

Mode of delivery at birth and development of asthma: A population-based cohort study

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Background: To test the hygiene hypothesis, previous studies have assessed the relationship between mode of delivery at birth and asthma incidence, but the results have been inconsistent because of potential selection and ascertainment biases.

Objective: To assess the relationship between mode of delivery at birth and asthma by following all children born in Rochester, Minn, between 1976 and 1982.

Methods: From the birth certificate, we determined mode of delivery (cesarean section vs vaginal delivery). Asthma status during the first 7 years of life was ascertained from comprehensive medical record reviews. The association between mode of delivery and asthma status was evaluated in a proportional hazards model adjusted for sex, birth weight, maternal education, and maternal age.

Results: The cumulative incidence rates of asthma among children who were born by cesarean section and vaginal delivery were 3.2% versus 2.6%, 4.6% versus 4.6%, 4.6% versus 5.8%, and 5.7% versus 6.7% at the 1st, 3rd, 5th, and 7th years of life, respectively. The adjusted hazard ratios for cesarean section in predicting asthma and wheezing episode were 0.93 (95% CI, 0.6-1.4; $P = .71$) and 0.93 (95% CI, 0.7-1.3; $P = .67$), respectively.

Conclusion: Mode of delivery is not associated with subsequent risk of developing childhood asthma or wheezing episodes. Because the effect of mode of delivery on a risk of developing asthma or wheezing episodes varies over time (ie, age), selection of the study subjects according to their ages may have influenced the findings of previous studies with a shorter follow-up period. (*J Allergy Clin Immunol* 2005;116:510-6.)

Key words: Mode of delivery, childhood asthma, wheezing episode, birth cohort, cesarean section

The hygiene hypothesis suggests that the immune system of newborns is polarized toward T_H2 cells, and subsequent exposure to microbial infections (eg, *Mycobacterium tuberculosis*,¹ measles virus,² hepatitis

A virus,³ exposure to day care and older siblings,⁴ and endotoxin⁵) creates a balanced T_H1/T_H2 response. To test this hypothesis, previous studies have examined whether mode of delivery at birth influences the risk of developing subsequent atopic conditions, because bacterial colonization of the gut in newborns born by cesarean section differs from that in newborns born by vaginal delivery.⁶⁻⁸ The results have been inconsistent; some studies found an increased risk of asthma or atopic conditions among children born by cesarean section compared with that among children born by vaginal delivery,⁹⁻¹² whereas others disputed it.¹³⁻¹⁶ Because all previous studies on the relationship between mode of delivery and subsequent development of asthma were retrospective cohort^{14,16} or cross-sectional studies,^{9-12,15,16} it is crucial to address selection and misclassification biases in either identifying the subjects or ascertaining the dependent (ie, asthma) or independent variables (ie, cesarean section). For these concerns, previous epidemiologic studies inadequately addressed selection or misclassification biases.

In addressing selection bias, the relationship between exposure to microbial infections and development of asthma seems to depend on age or life stages.^{4,17} The relative risks for microbial infections in predicting wheezing episodes were positive initially but subsequently became negative after about 4 years of age.^{4,17} Therefore, considering the relative short study period (eg, 2.9 years) of previous studies, selection of the study subjects according to age might be an important factor influencing their study findings.^{14,16} Furthermore, none of the previous studies based on birth cohorts has assessed comparability between the subjects who remained in their study areas and subjects who emigrated from the areas. This is important because ethnicity is a significant confounding factor for the relationship between mode of delivery and asthma incidence, and this concern was inadequately addressed.¹⁸⁻²⁹

For misclassification bias, all previous studies used a questionnaire to define asthma status of the subjects, but only 1 study ascertained asthma status on the basis of incident diagnoses of asthma derived from the International Classification of Diseases (version 8) and Read codes (codes commonly used in general practitioner practices in England).¹⁴ A significant discrepancy (eg, 21%) between doctors' diagnosis of asthma and parental report on asthma as well as children and adult perceptions of childhood asthma has been reported.^{30,31} Because the underlying biological or behavioral nature of mode of delivery in relation to disease or diagnosis of asthma

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Supported by the Scholarly Clinician Award of the Mayo Foundation.

Disclosure of potential conflict of interest: All authors—none disclosed.

Received for publication January 26, 2005; revised May 12, 2005; accepted for publication May 31, 2005.

Available online August 8, 2005.

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0091-6749/\$30.00

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doi:10.1016/j.jaci.2005.05.043

is difficult to determine at present, ascertainment of asthma status through medical records to avoid random error or differential misclassification bias is warranted. Also, none of the previous studies excluded deliveries preceded by prolonged rupture of membranes or converted cesarean section from vaginal delivery because of medical complications, so inclusion of these subgroups of children in the cesarean section group may be subject to misclassification bias, leading to support of a null hypothesis.

Nonetheless, the increasing trends in both cesarean section and asthma over the recent decades and their positive ecological correlation give us sufficient reasons to clarify the relationship.³²⁻³⁵ We conducted a population-based birth cohort study that followed all children born in Rochester, Minn, between 1976 and 1982 and identified asthma cases through 1983 by using predetermined criteria.

METHODS

Study design and setting

The study was a retrospective, population-based cohort study.

Rochester, Minn, is centrally located in Olmsted County, and greater than 60% of the county population resides within the city limits. In 1980, the population of Rochester was 57,890 (97% white). With the exception of a higher proportion of the working population employed in the health care industry, characteristics of the City of Rochester and Olmsted County populations were similar to those of the US white population.³⁶⁻³⁸ Population-based epidemiologic research is possible in this setting because medical care is virtually self-contained within the community and is delivered by only 2 medical centers that have maintained a common medical record system with their large affiliated hospitals and clinics for the past 90 years. This dossier-type medical record contains all inpatient and outpatient data that have been indexed in an automated form since 1935.³⁹

Study subjects

The study protocol was approved by Institutional Review Boards at Mayo Clinic and Olmsted Medical Center. Study subjects were obtained from a previously assembled database designed to examine the incidence of learning disabilities in children born to mothers who were residents of Rochester. Subjects available from the learning disability study were previously described in detail.^{38,40,41} All children born in Rochester between January 1, 1976, and December 31, 1982, were identified through computerized birth certificate information obtained from the Minnesota Department of Health, Division of Vital Statistics. A variety of information on these children was also obtained from the children's birth certificates, including mode of delivery, age of parents at birth, educational level of parents at birth, sex of children, ethnicity, legitimacy of marriage, birth weight, number of prenatal visits, weeks of gestation, Apgar scores, and complications of pregnancy, labor, and delivery.

Information on incident asthma cases for the children in the birth cohort was obtained through merging data from a previously assembled database designed to examine the incidence of asthma among all Rochester city residents between 1964 and 1983 with the data from the previously mentioned birth cohort. Because the 2 studies overlap between the years 1976 and 1982, it was possible for us to identify which children in the birth cohort were identified with asthma during those years. Thus, the subjects of the study were children who were residents of the City of Rochester and the asthma

TABLE I. Asthma criteria

Patients were considered to have *definite* asthma if a physician had made a diagnosis of asthma and/or if each of the following 3 conditions were present. They were considered to have *probable* asthma if only the first 2 conditions were present.

1. History of cough, dyspnea, and/or wheezing OR history of cough and/or dyspnea plus wheezing on examination,
2. Substantial variability in symptoms from time to time or periods of weeks or more when symptoms were absent, and
3. Two or more of the following:
 - Sleep disturbed by nocturnal cough and wheeze
 - Nonsmoker (14 y or older)
 - Nasal polyps
 - Blood eosinophilia > 300/uL
 - Positive wheal and flare skin tests OR elevated serum IgE
 - History of hay fever or infantile eczema OR cough, dyspnea, and wheezing regularly on exposure to an antigen
 - Pulmonary function tests showing one FEV₁ or forced vital capacity < 70% predicted and another with at least 20% improvement to an FEV₁ of >70% predicted OR methacholine challenge test showing 20% or greater decrease in FEV₁
 - Favorable clinical response to bronchodilator

Patients were excluded from the study if any of these conditions were present:

- Pulmonary function tests that showed FEV₁ to be consistently below 50% predicted or diminished diffusion capacity
- Tracheobronchial foreign body at or about the incidence date
- Hypogammaglobulinemia (IgG < 2.0 mg/mL) or other immunodeficiency disorder
- Wheezing occurring only in response to anesthesia or medications

The following diseases excluded the patient from study if they occurred before the incidence date:

- Bullous emphysema or pulmonary fibrosis on chest radiograph
- Alpha₁-antitrypsin phenotype ZZ alpha₁-antitrypsin
- Cystic fibrosis
- Other major chest disease such as juvenile kyphoscoliosis or bronchiectasis

cases were subjects who had onset of asthma from January 1, 1976, through December 31, 1983.

Ascertainment of asthma case (dependent variable)

The criteria for identifying incident asthma cases have been previously described,³⁶ and are detailed in Table I. Because diagnosis of asthma and wheezing episodes may be epidemiologically different, we conducted 2 separate analyses on the basis of different case definitions: (1) definite or probable asthma and (2) definite or probable asthma or single wheezing episodes. In this study, we combined both definite and probable asthma as incident asthma cases because most probable cases became definite asthma over time.³⁶

Independent variable

The independent variable in this study is mode of delivery at birth. Mode of delivery included vaginal, cesarean section, and cesarean section converted from vaginal delivery. Cesarean section converted from vaginal delivery refers to cases for which vaginal delivery was initially attempted but was unsuccessful because of some medical reasons (eg, failure to progress) and subsequently

cesarean section was performed to prevent medical complications. We categorized cesarean sections into emergency and elective cesarean sections according to the complications involved before and during delivery. Emergency versus elective cesarean section was determined independently by having the obstetric staff categorize the International Classification of Diseases diagnosis codes for the involved complications.

There were 324 cases of prolonged rupture of membrane (usually defined as longer than 18 hours) that were most likely to be treated with antibiotics prenatally and perinatally. Because previous studies reported that the prenatal exposure to antibiotics increased a risk of developing subsequent asthma (ie, confounding effect),⁴² we excluded all 324 cases of prolonged rupture of membrane as well as 12 additional cases in which the vaginal delivery was converted to cesarean section.

Statistical Analysis

Annual incidence density rates (per 100,000 person-years) as well as the cumulative incidence rates of asthma were calculated with regard to all pertinent variables listed in Table II. Age-specific and sex-specific annual incidence density rates (per 100,000 person-years) were calculated as the number of new cases of asthma diagnosed during the study period divided by the total person-years of observation. The total person-years of observation were the total time from birth to asthma diagnosis for the cases. For children in the birth cohort without a diagnosis of asthma during the study period, the total person-years were the total time from birth to emigration, death, or end of the study period (December 31, 1983). For standardization for age and sex, we used the 1980 US white population. Ninety-five percent CIs around the incidence density estimates were calculated on the basis of the assumption that the observed number of asthma cases follows a Poisson distribution. The cumulative incidence rates of asthma were calculated by using the Kaplan-Meier method, with each subject's duration of follow-up defined from the person-years described. Univariate Cox proportional hazards models were fit to evaluate the association between asthma status or wheezing episodes and each of the demographic and birth-related factors. A multivariate Cox proportional hazards model was fit to evaluate the association between asthma status or wheezing episodes and mode of delivery, after adjusting for the set of factors that were identified as significantly associated with asthma status on the basis of a stepwise variable selection process. The associations were summarized by calculating hazard ratios and corresponding 95% CIs. All calculated *P* values were 2-sided, and *P* values less than .05 were considered statistically significant. The analysis was performed by using the SAS software package (SAS Institute, Cary, NC).

Given the number of subjects and the number of asthma incidence cases, the study had 80% and 90% power to detect a hazard ratio of 1.66 and 1.80, respectively. This calculation was based on a 2-sided log-rank test with a type I error level of 5%.

RESULTS

Incidence cohort

During the period 1976 to 1982, 7463 children were born to mothers who were residents of the City of Rochester at the time of their delivery. Of these children, 21 children died, 324 children were born after prolonged rupture of membranes, and 12 were born after the vaginal procedure was converted to a cesarean section, yielding 7106 children in the birth cohort who met the study criteria. Of the remaining 7106 children, a total of 342 met the criteria for either definite or probable asthma between

1976 and 1983. An additional 151 children had single wheezing episodes during this period (of which 112 were before 2 years of age). The remaining 6613 children moved (18.5%) or died (0.7%) or were censored at the end of the study period (80.7%), all without a previous diagnosis of asthma (median follow-up of 3.8 person-years). The demographic characteristics of the birth cohort are shown in Table II.

Incidence (density) rates of asthma

The overall annual age-adjusted and sex-adjusted asthma (definite or probable) incidence rate was 1106 per 100,000 person-years. Children less than 1 year of age had an annual asthma incidence rate of 2608 per 100,000 person-years, children who were 1 to less than 5 years of age had an annual incidence rate of 805 per 100,000 person-years, and children who were 5 to 7 years of age had an annual incidence rate of 486 per 100,000 person-years. Cumulative asthma incidence rates were 2.5%, 4.5%, 5.5%, and 6.5% at the 1st, 3rd, 5th, and 7th years of life, respectively.

Mode of delivery and the incidence of asthma or wheezing episodes

Among the 7106 children, 714 (10.0%) were born by cesarean section. The overall annual incidence rate of asthma, with and without considering single wheezing episodes as cases, among children who were born by cesarean section and children who were born by vaginal delivery is summarized in Table III. There was no statistically significant association between mode of delivery at birth and the incidence of childhood asthma or wheezing episodes. Stratification of cesarean section into elective versus emergency cesarean section did not change these results: there were no significant differences in the incidence of asthma between children born by emergency cesarean section and those by vaginal delivery (hazard ratio for cesarean section, 1.2; 95% CI, 0.7-2.2; *P* = .49). Likewise, no difference in asthma incidence between children born by elective cesarean section and those born by vaginal delivery was observed (hazard ratio for cesarean section, 0.9; 95% CI, 0.5-1.4; *P* = .52). The results were similar using the alternative case definition (asthma or wheezing episodes; data not shown).

Multivariate model

On the basis of univariate Cox proportional hazards models, sex, birth weight, maternal education, and maternal age (all *P* < .05) were entered as independently associated with asthma incidence by using a stepwise variable selection process (*P* < .05). Gestational age was not included because of a colinear relationship with birth weight. Although Table II does not list all prenatal and perinatal diagnoses or complications with regard to asthma incidence, we found that only induction of labor was associated with asthma incidence (hazard ratio, 1.3; *P* = .033) in univariate analysis, but the statistical significance did not persist in our final model (*P* = .059).

TABLE II. Demographic and birth-related data of the 1976 to 1982 Rochester birth cohort and associations with asthma* incidence

Birth certificate data	Children in the birth cohort, n (%)	Asthma cases, n (%)	Unadjusted incidence rate per 100,000 person-years (95% CI)
Sex			
Male	3677 (52)	230 (67)	1719 (1504-1956)
Female	3429 (48)	112 (33)	873 (719-1051)
Ethnic group (n = 7 unknown)			
White	6819 (96)	331 (97)	1306 (1169-1455)
Other	280 (4)	11 (3)	1306 (653- 2339)
Birth weight, g (n = 17 unknown)			
<2500	256 (4)	19 (6)	2083 (1254-3253)
≥2500	6833 (96)	323 (94)	1280 (1144-1427)
Mother's age at birth, y			
≤18	146 (2)	4 (1)	798 (218-2046)
19-29	5235 (74)	251 (73)	1275 (1122-1443)
30-39	1691 (24)	86 (25)	1462 (1169-1806)
≥40	34 (0.5)	1 (0.3)	746 (19-4141)
Maternal education level			
Unknown	669	25	1588 (1028-2345)
Less than high school	422 (7)	24 (8)	1665 (1067-2478)
High school graduate	1978 (31)	96 (30)	1233 (999-1506)
Some college education	2042 (32)	126 (40)	1607 (1339-1913)
College graduate or above	1995 (31)	71 (22)	939 (733-1185)
Paternal education level			
Unknown	1112	45	1562 (1139-2090)
Less than high school	259 (4)	11 (4)	1162 (581-2081)
High school graduate	1569 (26)	92 (31)	1479 (1192-1814)
Some college education	1292 (22)	72 (24)	1402 (1097-1766)
College graduate or above	2874 (48)	122 (41)	1107 (920-1322)
Gestational age (n = 126 unknown)			
≥37 wk	6619 (95)	307 (92)	1253 (1117-1401)
<37 wk	361 (5)	28 (8)	2270 (1508-3281)
Induction of labor (n = 53 unknown)			
Yes	1402 (20)	82 (24)	1615 (1284-2005)
No	5651 (80)	256 (76)	1223 (1078-1383)
Intensive care unit (recorded only 1980-1982)			
No	2179 (98)	78 (96)	1908 (1508-2381)
Yes	34 (2)	3 (4)	5005 (1034-14599)
Number of prenatal visits (n = 113 unknown)			
<9 visits	1229 (18)	55 (17)	1277 (962-1662)
≥9 visits	5764 (82)	283 (83)	1315 (1167-1478)
Number of children at birth			
Single	6974 (98)	333 (97)	1294 (1159-1441)
Twin	132 (2)	9 (3)	1901 (869-3612)
Season of birth			
Winter	2246 (32)	105 (31)	1193 (976-1444)
Spring	1856 (26)	92 (27)	1312 (1057-1609)
Summer	1572 (22)	75 (22)	1352 (1063-1695)
Fall	1432 (20)	70 (20)	1447 (1128-1828)

*Asthma, defined on the basis of definite or probable cases in Table I.

Therefore, none of the other prenatal and perinatal complications or diagnoses was a confounding factor or covariate with regard to the relationship between mode of delivery and asthma. After adjusting for sex, birth weight, maternal education, and maternal age, the hazard ratios for cesarean section were 0.93 (95% CI, 0.6-1.4; $P = .71$; Table IV) in predicting asthma and 0.93 (95% CI, 0.7-1.3; $P = .67$) in predicting wheezing episodes.

DISCUSSION

Our study results show that mode of delivery at birth was not associated with risk of subsequent development of childhood asthma or wheezing episodes in the 1976 to 1982 Rochester birth cohort during their first 7 years of life. However, as depicted in Table III, the relationship between childhood asthma or wheezing episodes and

TABLE III. Comparison of the incidence of childhood asthma or wheezing episodes between children who were born by cesarean section and children who were born by vaginal delivery

Mode of delivery	Cumulative incidence of definite or probable asthma, % by age, y							Hazard ratio (95% CI)	P value
	0.5 y	1 y	1.5 y	2 y	3 y	5 y	7 y		
Cesarean section (N = 714)	1.7	3.2	4.1	4.4	4.6	4.6	5.7	0.97 (0.7-1.4)	.87
Vaginal delivery (N = 6392)	1.4	2.6	3.2	3.7	4.6	5.8	6.7		
Mode of delivery	Cumulative incidence of all wheezing episodes (definite/probable asthma/single wheezing episodes), % by age, y							Hazard ratio (95% CI)	P value
	0.5 y	1 y	1.5 y	2 y	3 y	5 y	7 y		
Cesarean section (N = 714)	1.9	4.5	5.5	6.4	6.6	6.9	7.9	0.97 (0.7-1.3)	.83
Vaginal delivery (N = 6392)	1.8	3.8	4.6	5.4	6.8	8.4	9.5		

TABLE IV. Summary of the results from a multivariate Cox proportional hazards model for the association between asthma status and demographic and birth-related factors

Factor	Multivariate analysis Hazard ratio (95% CI)*
Male sex	2.0 (1.6-2.6); <i>P</i> < .001
Birth weight	2.0 (1.1-3.5); <i>P</i> = .02
Maternal age	1.04 (1.01-1.06); <i>P</i> = .006
Maternal education level	
Less than high school	2.2 (1.4-3.7); <i>P</i> = .002
High school graduate	1.5 (1.1-2.1); <i>P</i> = .01
Some college education	1.9 (1.4-2.6); <i>P</i> < .001
College graduate or above	Referent
Delivered by cesarean section	0.93 (0.6-1.4); <i>P</i> = .71

*Hazard ratio per a 1-unit decrease in birth weight (grams) on the natural-log scale and per 1 y increase in maternal age, respectively.

mode of delivery at birth is not constant but varies over time.

According to our study results, during the first 2 years of life or so, children born by cesarean section were more likely to develop asthma (4.4%) as well as wheezing episodes (6.4%) compared with those born by vaginal delivery (3.7% for asthma and 5.4% including wheezing episodes). Subsequently, after 2 to 3 years of age, children born by cesarean section were less likely to develop asthma (1.3%) as well as wheezing episodes (1.5%) compared with those born by vaginal delivery (3% for asthma and 4.1% including wheezing episodes). Children born by cesarean section seem to have a higher incidence of all wheezing episodes (ie, definite or probable asthma at any age or single wheezing episodes) during the first 2 years of life, but there was no significant statistical and clinical difference (hazard ratio for cesarean section, 1.02; 95% CI, 0.8-1.4; *P* = .88). However, this nonproportional hazards violation is unlikely to cause completely inaccurate parameter estimates considering the size of hazard ratio and its *P* value as well as the results of a test statistic for a constant hazard ratio over time (*P* = .08). This nonproportional hazard for exposure to microbial infections in predicting wheezing has been reported previously.^{4,17} Stratification of cesarean section into elective versus emergency cesarean section did not influence the

results. Although the cumulative incidence of asthma over time of both groups (ie, children born by cesarean section and those by vaginal delivery) is crucial, none of the previous studies reported it.^{9-12,14-16} This epidemiologic concern becomes significant because the study findings based on younger children and a short-term follow-up may be biased, reflecting only the prethreshold relationship between mode of delivery and the incidence of atopic conditions (eg, before 1-2 years of age) carving out the threshold or postthreshold relationships.^{9,11}

Although the hygiene hypothesis suggests the protective role of exposure to microbial infections during early childhood in development of asthma,^{5,17,43,44} a considerable amount of literature posits provocative roles of microbial organisms in triggering T_H2 responses and development of atopy, suggesting "the bidirectional effects."^{13,45-57} The bidirectional effects of microbial agents on development of atopy are further complicated with a potentially increased susceptibility of individuals with asthma to microbial infections.⁵⁸ Our study results may reflect this complex interaction between host and microbial agents with heterogeneous effects on development of atopy in the context of timing of exposure. One important methodological challenge in relating our study results to supporting or disputing the hygiene hypothesis is heterogeneous and inconsistent colonization of microflora in the gut of infants born by either cesarean section or vaginal delivery over time.⁶ For example, lactobacillus colonization was more common in children born by vaginal delivery at 3 days of life compared with that of children born by cesarean section, but after 10 days, lactobacillus was more common in children born by cesarean section. Nonetheless, our study findings dispute the hygiene hypothesis. This is because either the underlying assumption of the hygiene hypothesis in assessing the influence of microbial organisms on development of atopy may be too simplistic conceptually and methodologically or the influence of microbial organisms on atopy may be weaker than what has been reported.

Strengths of our study include (1) a population-based longitudinal study design in a self-contained unified health care environment with access to medical information of all Rochester residents,⁵⁹ (2) Kaplan-Meier estimates of the cumulative incidence of asthma at different ages during

the first 7 years of life, (3) ascertainment of asthma by applying predetermined asthma criteria through a comprehensive medical record review, and (4) reasonable statistical power. In addition, a previous study compared the prenatal and perinatal complications or diagnoses between subjects in the birth cohort who moved and subjects who did not move from the community before 5 years of age, and few differences were found.³⁸

However, there are also inherent limitations in our study because of its retrospective design. Some potential confounders were not included in the model, eg, exposure to tobacco smoke or breast-feeding. These factors have been reported to be strongly associated with individual socioeconomic status, which has been included in the final model.⁶⁰ Also, including these variables is unlikely to change the final results because the β error in our study (ie, error of failing to reject a false-null hypothesis) was acceptable, and the concerns about not including certain variables become more relevant to a positive study (ie, rejects a null hypothesis) that is subject to a scrutiny for α error (ie, error of rejecting a true-null hypothesis). Because our study population is predominantly white (97%), our results may not be generalizable to populations of other races or ethnicity. However, at the cost of generalizability (ie, external validity), internal validity can be enhanced, minimizing the confounding effect of ethnicity on the study results.

In conclusion, mode of delivery is not associated with a subsequent risk of developing childhood asthma or wheezing episodes. The risks for cesarean section in association with asthma or wheezing episodes change over time, and thus, selection of the study subjects according to age might have potentially influenced the inconsistent findings in previous studies.

We thank Drs Robert Jacobson, Jill Swanson, Richard Bram, and Steve Jacobsen for their support. We thank Nicole Thompson, Lori Byrne, and Katrina Hodges for their administrative support and assistance.

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