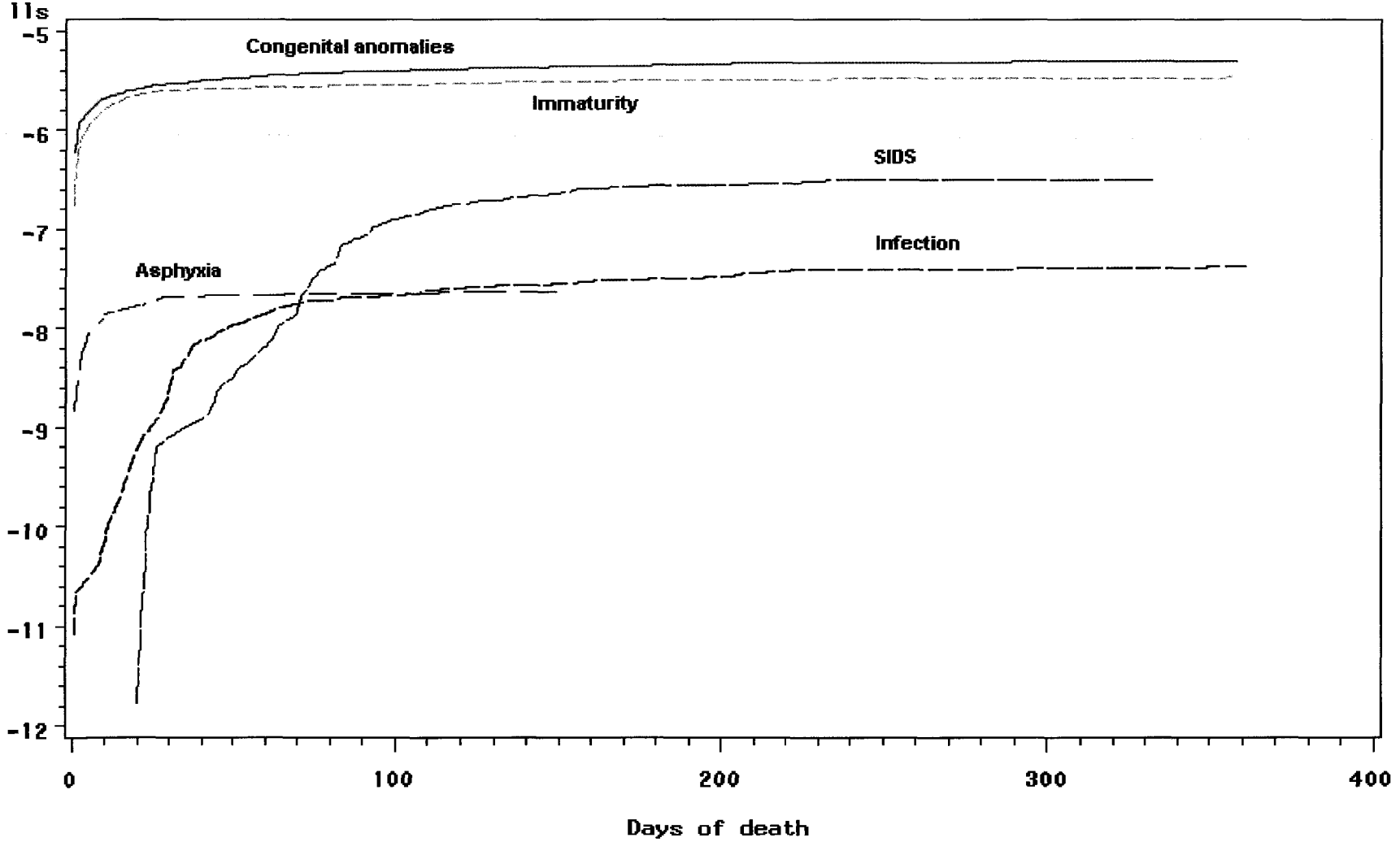
Appendix C-2: Adjusted hazard ratios and 95 percent confidence intervals in larger twins for five main causes of infant death in relation to various risk factors, 1995-97 USA matched multiple birth file

Variable	Adjusted hazard ratios and 95% confidence intervals				
	Congenital anomalies	Asphyxia	Immaturity	Infections	SIDS
Number of deaths	271	60	499	49	165
Percentage of birth weight discordance (%)	1.10 (1.05, 1.16)	1.09 (0.97, 1.22)	1.07 (1.02, 1.12)	0.95 (0.81, 1.12)	0.92 (0.83, 1.01)
Birth order within pairs					
First	1	1	1	1	1
Second	0.81 (0.63, 1.05)	0.92 (0.53, 1.58)	1.11 (0.92, 1.34)	1.13 (0.62, 2.04)	1.06 (0.77, 1.46)
Not stated	0.93 (0.60, 1.43)	1.08 (0.45, 2.58)	1.32 (0.96, 1.80)	1.09 (0.40, 2.99)	1.03 (0.60, 1.77)
Sex combination					
MM	0.78 (0.42, 1.45)	0.39 (0.10, 1.56)	0.99 (0.64, 1.55)	0.83 (0.25, 2.77)	2.52 (1.26, 5.04)
FM / MF	0.59 (0.35, 0.98)	0.63 (0.18, 2.15)	0.88 (0.60, 1.29)	1.37 (0.53, 3.52)	1.57 (0.91, 2.70)
FF	1	1	1	1	1
Maternal age (5 years)	1.06 (0.95, 1.18)	0.98 (0.78, 1.24)	0.94 (0.87, 1.02)	0.85 (0.64, 1.11)	0.71 (0.61, 0.83)
Maternal race					
White	1	1	1	1	1
Black	0.82 (0.58, 1.17)	0.54 (0.25, 1.15)	0.77 (0.61, 0.97)	1.44 (0.75, 2.79)	2.37 (1.65, 3.40)
Others	0.78 (0.40, 1.52)	0.39 (0.05, 2.82)	0.76 (0.46, 1.24)	0.73 (0.10, 5.39)	2.00 (0.97, 4.14)

Variable	Congenital anomalies	Asphyxia	Immaturity	Infections	SIDS
Maternal education (1 year)	0.97 (0.93, 1.02)	0.95 (0.85, 1.05)	1.01 (0.97, 1.05)	0.94 (0.82, 1.07)	0.94 (0.87, 1.00)
Marital status of mother					
Married	1	1	1	1	1
Unmarried	1.08 (0.79, 1.48)	1.03 (0.54, 1.97)	1.18 (0.94, 1.48)	0.59 (0.29, 1.20)	0.81 (0.56, 1.18)
Prenatal care initiation					
First trimester	1	1	1	1	1
2nd-3rd trimester	1.35 (0.96, 1.89)	1.97 (1.03, 3.77)	1.00 (0.76, 1.32)	0.62 (0.26, 1.49)	1.24 (0.85, 1.80)
No care	1.19 (0.52, 2.74)	2.16 (0.63, 7.39)	1.63 (1.10, 2.42)	0.94 (0.22, 4.04)	1.61 (0.69, 3.76)
Tobacco use during pregnancy					
Yes	0.72 (0.46, 1.13)	0.82 (0.36, 1.86)	1.13 (0.85, 1.51)	0.99 (0.42, 2.29)	3.35 (2.31, 4.86)
No	1	1	1	1	1
Unknown	0.99 (0.65, 1.52)	0.23 (0.07, 0.79)	0.99 (0.74, 1.34)	0.41 (0.11, 1.53)	0.92 (0.46, 1.82)
Gestation (1 Week)	0.88 (0.85, 0.91)	0.89 (0.83, 0.95)	0.56 (0.54, 0.58)	0.71 (0.66, 0.76)	0.92 (0.88, 0.96)
Sex					
Male	0.75 (0.43, 1.31)	0.37 (0.11, 1.26)	0.79 (0.53, 1.17)	1.01 (0.38, 2.66)	1.24 (0.70, 2.21)
Female	1	1	1	1	1
Z-score of birth weight-for-gestational-age	0.78 (0.68, 0.89)	1.09 (0.82, 1.45)	0.24 (0.21, 0.29)	0.42 (0.29, 0.60)	0.78 (0.66, 0.92)

Variable	Congenital anomalies	Asphyxia	Immaturity	Infections	SIDS
5-minute APGAR score					
<7	10.96 (7.95, 15.11)	54.93 (24.99, 120.71)	2.88 (2.33, 3.56)	1.26 (0.55, 2.88)	0.57 (0.21, 1.58)
>=7	1	1	1	1	1
Unknown	1.93 (1.18, 3.14)	14.92 (4.11, 54.15)	1.60 (1.14, 2.23)	1.80 (0.50, 6.39)	1.51 (0.75, 3.04)
Method of delivery					
C-section	0.65 (0.50, 0.85)	1.10 (0.65, 1.86)	1.18 (0.98, 1.41)	1.23 (0.69, 2.18)	1.26 (0.92, 1.71)
Vaginal	1	1	1	1	1
Medical risk factors of mother					
Reported	0.66 (0.46, 0.95)	0.75 (0.35, 1.61)	0.85 (0.64, 1.13)	1.02 (0.46, 2.25)	1.17 (0.78, 1.75)
Not reported	1	1	1	1	1
Unknown	0.67 (0.31, 1.43)	1.18 (0.34, 4.08)	1.27 (0.83, 1.94)	0.50 (0.09, 2.80)	1.01 (0.46, 2.23)
Obstetric complications					
Reported	1.10 (0.77, 1.58)	1.01 (0.50, 2.04)	0.92 (0.73, 1.17)	0.77 (0.30, 2.00)	1.48 (0.87, 2.53)
Not reported	1	1	1	1	1
Unknown	0.74 (0.31, 1.77)	0.24 (0.05, 1.15)	0.70 (0.41, 1.19)	0.70 (0.10, 5.14)	0.88 (0.33, 2.36)
Abnormal conditions of the newborns					
Reported	1.78 (1.30, 2.45)	2.78 (1.51, 5.12)	1.05 (0.86, 1.28)	1.37 (0.69, 2.71)	1.01 (0.57, 1.79)
Not reported	1	1	1	1	1
Unknown	1.28 (0.73, 2.24)	1.95 (0.56, 6.77)	1.33 (0.92, 1.94)	1.21 (0.36, 4.09)	0.13 (0.02, 0.90)

Appendix D-1: Log-log survivor plot for five main causes of infant death in smaller twins



Appendix D-2: Log-log survivor plot for five main causes of infant death in larger twins