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Impact of dairy restriction of children with Duarte galactosemia on breastfeeding of unaffected younger siblings

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B.S., Wake Forest University, 2015

Thesis Committee Chair: Stephanie Sherman, Ph.D.

An abstract of

A thesis submitted to the Faculty of the
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Abstract

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Background: Duarte galactosemia (DG) is a genetic condition characterized by 75% reduction in galactose-1-phosphate-uridylyltransferase (GALT) activity. While patients with complete GALT deficiency require immediate dietary galactose restriction, for decades it has been unclear whether infants with DG should be allowed to drink milk, a source of galactose. As a result, some families were advised to milk-restrict their DG infant; others were not. This research project examined whether being instructed to milk-restrict a child with DG impacted the likelihood that a younger unaffected sibling would be breastfed.

Methods: Participants in this cross-sectional study derived from a cohort of 325 children with DG and 249 unaffected siblings initially recruited for a study of developmental outcomes in DG. After exclusions, 135 unaffected children representing 135 separate families remained; 76 were born before their sibling with DG and 59 were born after. Unaffected younger siblings were classified by the galactose-restriction status of their DG sibling. The proportion of unaffected infants who were breastfed were compared according to three exposure groups: 1) born before a DG sibling, 2) born after a galactose-restricted DG sibling, and 3) born after a non-galactose-restricted DG sibling.

Results: We found that 76% of unaffected children born before a sibling with DG were breastfed, and that 71% of unaffected children born after an unrestricted DG sibling were also breastfed. These percentages were not significantly different as judged by a z-test ($p=0.7$). In contrast, only 53% of unaffected children born after a milk-restricted DG sibling were breastfed. This percentage was significantly different from the 76% expected ($p=0.0089$). Finally, when directly comparing breastfeeding percentages between unaffected siblings born after a sibling with DG who was versus was not galactose-restricted the trend remained but the difference was no longer significant ($p=.23$), likely reflecting the small size of one of the cohorts.

Conclusions: The observed decrease in breastfeeding of unaffected siblings born after galactose-restricted DG children suggests that this restriction not only impacted the breastmilk exposure of affected children, but also their subsequent siblings who had no medical reason not to be breastfed.

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Introduction

Diagnosis of galactosemia

Since it was first added to the Newborn Screening (NBS) test in 1963, galactosemia has gained attention as not only a potentially life-threatening disease for infants, but also as a confusing and complicated diagnosis for parents (1). Individuals with galactosemia inherit a deficiency in the enzymatic activity of galactose-1-phosphate uridylyltransferase (GALT), resulting in an accumulation of galactose metabolites in the body (2). The extent of GALT deficiency determines the type of transferase-associated galactosemia (2). Specifically, patients with nearly complete absence of GALT activity are diagnosed with Classic galactosemia (CG), while those with approximately 25% of normal activity are diagnosed with Duarte galactosemia (DG) (2).

Although DG has been detected in as many as 1 in 3,500 screened births in some states and is nearly ten times more common than CG; CG is a severe disease while DG is not. Specifically, individuals with CG can experience a life-threatening array of neonatal outcomes following milk exposure; those with DG do not (1, 3). Due to the extreme symptoms associated with CG, infants flagged by an abnormal NBS result for galactosemia are immediately taken off breast-milk (a source of galactose) and are fed low galactose formula (4). If subsequent tests confirm the diagnosis of CG, the recommended course of action is to place the patient on a lifelong galactose-restricted diet (5). However, whether galactose restriction is needed for DG patients has been a topic of debate among healthcare providers for decades and some parents of newborns with DG have been advised to galactose-restrict their baby while others have not (6).

Benefits of Breastfeeding

As a general rule, for all new mothers the current recommendation by the American College of Obstetricians and Gynecologists is to exclusively breastfeed infants for at least the first 6 months of life; however, recent estimates suggest that only 50% of new mothers will be breastfeeding at 6 months (7, 8). Breastfeeding provides a multitude of both physical and mental health benefits for both a newborn and a mother. A nested cohort study from a randomized trial of 2,862 infants who were exclusively breastfed for three months and 621 infants who were exclusively breastfed for at least six months found that the latter group were significantly less likely to experience gastrointestinal problems between the ages of 3-6 months than infants who were removed from breastmilk at three months (adjusted IDR: .35; 95% CI: .13, .96) (9). An increased risk for inadequate growth, appetite dysregulation, and obesity are a few of the other outcomes associated with not being breastfed (10).

Maternal benefits of breastfeeding are also important and are protective against a variety of negative health outcomes. For instance, maternal incidence of hypertension in a study of 55,636 women was found to be significantly elevated in mothers who did not breastfeed their first child compared to mothers who exclusively breastfed their first child for at least six months (HR: 1.29; 95% CI; 1.20, 1.40) (11). Other maternal health outcomes associated with not breastfeeding include an increased risk for breast cancer, ovarian cancer, obesity, and myocardial infarction (12).

Project Aims

Parents of children diagnosed with DG are told that DG is genetic and therefore, subsequent children are at a ¼ risk of also having DG. If these parents believe that milk is harmful for a child with DG, they may not want to breastfeed a subsequent baby until they know this child does not have DG; however, the results of this testing can take days or weeks to receive. This research project examined whether being instructed to place a child with DG on a galactose-restricted diet had ramifications for the breastfeeding of younger unaffected siblings. To test this possibility, we estimated an “expected” proportion of unaffected infants who were breastfed based on the unaffected siblings in our cohort who were born before their DG sibling. These infants were born into families unaware of their risk for DG. We then compared this expected proportion to that observed among unaffected siblings born after a sibling with DG, stratified by whether or not their affected sibling was placed on a galactose-restricted diet. We hypothesized that breastmilk feeding of unaffected siblings born after a DG sibling who was not galactose-restricted would match the expected proportion, but that breastmilk feeding of unaffected siblings born after a galactose-restricted DG sibling would be significantly lowered.

Potential Impact of Findings

There is an opportunity for public health intervention if the breastfeeding of unaffected children is influenced by having an older sibling with DG who was not breastfed. Breastfeeding of infants without DG does not need to be restricted. If parents of children with DG want to wait to breastfeed their subsequent child until they receive test results, they should be encouraged to pump and freeze until a diagnosis is confirmed. If the results are negative, the mother will still be able to provide breastmilk to her child despite the initial delay. Furthermore, if the breastfeeding of unaffected younger siblings is impacted in the presence of older galactose-restricted siblings, earlier testing of DG should be considered to avoid the potential ramifications of waiting for a diagnosis. These findings could potentially be applied to other genetic or metabolic disorders where breastmilk is contraindicated.

Materials and Methods

Study Population

Participants considered for this study included 325 children with DG and 249 unaffected siblings who enrolled and consented in Emory University IRB protocol 00081271. Parents completed a survey in RedCap containing questions on child diagnostic status, demographic characteristics, and diet. This project was based out of the Department of Human Genetics in the Emory University School of Medicine.

For this study, families with only one child were excluded, as were families that provided diet information on only one of their children. Multiples (i.e. twins, triplets) were also excluded, as breastfeeding practices are thought to differ after a multiparous birth (13). Individuals missing information on sex, diagnostic status, birth order, and age were also excluded. If multiple unaffected siblings were enrolled from a single family, only siblings born immediately before or immediately after the child with DG were included. After these exclusions, nine families were found to have both unaffected children born immediately before and immediately after their affected child. These nine families were randomized to retain either the younger sibling or the older sibling for subsequent analyses, but not both. For five of these families, the older child was removed from future analyses while for four families, the younger child was removed from future analyses. After all exclusions, 135 unaffected siblings representing 135 separate families were used for analyses.

Exposure definition

We defined three comparison groups: (1) being born before a DG sibling, (2) being born after a DG sibling who was galactose-restricted, and (3) being born after a DG sibling who was not galactose-restricted. These groups were determined by parental-report of age in relation to their sibling with DG and were cross-checked with reported birth order as a quality control measure. 76 unaffected siblings were born before their DG sibling while 59 unaffected siblings were born after their DG sibling. The latter group was then stratified based on whether or not the DG sibling was on a galactose-restricted diet (Figure 1).

It is important to note that all analyses for this study involved individuals without DG, and that data from the siblings with DG were only used to classify unaffected children into appropriate exposure groups. Specifically, the galactose-restriction status of the DG sibling's diet was used to classify unaffected younger siblings as being born after a DG sibling on a galactose-restricted diet (n = 45) or as being born after a DG sibling not on a galactose-restricted diet (n = 14). DG subjects were considered as having been on a galactose-restricted diet if they did not consume breastmilk or dairy between 2 to 6 months of age. If the DG subject consumed either breastmilk or dairy between 2 to 6 months of age, they were considered as having not been galactose-restricted. Diet during the first month of life for infants with DG was not included because many would not have received a diagnosis until well into this time frame.

Outcome definition

The outcome for this study was a dichotomous variable that was based on the proportion of unaffected siblings who consumed breastmilk during the first month of life. The first month of life was the time frame studied for unaffected siblings because it reflected the mother's intention of whether or not she planned to breastfeed the baby. If the unaffected sibling consumed either exclusively breastmilk or at least some breastmilk during this age range, they were considered as having consumed breastmilk. The proportion of unaffected siblings who consumed breastmilk between birth and one month of age was the outcome of interest for this study.

Covariates

The distribution of other demographic characteristics of the study sample by exposure (age relative to the DG sibling) and outcome status (consumed breastmilk) are presented in **Table 1** and **Table 2**, respectively. These included marital status of parents at the time of data collection, race/ethnicity, date of birth, child's age at the time of data collection, highest education level completed by either parent at the time of data collection, and income adjusted for state of residence at the time of data collection. Marital status was dichotomized as married versus not married and because of the composition of our study cohort, race/ethnicity was dichotomized as white/non-Hispanic versus other. Income adjusted for state of residence was reported as perception of income as above average, average, or below average for a respective state. Highest parental education was reported as graduate degree, bachelor's degree, or less than bachelor's degree. These covariates were categorical and were expressed as counts and percents. Chi-square and Fisher's exact tests were used to identify differences in these covariates by exposure and outcome levels.

The only continuous variable used in this analysis was child age at the time of data collection and this was reported as mean and standard deviation. To compare mean ages across levels of the exposure and the outcome, student's t-tests were used.

While the time frame of interest for unaffected siblings was the first month of life, these covariates were collected from families when the unaffected siblings were 6-12 years old. Therefore, because these characteristics were unknown during the first month of the child's life, these variables were not included as covariates in the analyses. As a result, all logistic regression models were unadjusted.

Analyses

For the first analysis, individuals born before a DG sibling were the referent group and provided the "expected" proportion of unaffected siblings who were breastfed prior to any knowledge of DG in the family. Two techniques were used to compare this proportion with the proportions unaffected siblings who were breastfed when born after a galactose-restricted versus after a non-galactose-restricted DG sibling. These methods were two-proportion z-tests and unconditional logistic regression models. Specifically, logistic regression models were used to estimate odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) for the likelihood of breastmilk consumption by exposure status.

Second, a two-proportion z-test was used to compare the proportions of unaffected younger siblings who were breastfed based on whether or not the DG sibling was galactose-restricted.

Although multiple analyses were performed, there was no need for multiple test correction since three independent groups of families were compared. These groups were: families with an unaffected child born before their DG child; families with an unaffected child born after their galactose-restricted DG child; and families with an unaffected child born after their non-galactose-restricted DG child. To be clear, no family was counted in more than one group. Therefore, two-sided p-values of less than .05 were used to assess significance. SAS 9.4 software (SAS Institute, Inc., Cary, NC) was used for all analyses.

Results

Demographic characteristics of the three comparison groups are shown in **Table 1**. Unaffected older siblings, unaffected younger siblings of galactose-restricted DG subjects, and unaffected younger siblings of non-galactose-restricted DG subjects did not differ for the majority of covariates collected in the survey. As expected, age, birth order, and year of birth differed between unaffected siblings born before versus after a DG sibling. Marital status at the time of survey completion also differed between unaffected siblings born before and born after a sibling with DG (p = .03). However, surveys were completed 6-12 years after the birth of the child, so that data on marital status at the time the child was an infant was unknown. Gender, income adjusted for state of residence, race, and highest parental education were not found to differ by birth order relative to their sibling with DG. Of note, family income did not associate with dairy-restriction of diet for children with DG in the study, consistent with the expectation that some families were advised by a health care provider to galactose-restrict their DG infant while others were not, independent of family socioeconomic status. Due to the small sample sizes, such associations were not determined for parental marital status at the time of data collection or highest parental education at the time of data collection.

Demographic characteristics by breastfeeding status (outcome measure) can be seen in **Table 2**. Like exposure status, demographic characteristics did not differ considerably with respect to the outcome. Age, gender, race, and year of birth were not significantly different between unaffected siblings who were breastfed and unaffected siblings who were not breastfed. In contrast, at the time of the survey income adjusted for state of residence, parental marital status, highest level of education of the parents, and birth order were found to differ by breastfeeding status. The results suggest that children who were breastfed were more likely than children who were not breastfed to be from families who reported above average incomes for their state of residence, from families with married parents, and from families where the parents had graduate or bachelor's degrees. These trends follow expectation from prior studies in other cohorts (14).

The expected proportion of infants who were breastfed was calculated from the experience of unaffected children born before their DG siblings. 76% of unaffected older siblings of individuals with DG were breastfed, which was subsequently used as the estimated proportion of unaffected siblings who were breasted in the study population. This proportion was compared to the proportions found among unaffected younger siblings of galactose-restricted DG siblings and unaffected younger siblings of non-galactose-restricted DG siblings in the analyses. Second, proportions found among unaffected younger siblings of galactose-restricted DG siblings and unaffected younger siblings of non-galactose-restricted DG siblings were compared to directly examine the differences between unaffected younger siblings according to galactose-restriction.

Comparison 1-breastfeeding of unaffected siblings born before a DG sibling vs. after a DG sibling on a galactose-restricted diet

A two-proportion z-test was used to assess the difference in the proportion of siblings born before a DG sibling who were breastfed (n = 76) to the proportion of siblings born after a galactose-restricted DG sibling who were breastfed (n = 45). We found that unaffected siblings born before a sibling with DG were significantly more likely to be breastfed than unaffected siblings born after a DG sibling who was galactose-restricted (76% vs. 53%; p = .0089; **Table 3**). The results from unadjusted unconditional logistic regression supported this finding and suggested that unaffected siblings born after a galactose-restricted DG sibling were 64% less likely to be breastfed than unaffected siblings born before a DG sibling. The odds of breastfeeding an unaffected sibling born after a DG sibling on a galactose-restricted diet compared to an unaffected sibling born before a DG sibling was 0.36 (95% CI: 0.16, .78, p = .01).

Comparison 2-breastfeeding of unaffected siblings born before a DG sibling vs. after a DG sibling who was not galactose-restricted

A two-proportion z-test was used to assess the difference in the proportion of siblings born before a DG sibling who were breastfed (n = 76) to the proportion of siblings born after a non-galactose-restricted DG sibling who were breastfed (n = 14). Here, the two proportions (76% vs. 71%) were not found to be significantly different (p = .70; **Table 3**). The results from unconditional logistic regression suggested that unaffected siblings born after a non-galactose-restricted DG sibling were not less likely to be breastfed than subjects born before a DG sibling. The odds of breastfeeding an unaffected sibling born after a DG sibling not on a galactose-restricted diet compared to an unaffected sibling born before a DG sibling was 0.78 (95% CI: 0.22, 2.77, p = .70). This difference was not statistically significant.

Comparison 3-breastfeeding of unaffected siblings born after a DG sibling who was galactose-restricted vs. after a DG sibling who was not galactose-restricted

A two-proportion z-test was used to assess the difference in the proportion of siblings born after a galactose-restricted DG sibling who were breastfed (n = 45) to the proportion of siblings born after a non-galactose-restricted DG sibling who were breastfed (n = 14). Here, the two proportions (53% vs. 71%) were not found to be significantly different (p = .23; **Table 3**), likely reflecting the small size of one of the samples.

Discussion

The results of the analyses conducted in this study support the original hypothesis and motivation for this study. Specifically, we found that unaffected siblings born after a DG sibling who was restricted from galactose were significantly less likely to consume breastmilk than unaffected children born before a sibling with DG; this impact was not observed when comparing unaffected children born after a sibling with DG who was not restricted for galactose. The observed decrease in breastfeeding of unaffected siblings born after a galactose-restricted DG sibling suggests that the decision to milk-restrict not only impacted the children with DG, but also their subsequent unaffected siblings. Of note, the impact on the unaffected younger siblings goes beyond the first month of life. A sub-analysis also found that among unaffected siblings not breastfed in the first month of life, none were breastfed when they were 2-6 months of age. This suggests that the initial delay is leading to a long-term decision that lasts through the entire recommended duration of breastfeeding (8).

The phrase “breast is best” is a motto that should be followed if circumstances allow. Unfortunately, many lifestyle factors influence the initiation and duration of breastfeeding. A cross-sectional study from the Arkansas Pregnancy Risk Assessment Monitoring System (PRAMS) that included 7,127 mothers of singleton births found the primary reasons for women not initiating breastfeeding (n = 2,917) included not liking breastfeeding, having work or school obligations, and having other children (15). The results of the current study suggest that milk-restricting an older sibling for a genetic cause adds to an already long list of breastfeeding barriers.

In conclusion, our findings do suggest a statistically significant consequence for the breastfeeding of unaffected younger siblings of children with DG who were removed from breastmilk when compared to unaffected older siblings. Although the comparison of proportions among unaffected younger siblings did not suggest a significant difference, the proportions were notably different (71% vs 53%) and the comparison was limited by sample size. Healthcare practitioners should address residual hesitations surrounding the breastfeeding of unaffected children and reassure parents that, if able, breastfeeding is the most beneficial option for both healthy newborns and their mothers.

Strengths and Limitations

This study had a number of important limitations. Because the data were collected using retrospective surveys, there was potential for recall bias. The average age of the unaffected siblings at the time of the survey represented the approximate length of time since the individual was breastfed. The time since the outcome occurred (age at survey) differed by exposure status, which could result in differential recall bias of the outcome. Second, the relatively small sample size used in this analysis restricted the power to detect small differences in associations. The original sample size was further reduced when individuals born after a sibling with DG were stratified by the extent of galactose restriction of their DG sibling. Third, data on potential confounders were unavailable during the relevant time period of the analyses. Specifically, the survey did not differentiate between current levels of covariates and the levels when the outcome occurred. Future questionnaires should be clearer on the timeframe of interest. Fourth, although an attempt was made to gather demographic characteristics, many vital risk factors were not collected. For instance, maternal age could be associated with the number of children in a family and with decisions on whether to breastfeed (16). Therefore, residual confounding by unmeasured confounders such as maternal age was a possibility. Finally, because our reference and test groups were independent, we cannot know whether the reference group accurately predicts the intention to breastfeed of the other groups. That the observed rate of breastfeeding in a second comparison group also closely matched the reference group helps to minimize this concern. That said, it would have been useful to include a question on the survey on breastfeeding intentions and reasons for cessation of breastfeeding.

The primary strength of this study was the straightforward ascertainment of the exposure for each of the three aims. Birth order was not only easy to report by the participants, but it was also readily verified through other covariates we gathered.

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Tables

Table 1. Demographics of study sample stratified by the exposure variable among unaffected siblings in relation to sibling with DG. These data were collected from families when their unaffected child was 6-12 years old.

Covariate	Born before DG sibling (n=76)	Born after non-galactose-restricted DG sibling[a] (n=14)	Born after galactose-restricted DG sibling[b] (n=45)	Combined (N=135)	P-value (test)
Child age in years at time of data collection, mean (SD)	10.1 (1.54)	8.6 (1.52)	7.6 (1.54)	9.1 (1.91)	<.0001 (t)
Child gender, n (%)					
Male	39 (51%)	6 (43%)	25 (56%)	70	
Female	37 (49%)	8 (57%)	20 (44%)	65	.70 (Chi square)
Family income adjusted for state of residence at time of data collection, n (%)					
Above average	47 (63%)	8 (57%)	26 (59%)	81	
Average	13 (17%)	3 (21%)	10 (23%)	26	
Below average	15 (20%)	3 (21%)	8 (18%)	26	.95 (Fisher's)
Parental marital status at time of data collection, n (%)					
Married	40 (85%)	7 (78%)	13 (57%)	60	
Not married	7 (15%)	2 (22%)	10 (43%)	19	.03 (Fisher's)
Child race, n (%)					
White, non-Hispanic	66 (87%)	14 (100%)	37 (82%)	117	
Other	10 (13%)	0 (0%)	8 (18%)	18	.29 (Fisher's)
Child year of birth, n (%)					
2003-2006	39 (51%)	4 (29%)	4 (9%)	47	
2007-2008	32 (42%)	6 (43%)	17 (38%)	55	
2009-2011	5 (7%)	4 (29%)	24 (53%)	33	<.0001 (Fisher's)
Highest parental education at time of data collection, n (%)					
Graduate degree	29 (39%)	4 (29%)	14 (32%)	47	
Bachelor's degree	18 (24%)	5 (36%)	11 (25%)	34	
Less than bachelor's	27 (36%)	5 (36%)	19 (43%)	51	.81 (Fisher's)

[a] Individuals born after a non-galactose restricted sibling with DG, defined as having consumed breastmilk or dairy between the ages of 2-6 months

[b] Individuals born after a galactose-restricted sibling with DG, defined as not having consumed breastmilk or dairy between the ages of 2-6 months

Table 2. Demographics of study sample stratified by the outcome variable defined as breastmilk consumption among all unaffected siblings in this study. These data were collected from families when their unaffected child was 6-12 years old.

Covariate	Consumed breastmilk* (n=92)	Did not consume breastmilk** (n=43)	Combined (N=135)	P-value (test)
Child age in years at time of data collection, mean (SD)	9.3 (1.85)	8.7 (2.01)	9.1 (1.91)	.11 (t)
Child gender, n (%)				
Male	45 (64%)	25 (36%)	70	
Female	47 (72%)	18 (28%)	65	.32 (Chi square)
Family income adjusted for state of residence at time of data collection, n (%)				
Above Average	62 (77%)	19 (23%)	81	
Average	12 (46%)	14 (54%)	26	
Below Average	16 (62%)	10 (38%)	26	0.01 (Chi square)
Parental marital status at time of data collection, n (%)				
Married	46 (77%)	14 (23%)	60	
Not Married	6 (32%)	13 (68%)	19	<.001 (Chi square)
Child race, n (%)				
White, non-Hispanic	81 (69%)	36 (31%)	117	
Other	11 (61%)	7 (39%)	18	.49 (Chi square)
Child year of birth, n (%)				
2003-2006	33 (70%)	14 (30%)	47	
2007-2008	38 (69%)	17 (31%)	55	
2009-2011	21 (64%)	12 (36%)	33	0.81 (Chi square)
Highest parental education at time of data collection, n (%)				
Graduate Degree	37 (79%)	10 (21%)	47	
Bachelor's Degree	27 (79%)	7 (21%)	34	
Less than Bachelor's	25 (49%)	26 (51%)	51	.002 (Chi square)

*Individuals were considered as having consumed breastmilk if they consumed any breastmilk between birth to one month of age

**Individuals were considered as not having consumed breastmilk if they did not consume any breastmilk between birth to one month of age

Table 3: Proportions, unadjusted OR's, and 95% CI's for breastmilk consumption of unaffected siblings born 1) before a DG sibling, 2) born after a galactose-restricted DG sibling, and 3) born after a non-galactose-restricted DG sibling.

Exposure group	Consumed Breastmilk*	Did not consume breastmilk**	Total infants in cohort	P-value: z-test comparison of unaffected younger siblings to unaffected older siblings	P-value: z-test comparison of unaffected younger siblings by galactose-restriction of DG sibling	OR (95% CI)
Born before DG sibling (n, %)	58 (76.3%)	18 (23.7%)	76	-	-	1
Born after DG sibling:						
galactose-restricted DG sibling[a] (n, %)	24 (53.3%)	21 (46.7%)	45	0.01	-	.36 (.16, .78)
non-galactose-restricted DG sibling[b] (n, %)	10 (71.4%)	4 (28.6%)	14	0.70	0.23	.78 (.22, 2.77)

*Individuals were considered as having consumed breastmilk if they consumed any breastmilk between birth to one month of age

**Individuals were considered as not having consumed breastmilk if they did not consume any breastmilk between birth to one month of age

[a] Individuals born after a galactose-restricted sibling with DG, defined as not having consumed breastmilk or dairy between the ages of 2-6 months

[b] Individuals born after a non-galactose-restricted sibling with DG, defined as having consumed breastmilk or dairy between the ages of 2-6 months

Figures

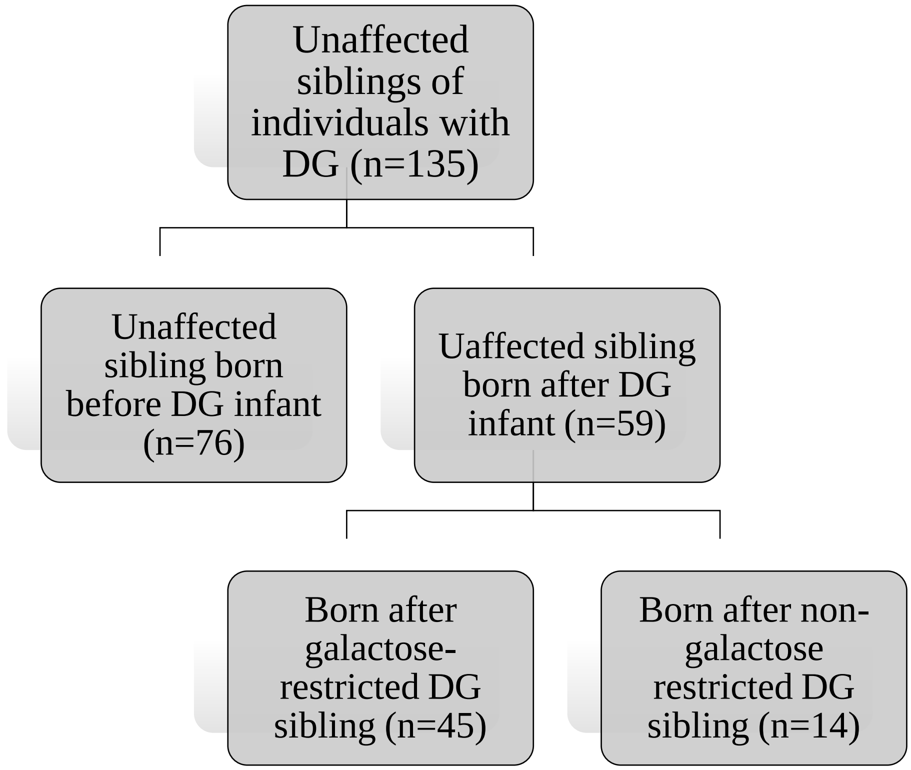

Figure 1: Distribution of unaffected siblings by birth in relation to sibling with DG. 76 unaffected siblings were born before their DG sibling and 59 were born after their sibling with DG. Among the 59 younger siblings, 45 were born after a sibling with DG on a galactose-restricted diet while 14 were born after a sibling with DG not on a galactose-restricted diet.