Symposium: Calcium-Related Chronic Diseases in Ethnic Minorities: Can Dairy Consumption Reduce Health Disparities?

Lactose Intolerance Symptoms Assessed by Meta-Analysis: A Grain of Truth That Leads to Exaggeration[1,2]

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ABSTRACT A meta-analysis was conducted to compare the lactose intolerance symptoms of lactose maldigesters after consuming lactose (as milk, lactose dissolved in water, milk products, or commercial product) with responses after a placebo under masked conditions. An English language MEDLINE search was conducted using the medical subject heading of "lactose intolerance" from 1966 to January 2002. From an initial 1,553 citations, 2 independent reviewers selected 21 studies based on study design (randomized, crossover, blind) and use of an amount of lactose likely to be found in a meal (7–25 g) and a placebo among subjects free of gastrointestinal problems and >4 years old. Mean severity of symptom responses were analyzed as standardized differences, and the presence or absence of a symptom was estimated as pooled incidence differences (ID). For severity of flatulence, the standardized difference was 0.18 (95% confidence interval [CI] −0.16 to +0.52). The CIs for abdominal bloating and pain, degree of diarrhea, frequency of bowel movements per day, and frequency of diarrhea per day also included 0. For abdominal bloating, the ID was 5.9 more people per 100 with symptoms after lactose than placebo (CI −0.07 to +0.19). This same nonsignificant relationship was found for abdominal pain. The ID for diarrhea or loose stools was 0.15 (CI 0.03 to 0.28). Although the incidence of diarrhea was significantly higher, the size of the effect was very small. The results indicate that lactose is not a major cause of symptoms for lactose maldigesters following usual intakes of dairy foods, that is, 1 cup. J. Nutr. 136: 1107–1113, 2006.

KEY WORDS: • *lactose intolerance* • *milk intolerance* • *meta-analysis* • *lactose digestion* • *flatulence*

Osteoporosis is the most readily identifiable health issue associated with inadequate calcium intake and is responsible for >1.5 million fractures annually (1–3). The Institute of Medicine has set the Adequate Intake (AI) levels for calcium at 1,000 mg per day for men and women and 1,300 mg for adolescents (4) to maximize bone density and minimize the risk for osteoporosis. Calcium intake depends, in large part, on an intake of dairy foods, and hence, the Dietary Guidelines for Americans (5) recommends consuming 3 cups/d of fat-free or low-fat milk or equivalent milk product. Data from the National Health and Nutrition Examination Survey, 1999–2000, support the observation that calcium intake is less than desirable (6). The average calcium intake among 8,604 subjects including all ages except nursing infants and children was 863 mg per day based on data from one 24-h dietary recall.

Despite the importance of dairy products, many individuals avoid these foods to prevent symptoms believed to result from lactose maldigestion (7,8). However, masked studies have shown no significant differences in symptoms after the ingestion of single servings of dairy foods containing lactose such as the 12.5 g lactose found in 240 mL (1 cup) milk as compared with 240 mL lactose-hydrolyzed milk (9). Most of these studies are very small in size, thus limiting our understanding of the actual incidence of lactose intolerance symptoms in certain populations. Therefore, we conducted a meta-analysis of existing literature to quantitatively determine the severity of symptoms of lactose intolerance from existing clinical trials. We also used meta-analysis to estimate the incidence of lactose intolerance symptoms by comparing the occurrence of symptoms among lactose maldigesters after consuming milk or other lactose-containing foods compared with placebo under masked conditions.

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MATERIALS AND METHODS

Data acquisition and abstraction. We searched the English-language literature for studies using the medical subject heading (MeSH) of "lactose intolerance" by a MEDLINE search (1966 through January 2002). The search found 1,553 citations. Two reviewers trained in the biological sciences independently screened the titles using the terms *symptoms* and *study design* (randomized, crossover, masked). Articles were eliminated if the study population included individuals who were malnourished, taking prescription medications, or diagnosed with gastrointestinal (GI) disorders or AIDS. We identified 108 citations as potentially relating to the primary aim of this meta-analysis. The titles and abstracts of these articles were further examined using the same screening criteria. Secondary articles pertaining to prevalence estimates of lactose maldigestion ($n = 167$), methods for assessing lactose maldigestion and/or intolerance ($n = 43$), and policy papers were also collected ($n = 89$). These secondary papers were used to scan for citations not identified in the literature search. The citations from a review conducted by Scrimshaw and Murray (10) were also reviewed to ensure completeness.

A total of 53 articles were identified as potentially relevant, and additional references from these articles were examined. Two reviewers independently reviewed each article to determine whether the study met the criteria for eligibility for further analysis: crossover study design with a lactose-free or low-lactose product (0–4 g) and an equivalent product containing an amount of lactose likely to be found in a meal (7–25 g), an attempt to mask subjects to the lactose content of each product, and symptom responses clearly reported as a rating of severity or frequency of occurrence by lactose exposure level; results from lactose maldigesters separate from lactose digesters or ill subjects, and age of subjects >4 y. Fourteen of the articles were excluded for lack of a lactose-free control or for a study design not masked (11–24). Ten articles were excluded because of unclear reporting of symptoms (25–34). Five articles had cross-sectional study designs or results that were not separated by disparate groups (7,8,35–37). Two articles were excluded because the lactose dose was too high (38,39), and 1 article specifically examined pharmacological effects (40). Therefore, 21 articles were eligible for inclusion.

If symptoms were reported following multiple levels of lactose, the symptomatic response to the lactose amount closest to a serving of milk (12 g) was used. In studies in which test products varied in fat content, symptomatic responses to the test products with the lowest fat content were selected. Within an article, the trials using a lactose-hydrolyzed product as control were used in preference to trials using a product accompanied by an oral enzyme control. In 1 article (41), results were presented for 2 samples of subjects. The data from the group with the lowest prevalence of past GI symptoms were used for this meta-analysis. One study (42) identified lactose maldigesters as symptomatic and asymptomatic; data from the former group were used.

Six studies used a quantitative scale for measuring self-reported severity of symptoms (42–47). Ten studies reported symptoms as incidence without regard to severity of the symptoms (41,48–56); and 5 studies reported both symptom occurrence and severity (57–61).

Study quality was independently evaluated using previously published recommendations (62,63). Reports were reviewed by 2 individuals for the presence or absence of 11 factors of a well-designed study, e.g., level of masking, clear definition of exclusion criteria, sampling frame, and experimental design. The maximum achievable score was 13. After completing the quality scoring of the 21 reports, each reviewer rescored 6 reports a minimum of 1 week later. The intrareviewer reliabilities were $r = 0.99$ ($P = 0.007$) for reviewer 1 and $r = 0.76$ ($P = 0.078$) for reviewer 2, indicating acceptable reliability of scoring. The interreviewer reliability was excellent, $r = 0.85$, ($P < 0.001$). Therefore, the final study quality score was an average between the 2 reviewers. Studies at or above the group median, 9.5, were considered of highest quality.

Data synthesis and statistical analysis. Symptom effect size was defined as the mean self-reported severity of symptom rating following a lactose dose less the mean self-reported severity of symptom rating following the placebo, divided by the pooled SD of both values. This method was selected from Pettiti (64, p. 123) for studies using different scales to measure effect (responses). This severity of symptom effect size was calculated from data collected at the longest time reported from exposure.

The SEM or SD was calculated from the raw data points directly or measured in the error bars of graphic displays (42,46,58,60). The SD was estimated for 4 studies (57,58,60,61) by dividing the interquartile range by 1.36. In one study (47), averages for symptom response were reported by lactose maldigesters experiencing symptoms and lactose maldigesters experiencing major symptoms. These 2 groups were pooled using standard methods (64).

Symptom effect sizes were calculated from the 11 eligible studies by type of symptom among the lactose maldigesters. The summary estimates of symptom effect were calculated with weights based on sample size and sample variance (64). The pooled symptom effect size and a 95% confidence interval (CI) were calculated for each reported symptom based on the number of studies providing data on each endpoint, that is, abdominal bloating ($n = 4$), abdominal pain ($n = 6$), degree of loose stools or diarrhea ($n = 3$), flatulence ($n = 6$), 3–4 symptoms combined ($n = 5$), bowel movements, frequency/d ($n = 3$), diarrhea, frequency/d ($n = 3$), and passage of flatus, frequency/d ($n = 4$).

The difference in incidence of symptoms was computed using the proportion of total subjects reporting symptoms after lactose and after placebo (64). We defined incidence difference as the proportion of individuals reporting symptoms following the lactose exposure less the proportion of individuals reporting symptoms following the placebo, divided by the pooled SD of the 2 proportions (64). Some reports divided occurrence of symptoms into mild and severe. These were combined as positive for symptoms. Incidence differences were calculated from the 15 eligible studies by symptom among the lactose maldigesters. The summary estimates of incidence differences were calculated with weights based on sample size (64). The pooled incidence difference and a 95% confidence interval (CI) were calculated for abdominal bloating ($n = 4$), abdominal pain ($n = 6$), degree of loose stools or diarrhea ($n = 4$), flatulence ($n = 5$), and multiple symptoms combined ($n = 11$). P-values < 0.05 were considered significant.

The effect sizes for all pooled estimates were examined with a chi-square test for homogeneity to test the hypothesis that the studies were derived from a population with similar effect sizes (64). Any differences in homogeneity were examined by subgroup analysis.

RESULTS

Description of studies. Of the 21 studies (Table 1) comparing effects of lactose and a placebo, 11 studies (42–47,57–61) examined the self-reported severity of symptoms, and 15 studies (41,48–61) reported the incidence of symptoms without regard to severity. Five of the 21 studies contained both severity of symptoms and incidence (57–61). Lactose doses were ~7–25 g/dose. All eligible reports were described as randomized with regard to treatment order. Seven studies (42–44,46,58,60,61) of the 11 reporting symptoms were double-masked to the lactose exposure at time of administration, and 11 (41,50–56,58,60,61) of the 15 studies reporting incidence of symptoms were double-masked.

Severity of symptoms. Symptom rating scales for self-reporting severity of symptoms was not consistent across the studies. Therefore, no pooled estimate for severity includes all 11 studies. Studies contributing data to a given symptom are listed by first author in Figure 1 for severity of symptom and in Figure 2 for frequency of a symptom, an alternative form of severity. Five reports included a summary score to represent the product of multiple symptoms (47,57–60); however, the severity of abdominal pain and severity of flatulence were the only 2 symptoms consistently included in these summary scores. The difference in severity of symptom rating scales required that the pooled estimate use a method that accounts for dissimilarity in

TABLE 1

Characteristics of 21 studies reporting either severity of symptom scores, incidence, or both following lactose dose or placebo in lactose maldigesters listed chronologically

First author (year published)	*n*	Sex (*n*)	Age, mean, y (range)	Race/ethnic groups as reported by authors, *n*	Administration of lactose and placebo[1]	Lactose, *g*		Duration of symptom recording	Quality score[2]
						Treatment	Placebo		
Suarez (43) (1998)	31	F (31)	46.9	Asian 9, Black 2, Hispanic 5, Jewish 4, White 10	240 mL 1% fat milk, 28 g hard cheese, 240 g low-fat yogurt with self-selected breakfast and dinner	34/d or 11/dose	2	1 wk	13
Vesa (57) (1997)	30	F (27) M (3)	46 (18–74)	Estonian	200 mL 0.1% fat milk before self-selected breakfast and lunch	19.6/d or 9.8/dose	0	2 d	9.25
Suarez (42) (1997)	19	F (10) M (9)	34 (18–43)	Asian 12, Black 2, Latin 1, White 4	240 mL 2% fat milk with self-selected breakfast and dinner	23.6/d or 11.8/dose	0	1 wk	11
Hertzler (45) (1996a)	20	F (5) M (15)	30	Asian 14, Black 2, Hispanic 2, White 2	250 mL tap water with dissolved lactose with self-selected breakfast, lunch, and dinner	42/d[3] or 14/dose	0	10 d	7.25
Vesa (58) (1996)	39	F (24) M (15)	47.2 (27–70)	Finnish	200 mL fat-free milk for breakfast	7/dose	0	1 d	10
Hertzler (46) (1996b)	13	F (6) M (7)	32 (21–42)	–[4]	240 mL tap water with dissolved lactose for breakfast	12/dose	0	1 d	9.5
Suzrez (44) (1995)	21	F (13) M (8)	29.4 (18–50)	Asian 7, Black 1, Hispanic 5, White 8	240 mL 2% fat milk with standard breakfast	12.1/dose	0	1 wk	12.6
Rosado (47) (1994)	211	–	(13–60)	Northern, Central, and Southern Mexico	360 mL whole milk for breakfast	18/dose	0.25	1 d	8.1
Brand (48) (1991)	6	F (5) M (1)	32.7 (29–44)	Asian	300 mL whole milk for breakfast	14.4/dose	<0.25	1 d	7.5
Onwulata (49) (1989)	10	F (4) M (6)	27.6 (23–36)	Country of origin in Africa 6, country of origin US 4	400 mL whole milk for breakfast	18/dose	5	1 d	7
Martini (59) (1988)	12	F (5) M (7)	(21–58)	Asian 8, Black 1, Jewish 2, Italian 1	240 mL commercially manufactured food supplement with a standard breakfast	19/dose	0	1 d	8
Cavalli-Sforza (50) (1986)	40	F (–) M (–)	(18–69)	Italian	250 mL skim milk with self selected meal	12.75/dose	1.6	1 d	9.75
Rosado (51) (1984)	25	F (–) M (–)	(19–53)	Majority of Mexican descent	360 mL whole milk	18/dose	–	1 d	9.9
Sorensen (60) (1983)	35	F (19) M (16)	(20–60)	Residents of Denmark originally from Latin America	250 mL skim milk with breakfast of white bread and butter	11.3/dose	1.6	1 d	9
Pedersen (61) (1982)	11	F (7) M (4)	43 (20–67)	–	500 mL regular milk for breakfast	25/dose	3.75	1 d	9.1
Lisker (41) (1980)	101	F (101)[5]	(5–14)	Residents of Mexico	250 mL whole milk for breakfast	12.5/dose	0	1 d	8.4
Kwon (52) (1980)	45	–	(14–19)	Black 21, Asian 4, White 20	240 mL 1% fat chocolate dairy drink for breakfast	10.8/dose	0	1 d	9.5
Haverberg (53) (1980)	67	–	(14–19)	Black 48, Latin American 5, White 14	240 mL 1% fat chocolate dairy drink for breakfast	10.8/dose	0	1 d	10.25
Rorick (54) (1979)	7[6]	F (–) M (–)	(60–97)	Black 5, Jewish 7, Northern and Western European 8, Southern Italian 3	240 mL 1% fat chocolate dairy drink with standard lunch	10.8/dose	0	1 d	9.6
Lisker (55) (1978)	97	F (–) M (–)	(16–50)	Residents of Mexico	250 mL milk for breakfast	12.5/dose	0	6 h	10
Paige (56) (1975)	22	–	(13–19)	Black	240 mL whole milk for breakfast	12/dose	0	90 min	9.25

[1] The placebo was usually lactose-hydrolyzed milk or yogurt. When lactose was dissolved in water, then the placebo was a sweetener dissolved in water.
[2] See "Methods" section for a description of this variable. Studies at or above 9.5 were considered of highest quality.
[3] This represents only the first day in the protocol comparing lactose and dextrose.
[4] – indicates not specified.
[5] The number of subjects represents the urban population from this study.
[6] Of the 23 subjects in this study, information was adequately provided for 7.

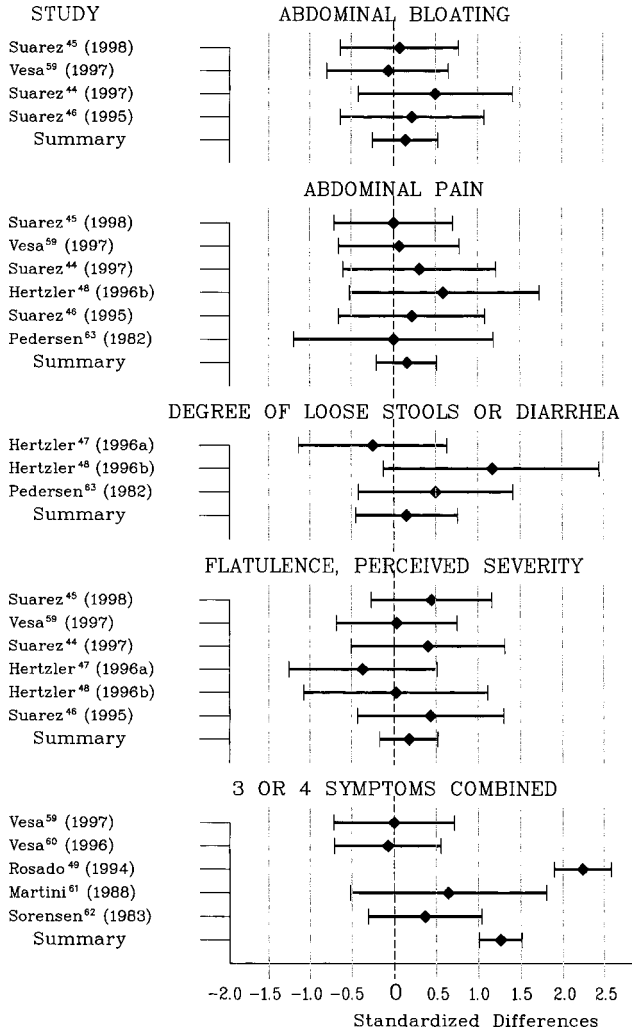

FIGURE 1 Symptom effect sizes of studies reporting severity of symptoms following lactose or placebo among lactose maldigesters presented as standardized differences (SD). A SD of 0 indicates that the severity of symptoms reported following lactose is not different from the severity reported after placebo. The 3- or 4-symptom combined group represents a cumulative score of different symptoms as reported in the studies. The lactose doses ranged from 7 to 25 g/dose. The SDs are for both men and women between ages of 13 and 74 years. The summary includes all studies within each symptom group.

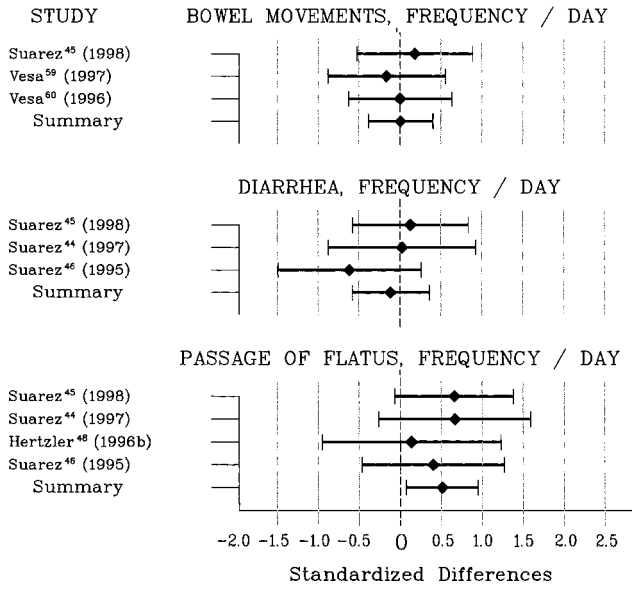

FIGURE 2 Symptom effect sizes of studies reporting frequency of symptoms following lactose or placebo among lactose maldigesters presented as standardized differences (SD). A SD of 0 indicates that the frequency of symptoms reported following lactose is not different from the frequency reported after placebo. The lactose doses ranged from 7 to 25 g/dose. The SDs are for both men and women between the ages of 13 and 74 years. The summary includes all studies within each symptom group.

the measures. The frequency scales, e.g., bowel movements/d, were recorded as absolute numbers.

The overall pooled symptom effect sizes for a variety of symptoms after lactose compared with placebo are summarized in Figures 1 and 2. For perceived severity of flatulence from 6 eligible reports, the pooled symptom effect size was 0.18 (95% CI, −0.159 to +0.523). The 95% CI for abdominal bloating, abdominal pain, degree of diarrhea, frequency of bowel movements, and frequency of diarrhea also included 0. The pooled symptom effect size for the multiple symptoms combined was 1.26 (95% CI 1.00 to 1.51); however, the test of homogeneity among this cluster of 5 reports was highly significant, ($P <$ 0.001), suggesting heterogeneity. The study of Rosado et al. (47) used a dual rating system unlike the rating systems used in the other reports. Without this study, the pooled symptom effect size was 0.12 (95% CI −0.25 to +0.48), and the test of homogeneity failed to reach significance ($\chi^2 = 3.72$ with 3 *df*; $P > 0.75$).

Frequency of flatulence as a measure of severity after consumption of lactose was significantly greater than that after placebo; pooled symptom effect size was 0.51 (95% CI 0.08 to 0.95). When this estimate was restricted to the highest-quality studies (42–44), the frequency of flatulence was not significantly greater for the lactose exposure compared with placebo. The pooled symptom effect size for frequency of flatulence among the highest-quality studies was 0.35 (95% CI −0.12 to 0.82).

Incidence of symptoms. The overall incidence differences for a variety of symptoms after consumption of lactose compared with placebo are summarized in Figures 3 and 4. For abdominal bloating from 4 eligible studies, the pooled incidence difference was 5.9 more people per 100 reported symptoms after lactose consumption compared with placebo (95% CI −0.07 to +0.19). The 95% CI for abdominal pain also included 0. The pooled incidence difference for diarrhea was 0.15 (95% CI 0.02 to 0.28). Of the 4 studies that included incidence of diarrhea, only 1 (54) study was classified as highest quality and reported no difference in diarrhea following intake of lactose or placebo. The incidence difference for flatulence based on the highest-quality studies (54,58) included 0, i.e., −0.03 (95% CI −0.23 to 0.17).

The pooled rate difference for the summary incidence of multiple symptoms was 0.14 (95% CI 0.09 to 0.19). The test of homogeneity among this cluster of 11 reports was highly significant ($P < 0.001$), suggesting heterogeneity. When the analysis is limited to the studies receiving quality scores above the median (51–55), the pooled rate difference was slightly higher at 0.16 (95% CI 0.10 to 0.23); however, the problem of heterogeneity still persisted. Because the onset of symptoms measured in the studies was inconsistent, pooling the rates for these different symptoms may not be sensible or practical.

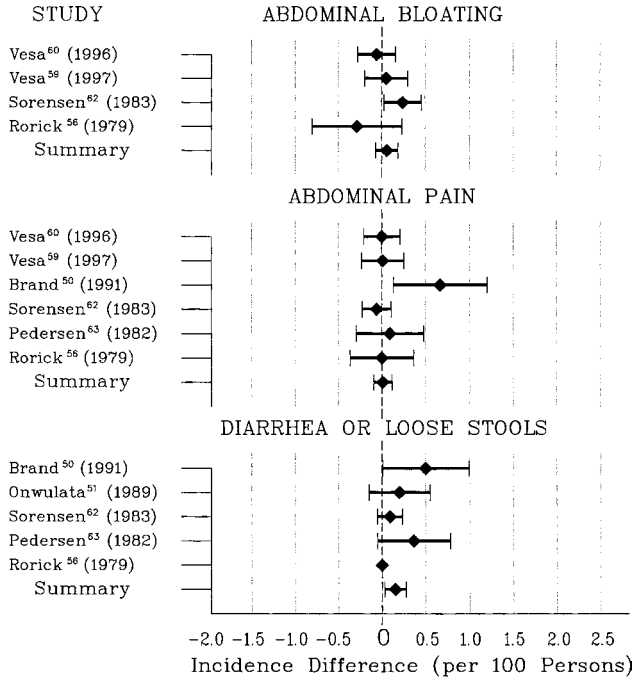

FIGURE 3 Incidence difference of studies reporting symptoms following lactose or placebo among lactose maldigesters, presented as incidence differences (ID) per 100 persons for abdominal bloating, abdominal pain, and diarrhea or loose stools. An ID of 0 indicates that the incidence of symptoms reported after lactose is not from that after placebo. The lactose doses ranged from 7 to 25 g/dose. The SDs are for both men and women between ages 5 and 74 years. The summary includes all studies within each symptom group.

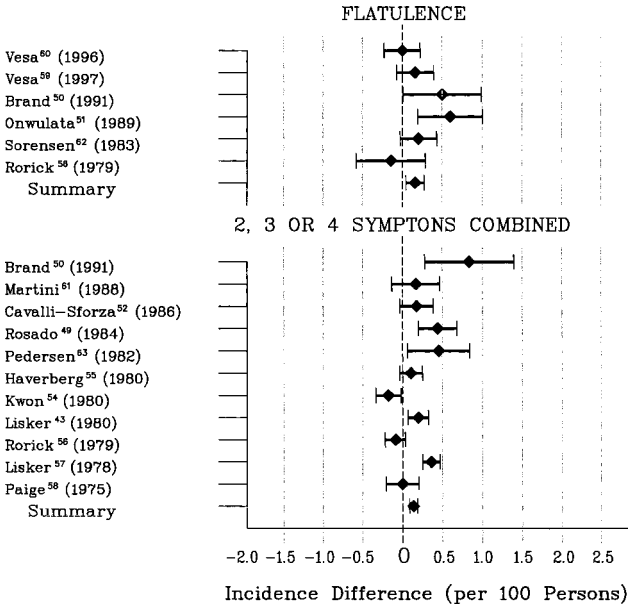

FIGURE 4 Incidence difference of studies reporting onset of symptoms following lactose or placebo among lactose maldigesters presented as incidence differences (ID) per 100 persons for flatulence. The 2-, 3-, or 4-symptom groups represent a cumulative incidence of multiple symptoms; no study combined the same set of symptoms. An ID of 0 indicates that the incidence of symptoms after lactose is not different from that after placebo. The lactose doses ranged from 7 to 25 g/dose. The SDs are for both men and women between ages 5 and 74 years. The summary includes all studies within each symptom group.

DISCUSSION

These results indicate that the severity of GI symptoms reported by lactose maldigesters were not different after they consumed an amount of lactose equivalent to a cup of milk (~12 g lactose) or receiving a placebo under masked conditions. This included perceived severity of abdominal bloating, abdominal pain, degree of loose stools or diarrhea and flatulence. Even the frequency of bowel movements and diarrhea after a normal dietary lactose dose compared with placebo were not different. The only symptom perceived to be worse after lactose than placebo was frequency of flatus per day, and this symptom was not significantly worse when analysis was limited to high quality studies. The actual incidence of symptoms of abdominal bloating, abdominal pain, and flatulence were not different after an intake of lactose equivalent to a cup of milk compared with placebo. The data for incidence difference of loose stools or diarrhea were inconsistent.

The differences in severity of symptoms between lactose and placebo were small despite the use of assumptions throughout the data abstraction that would potentially contribute to increased intolerance symptoms. The studies included a large proportion of adults, and symptom responses following ingestion of lower-fat dairy products were used over higher-fat choices. These 2 factors are putatively associated with risk for elevated symptom severity (65).

There are limitations of meta-analysis. Results are combined from studies that may differ in methodology and include noncomparable populations. This was especially problematic when the multiple symptom results were pooled. In almost all cases, the symptoms included in the "sum of all symptoms" reported from each study were not the same symptoms; for example, one study would include abdominal pain, flatulence, and loose stools or diarrhea, whereas another would include bloating, flatulence, and diarrhea. Thus, it was not surprising that these outcomes displayed heterogeneity. Some argue that a single summary estimate of effect should not be calculated from disparate study results (66). However, several important studies (41,50–53,55,59) only reported sum of symptoms results, and therefore the decision was made to include these studies. Their inclusion does emphasize the possible limitation of reporting 1 multiple-symptoms response rather than individual symptoms. Another problem with meta-analysis is publication bias, that is, not publishing small negative studies. On the other hand, published negative studies were included in our summary estimates because these studies are more likely to be published with regard to lactose maldigestion and intolerance.

The dose of lactose consumed is likely a key factor in determining the potential for symptoms of lactose intolerance. Unfortunately, in this analysis, there was insufficient variation in the study doses to distinguish a dose–response relationship. The dose is closely related to the amount of fluid milk consumed because fluid milk is the major source of lactose in the diet. The dose of lactose that results in symptoms in the majority of a population of maldigesters is probably near 25 g (that found in ~2 cups of milk), whereas doses below 12 g are not noticeable in masked conditions (45). Johnson et al. (26) demonstrated that African American young adults who claim intolerance to moderate amounts of milk could ultimately adapt and tolerate 12 g lactose in milk after introducing and increasing milk intake over a 6- to 12-week period.

Some maldigesters who have experienced symptoms following the consumption of large amounts of milk may become psychologically sensitized to the consumption of any amount of milk (42). Subjects have complained that even a very small amount of milk in coffee results in symptoms of intolerance.

Others just state that they "do not like milk" and choose to avoid it. Such avoidance of milk is likely a major obstacle in obtaining adequate calcium in the U.S. diet. Further, the recent American trend of larger portion sizes (67) exacerbates individuals consuming amounts of lactose that can be tolerated. Lactose in large servings of frozen yogurts, shakes, and milk may exceed that which can be tolerated by maldigesters. Physicians and other health care workers need to work with patients to urge consumption of single servings of dairy products throughout the day, preferably with meals (42) and reiterate that the serving size for milk is 1 cup for children and adults (5).

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