

Do patients with lactose intolerance exhibit more frequent comorbidities than patients without lactose intolerance? An analysis of routine data from German medical practices

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Abstract

Background The increase in food intolerances poses a burgeoning problem in our society. Food intolerances not only lead to physical impairment of the individual patient but also result in a high socio-economic burden due to factors such as the treatment required as well as absenteeism. The present study aimed to explore whether lactose intolerant (LI) patients exhibit more frequent comorbidities than non-LI patients.

Methods The study was conducted on a case-control basis and the results were determined using routine data analysis. Routine data from the IMS Disease Analyzer database were used for this purpose. A total of 6,758 data records were processed and analyzed.

Results There were significant correlations between LI and the incidence of osteoporosis, changes in mental status, and the presence of additional food intolerances. Comparing 3,379 LI vs. 3,379 non-LI patients, 34.5% vs. 17.7% ($P<0.0001$) suffered from abdominal pain; 30.6% vs. 17.2% ($P<0.0001$) from gastrointestinal infections; and 20.9% vs. 16.0% ($P=0.0053$) from depression. Adjusted odds ratios (OR) were the highest for fructose intolerance ($n=229$ LI vs. $n=7$ non-LI; OR 31.06; $P<0.0001$), irritable bowel syndrome ($n=247$ LI vs. $n=44$ non-LI; OR 5.23; $P<0.0001$), and bloating ($n=351$ LI vs. $n=68$ non-LI; OR 4.94; $P<0.0001$).

Conclusion The study confirms that LI should not be regarded as an isolated illness but considered a possible trigger for further diseases. Additional research is necessary to assert more precise statements.

Keywords Lactose intolerance, maldigestion, comorbidity, health services research, routine data

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Introduction

Although the intolerance of milk and milk products is not a disease unique to modern times, it was only at the beginning of the 19th century [1] that it garnered the attention of the scientific community. In most people, a deficiency of the enzyme lactase-phlorizin hydrolase ("lactase"), which splits the disaccharide lactose contained in milk into galactose and glucose, causes this problem. Lactose ingested with food is only hydrolyzed insufficiently in individuals who suffer from lactose intolerance (LI) [2]. The inadequate splitting of lactose in the colon results in short-chain fatty acids, hydrogen, carbon dioxide, and methane [3]. Most sufferers complain of abdominal discomfort, bloating, flatulence, and osmotic diarrhea. However, non-specific symptoms such as headaches, depression, chronic fatigue, concentration problems, and muscle pain may also be related to LI [4].

Tolerance of dairy products varies greatly between patients [5]. Approximately 70% of the global population have lactase non-persistence [6], whereas in Germany and Austria about 20-25% of the population are affected by this condition [7].

Therapy involves a low-lactose/lactose-free diet. Numerous studies have been conducted regarding the development, pathophysiology, and treatment of LI, yet only few publications have dealt with the comorbidities resulting from this food intolerance. LI has been associated with osteoporosis [1,8,9], depression [4], and ovarian cancer [10]. To this end, the present study aimed to explore whether there is a morbidity difference between patients with medically diagnosed LI and patients without LI in general medical practices.

Patients and methods

Database

Anonymous data from the IMS Disease Analyzer Database were used for the present study. In addition to general practitioners and internal specialists, the database also includes data from various medical specializations in Germany. The database provides a complete listing of all relevant patient information per practice. The data was obtained directly from computers used in the respective practices and checked for plausibility, combined with additional relevant information such as pharmaceutical pricing, ATC and ICD coding. The database is updated monthly and contains only anonymous data in accordance with privacy regulations; it is not possible to identify individual physicians or patients [11].

The representativeness of the Disease Analyzer database has been scientifically tested and proven [12]. Scientific studies based on data from the "Disease Analyzer" database and, in most instances, conducted in collaboration with universities and research centers have examined various diseases such as diabetes mellitus, hypertension, osteoporosis, and diseases in childhood [12-15].

Study population

Initially, all patients who had a confirmed diagnosis of LI (ICD 10: E73) in 2012 were selected. These patients had to have consulted a physician both in the first and second half of 2012 and had to have been observable in the practice for at least 365 days prior to the LI diagnosis. 3,959 LI patients met the inclusion criteria. The control group was composed of patients who had visited the practice at least once in both halves of 2012 and were observable for one year prior but whose entire medical history did not include an LI diagnosis. Both diagnostic groups included men and women of all ages as well as statutorily and privately insured patients. The data were then matched by age (45.7 years), gender (27.3% male), insurance status (3.4% privately insured), and treating physician. This

resulted in 3,379 LI patients and 3,379 non-LI patients (control group).

Morbidity status

During the first stage, LI and non-LI groups were compared in terms of the Charlson Comorbidity Score (CCS) [16]. The occurrence of selected diseases of the digestive system (abdominal and pelvic pain, nausea and vomiting, dysphagia, flatulence, esophagitis, gastritis, ulcers, functional dyspepsia, gastroenteritis and colitis, irritable bowel syndrome, and malignant neoplasms of the digestive organs), the musculoskeletal system (inflammatory polyarthropathies, arthrosis, deformities of the spine and back, spondylopathies, back pain, and osteoporosis), as well as mental disorders (depression, panic and anxiety disorders, somatoform disorders, schizophrenia, and bipolar affective disorders) was subsequently examined in both groups.

Statistical analysis

The probability of a selected comorbidity diagnosis in LI patients compared with the non-LI group was evaluated descriptively and by means of a multivariate logistic regression. The following variables were included in the model: age, gender, insurance status, health insurance providers (AOK, BKK, TK, other), specialist group (pediatrician vs. general practitioner), region (old vs. new federal states), city size (<100,000 inhabitants vs. ≥100,000 inhabitants). All other concomitant diagnoses as well as the calculated variable from the Charlson comorbidity index were included in the model as potential covariates "n" in order to exclude their influence on the effect of LI through the adjustment. An odds ratio and the corresponding 95% confidence intervals and P-values for the significance of differences between the patients with and without LI were specified for each analyzed disease. The significance level was set at $P \leq 0.05$. Calculations were performed using the SAS 9.3 statistical software.

Results

Of the 6,758 patient data sets used, 27% (n=1,844) comprised males and 73% (n=4,914) females, with an average age of 45 years. At first glance, the comparison using the Charlson comorbidity index showed differences between the two patient groups in terms of liver diseases (8.0% LI vs. 5.6% non-LI; $P < 0.0001$) and peptic ulcers (2.3% LI vs. 1.2% non-LI; $P = 0.0374$). As explained in the methods section, all variables given in Table 1 (i.e. all Charlson comorbidity index diagnoses and further concomitant diagnoses) were included in our regression model. After these adjustments, however, this difference disappeared, whereby both study groups were comparable (Fig. 1).

The most common complaints of LI patients were abdominal discomfort, bloating, vomiting, heartburn, and indigestion (Table 1). In addition, these patients suffered from “irritable bowel syndrome” much more frequently than non-LI patients (7.3% LI vs. 1.3% non-LI; $P < 0.0001$; OR 5.23). A highly significant correlation between lactose and fructose malabsorption could also be noted (6.8% LI vs. 0.2% non-LI; $P < 0.0001$; OR 31.06) (Table 2). The analysis of musculoskeletal diseases demonstrated that LI individuals suffered from osteoporosis more frequently than non-LI individuals (4.7% LI vs. 3.3% non-LI; $P = 0.0016$, OR 1.51) (Table 3). Mental illnesses could also be found significantly more often in LI patients (Table 4). This is true in particular for depression (20.9% LI vs. 16.0% non-LI; $P = 0.0053$; OR 1.21), anxiety and panic disorders (8.6% LI vs. 5.7% non-LI; $P = 0.0091$; OR 1.30), as well as somatoform disorders (17.5% LI vs. 10.8% non-LI; $P < 0.0001$; OR 1.46). No correlation was found between LI and

malignant cancers of the stomach (0.9% LI vs. 0.6% non-LI; $P = 0.1363$; OR 1.57).

Discussion

It is evident that patients who suffered from LI also experienced osteoporosis and depression more frequently compared to non-LI patients. These patients also often suffered from irritable bowel syndrome and other food intolerances, especially fructose malabsorption. As in many previous studies, patients in the present study population who suffered from LI reported abdominal discomfort, bloating, and digestive problems as their most common symptoms [3,17]. Likewise, other scientific studies confirmed that lactose malabsorption is often accompanied by fructose malabsorption [1]. The

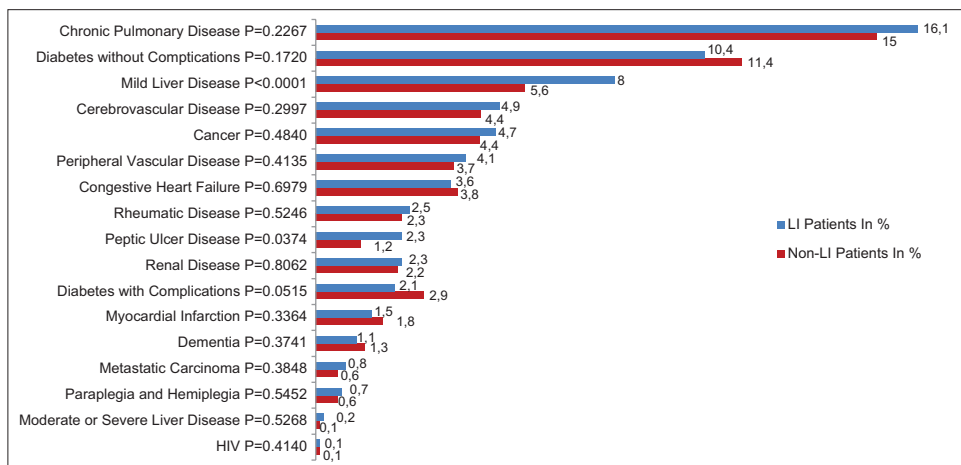


Figure 1 Comparison of concomitant diseases between patients with and without lactose intolerance using the Charlson comorbidity index*
*Lactose-intolerant patients 0.31 (SD 0.96), lactose-tolerant patients 0.32 (SD 0.94), $P = 0.6009$ (χ^2 -test)

Table 1 Symptoms and diseases of the digestive system in patients with and without lactose intolerance (LI) after matching

Diagnoses (ICD-10 code)	LI patients in % (n=3,379)	Non-LI patients in % (n=3,379)	Adjusted OR for LI (95% CI)**	P-value*
Abdominal pain (R10)	34.5 (n=1,166)	17.7 (n=598)	2.11 (1.87-2.37)	<0.0001
Nausea and vomiting (R11)	14.0 (n=473)	8.7 (n=294)	1.40 (1.19-1.65)	<0.0001
Difficulty swallowing (R13)	1.2 (n=41)	0.7 (n=24)	1.29 (0.77-2.18)	0.3357
Bloating (R14)	10.4 (n=351)	2.0 (n=68)	4.94 (3.78-6.46)	<0.0001
Heartburn (K20-22)	19.8 (n=669)	10.7 (n=362)	1.80 (1.56-2.08)	<0.00001
Stomach/duodenal ulcer (K25-28)	2.3 (n=78)	1.2 (n=41)	1.52 (1.03-2.25)	0.0374
Gastrointestinal infections (K29)	30.6 (n=1,034)	17.2 (n=581)	1.93 (1.71-2.17)	<0.0001
Indigestion (K30)	3.9 (n=132)	1.3 (n=44)	2.50 (1.77-3.55)	<0.0001
Non-infectious gastrointestinal inflammation (K52)	10.6 (n=358)	5.4 (n=182)	1.90 (1.57-2.30)	<0.0001
Irritable bowel syndrome (K58)	7.3 (n=247)	1.3 (n=44)	5.23 (3.77-7.27)	<0.0001
Malignant tumors of the stomach (C15-21)	0.9 (n=30)	0.6 (n=20)	1.57 (0.87-2.86)	0.1363

*Multivariate logistic regression: $P \leq 0.05$, **Adjusted OR by age, gender, insurance status, health insurance provider, medical specialist group, region, city size, other comorbidities, covariates from the CCS

Table 2 Fructose intolerance in patients with and without lactose intolerance (LI) after matching

Diagnosis (ICD-10 code)	LI patients in % (n=3,379)	Non-LI patients in % (n=3,379)	Adjusted OR for LI (95% CI)**	P-value*
Fructose intolerance (E741)	6.8 (n=229)	0.2 (n=7)	31.06 (14.58-66.15)	<0.0001

*Multivariate logistic regression: P≤0.05, **Adjusted OR by age, gender, insurance status, health insurance provider, medical specialist group, region, city size, other comorbidities, covariates from the CCS

Table 3 Diseases of the musculoskeletal system in patients with and without lactose intolerance (LI) after matching

Diagnoses (ICD 10 code)	LI patients in % (n=3,379)	Non-LI patients in % (n=3,379)	Adjusted OR for LI (95% CI)**	P-value*
Inflammatory polyarthropathies (M05-14)	5.3 (n=179)	5.5 (n=186)	0.85 (0.66-1.10)	0.2226
Arthrosis (M15-19)	14.6 (n=493)	12.7 (n=429)	1.09 (0.93-1.27)	0.3064
Dorsopathies (M40-43)	8.9 (n=301)	6.2 (n=209)	1.26 (1.04-1.53)	0.0177
Deformities of the spine (M45-49)	9.7 (n=328)	7.3 (n=247)	1.14 (0.95-1.38)	0.1633
Back pain (M54)	46.1 (n=1,558)	40.9 (n=1,382)	1.07 (0.96-1.18)	0.2191
Osteoporosis (M80-81)	4.7 (n=159)	3.3 (n=112)	1.51 (1.17-1.96)	0.0016

*Multivariate logistic regression: P≤0.05, **Adjusted OR by age, gender, insurance status, health insurance provider, medical specialist group, region, city size, other comorbidities, covariates from the CCS

Table 4 Mental illness in patients with or without lactose intolerance (LI) after matching

Diagnoses (ICD-10 code)	LI patients in % (n=3,379)	Non-LI patients in % (n=3,379)	Adjusted OR for LI (95% CI)**	P-value*
Depression (F32-33)	20.9 (n=706)	16.0 (n=541)	1.21 (1.06-1.38)	0.0053
Panic or generalized anxiety disorders (F41)	8.6 (n=291)	5.7 (n=193)	1.30 (1.07-1.59)	0.0091
Somatoform disorders (F45)	17.5 (n=591)	10.8 (n=365)	1.46 (1.26-1.69)	<0.0001
Other affective disorders (F30, F31, F34, F39)	1.6 (n=54)	1.0 (n=34)	1.42 (0.90-2.23)	0.1299
Schizophrenia (F20-29)	1.3 (n=44)	1.2 (n=41)	1.04 (0.61-1.75)	0.8892

*Multivariate logistic regression: P≤0.05, **Adjusted OR by age, gender, insurance status, health insurance provider, medical specialist group, region, city size, other comorbidities, covariates from the CCS

study published by Mishkin *et al* [18] found that both food intolerances were present concomitantly in 60% of cases.

What was most striking was the strongly significant correlation between the two diagnoses of LI and irritable bowel syndrome. Previous studies indicate that patients suffering from the above-mentioned symptoms are often wrongly diagnosed with irritable bowel syndrome. Böhmer and Tuynman [19] were able to demonstrate that the symptoms in subjects with irritable bowel syndrome were reduced or completely eliminated in 87% of cases after adopting a lactose-free diet. Similar findings were reported by Newcomer and McGill [20] and Schöfl *et al* [21]. However, it should be noted that the preceding studies were conducted in the early 90s and that it is only in recent years that LI has gained greater attention among physicians. A study conducted by Farup *et al* in 2004 [22] showed no relationship between lactose malabsorption and irritable bowel syndrome. The study published in 2005 by Nucera *et al* [23] provides one possible explanation for the association: the authors discovered that patients with irritable bowel syndrome frequently exhibited bacterial overgrowth in the intestines, which subsequently distorted breath tests used to diagnose lactose, fructose, and sorbitol intolerances in such

a way that they often yielded positive results even though the patients did not suffer from any intolerances. A possible correlation could not be clearly established in the present work based on the existing literature. It can be assumed that patients who suffer from LI often continue to consume dairy products despite their condition, leading to permanent irritation of the gastrointestinal tract, which in turn leads to irritable bowel syndrome.

The results obtained also indicate that people who could not tolerate dairy products suffered from osteoporosis more frequently. Due to the presumably reduced consumption of milk, LI patients commonly ingest too little calcium, high amounts of which can be found in milk. The inadequate calcium intake leads to demineralization of the bones with subsequent reduction in bone density [8]. This phenomenon [24] was previously demonstrated in children between three and ten years of age. Children eating a low-dairy diet were smaller and had thinner bones with lower bone mineral density than children who drank milk regularly. In addition, a correlation between the severity of osteoporosis and the severity of LI could be confirmed [9]. The calcium shortage and resulting osteoporotic bones at a later age could also significantly

increase the risk of hip fractures in LI patients over 80 years of age [25]. If patients nevertheless consume a diet rich in calcium, the question arises whether LI patients can only partly absorb other minerals, such as calcium for example, in addition to enduring insufficient break-down of lactose. However, studies show that calcium is readily absorbed in the gastrointestinal tract even in patients suffering from LI [26,27]. The development of osteoporosis can thus not be explained by insufficient absorption of calcium in the digestive tract but is likely caused by inadequate calcium intake. As adjunctive therapy it is therefore advisable to ingest the required mineral through alternative sources to prevent secondary diseases. A diet rich in green vegetables [28] or the taking of food supplements is recommended.

Furthermore, the present results demonstrated that depression and LI often occur together. To date, this issue has not yet been adequately addressed in scientific literature. However, numerous studies confirm a significant correlation between fructose intolerance and depression [4]. Fructose-intolerant patients more often exhibit a lack of serotonin, “happiness hormone”. A higher intestinal fructose concentration appears to have an effect on L-tryptophan metabolism by reducing the availability of tryptophan for biosynthesis of serotonin [29]. The biochemical approach thus provides a plausible explanation for the correlation between depression and fructose malabsorption. As mentioned previously, lactose and fructose intolerance frequently occur together. The psychological changes are therefore presumably not ascribed to LI, but to concomitant fructose intolerance.

At first glance, the results show that liver diseases and stomach ulcers are present in several cases in addition to LI. It must be noted, however, that we were unable to adjust for the necessary variables in both diseases. For example, the alcohol consumption of patients would have to be included in order to arrive at significant results regarding the question of whether liver diseases arise due to the inability to break down lactose or the toxic effect of the alcohol.

Therefore, these diagnoses can only partly be attributed to LI.

Since the present work was based on a routine data analysis, corresponding limitations of the data used must be clearly identified. Routine data were not explicitly collected with predefined questions in mind, and as a consequence, not all relevant information, such as lifestyle habits of the patients, was available. It must also be borne in mind that it could not be clearly ascertained which disease was the cause and which disease ultimately occurred as comorbidity. Furthermore, the validity of the data could not be guaranteed, since documentation varied between individual physicians.

The conclusions of the present study are twofold: LI is not to be regarded as an isolated illness, nor are the resulting diseases to be underestimated. Since this was a routine data analysis, no clear statement can be made with regard to the issue whether LI triggers other diseases. To aptly answer this question, further studies are required which involve monitoring LI patients over a longer period of time and simultaneously record their lifestyle habits.

Summary Box

What is already known:

- Approximately 70% of the global population have lactase non-persistence
- Affected persons complain of abdominal discomfort, bloating, flatulence, and osmotic diarrhea. However, non-specific symptoms such as headaches, depression, chronic fatigue, concentration problems, and muscle pain can also be attributed to lactose intolerance (LI)
- Patients also often suffer from irritable bowel syndrome and other food intolerances, especially fructose malabsorption
- These coincidences may be known from clinical expertise, but they have not yet been confirmed by analyses of large routine databases deriving from daily practice in outpatient care

What the new findings are:

- On a population-based level, the study at hand showed significant correlations between LI and the incidence of osteoporosis and the presence of additional food intolerances
- Furthermore, the present results demonstrated that depression and LI often occur together. To date, this issue has not yet been adequately addressed in scientific literature
- The findings confirmed observational awareness based on clinical experience by obtaining insight from in-depth analyses of unbiased data within the expanding discipline of health services research

Ethics

According to published guidelines on routine data analyses [Swart E, Gothe H, Geyer S, Jaunzeme J, Maier B, Grobe TG, Ihle P. Good practice of secondary data analysis (GPS): guidelines and recommendations. Third Revision 2012/2014. *Gesundheitswesen* 2015;77:120-126] using anonymized data from office-based physicians does not require an approval by the ethics committee on human research.

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