Journal of Eating Disorders

RESEARCH Open Access

Zinc levels in severe eating disorders

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Abstract

Purpose Severe eating and feeding disorders including Anorexia Nervosa of both restricting (AN-R) and binge-purge (AN-BP) subtypes and Avoidant Restrictive Food Intake Disorder (ARFID) lead to multiple macronutrient and micronutrient deficiencies, including zinc, in the setting of inadequate dietary intake. We investigated whether zinc levels correlated with severe malnutrition, with particular subtypes of eating disorders (EDs), and the effect of the refeeding process.

Methods This prospective study included 92 adult patients with severe AN or ARFID hospitalized in a medical stabilization unit. Denver Health staff were recruited as controls. Blood samples were drawn within four days of admission and 72 h of discharge. All inferential analyses were performed using general linear models.

Results Admission zinc levels were statistically significantly lower in cases compared to controls. Admission zinc levels were significantly higher for patients with AN-R than patients with AN-BP. Zinc levels decreased significantly during treatment in cases, compared to controls. ED diagnoses and percent ideal body weight (%IBW) did not appear to predict changes in zinc levels during admission.

Conclusions Given zinc's pervasive roles in metabolism throughout the body as well as common symptoms of deficiency including impaired taste and smell, decreased appetite, and depression, zinc levels could be relevant to the high relapse rate in severe ED. The observed decrease in zinc, which was larger in cases than controls, during refeeding suggests the possibility of a "refeeding hypozincemia" which may present a new therapeutic target. These characteristics make zinc an intriguing focus of future study that could impact the recidivism rate in severe ED.

Level of evidence III Evidence obtained from well-designed cohort or case-control analytic studies.

Plain English summary

Severe eating disorders lead to multiple nutrient deficiencies, including zinc. Given zinc's extensive roles in metabolism throughout the body, common symptoms of deficiency including impaired taste and smell, decreased appetite, and depression, zinc may be relevant to the high relapse rate among those suffering from severe ED. This study examines serum zinc levels in a unique group of people with severe malnutrition during the refeeding process undertaken while hospitalized. Zinc levels were lowest in patients diagnosed with AN-BP and fell during hospitalization. The decrease in zinc levels suggests "refeeding hypozincemia" which may present a new role for zinc supplementation to reduce relapse, given zinc's role in taste, appetite, and quality of life.

Keywords Zinc, Severe eating disorder, Anorexia nervosa, ARFID, Malnutrition

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Introduction

Anorexia nervosa (AN) is characterized by a fear of gaining weight leading to restrictive patterns of eating and/or forms of purging (examples include vomiting, laxative, diuretic, and diet pill abuse) resulting in a reduced net calorie intake and marked weight loss. Additionally, per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-V TR) [1], individuals with avoidant/restrictive food intake disorder (ARFID) present with at least one of the following characteristics: significant weight loss or failure to achieve expected weight gain, significant food restriction causing nutritional deficiency, interference in psychosocial functioning, and lack of body image distress/ drive for thinness/ or fear of weight gain. In the DSM-V TR [1], in order to inform treatment options, eating disorders have a severity index based on body mass index (BMI) with "severe" defined as BMI of 15–15.99 and "extreme" as BMI of < 15. The lifetime prevalence of AN is estimated to be 0.1–3.6% [2], is known to be chronic, has high rates of relapse [3], and has the highest mortality rate of any mental illness after opioid use disorder.

Anorexia nervosa of both restricting (AN-R) and binge-purge (AN-BP) subtypes are thought to lead to multiple macronutrient and micronutrient deficiencies in the setting of inadequate dietary intake. Habits such as restriction of high fat and energy-dense foods, as well as extremely limited food regimens, can lead to intake of only certain nutrients and a paucity of others [4]. A 2019 study investigating AN compared to healthy leanness in children showed that zinc intake was significantly reduced in children and adolescents with AN in part due to their restriction of fat [5]. It is also hypothesized that not only lower intake of zinc but also behaviors such as binging on low zinc-containing foods, abusing laxatives leading to diarrhea, and vomiting could contribute to lower serum zinc levels, though these associations have not been established [6]. In their 2018 study examining the differences in serum zinc levels between acutely ill and recovered adolescents and young adults with AN, Zepf et al. found a significant difference in zinc between the two groups. However, the median body weight in the sick group was significantly higher (BMI 20.8) than those typically managed at the ACUTE Center for Eating Disorders and Malnutrition (ACUTE), a medical stabilization unit for the treatment of patients with severe forms of eating disorders (EDs) [7]. Between 2018 and 2021, the average admission BMI for ACUTE was 13 [8] and in this study specifically, the average BMI was 12.8. Zinc has been shown, in limited studies, to have the highest deficiency prevalence of 64.3% in severely malnourished inpatients with AN [9]. Multiple additional studies by Bakan and Birmingham have examined oral zinc supplementation in patients with AN to promote increased rate of weight gain [10–13].

Zinc is a critical micronutrient found in a variety of foods including oysters, red meat, poultry, beans, nuts, whole grains, fortified breakfast cereals, and dairy products [14]. Zinc's function in the body is vast, encompassing catalytic functions in the form of zinc metalloenzymes required for the metabolism of carbohydrate, fat, and protein. It plays a structural role in proteins, cell membranes, nucleic acids, and ribosomes, and regulates gene transcription, cell signaling, hormone release, and apoptosis [15]. Zinc distribution in the body is mostly intracellular, particularly in muscle tissue, and is largely protein-bound, which can make testing complicated to obtain and interpret [16, 17]. Common symptoms of zinc deficiency line up distinctly well with those symptoms of AN including decreased taste and smell, decreased appetite and food avoidance, impaired digestion and absorption, hormonal imbalances, skin lesions and hair loss, mental and emotional instability, and depression [10, 18]. Further, the COVID-19 pandemic has demonstrated the decreased quality of life and weight disruption experienced by people with diminished senses of taste and smell [19].

Unfortunately, people suffering from AN also experience a high relapse and recidivism rate with multiple studies showing that the highest rates of relapse occur four to nine months post treatment [20, 21]. With rat models [22], low birth weight infant studies [23], and periods of rapid growth [24] demonstrating increasing zinc demands with increasing body weight, zinc deficiency may contribute to relapse during the initial phases of recovery. Further, there may be a pathology analogous to refeeding hypophosphatemia, in which zinc is excessively utilized during the refeeding process. Livingstone suggested increased demand for cofactors in anabolic processes of protein synthesis and tissue growth "should be considered part of refeeding syndrome," [15] and ASPEN 2004 parenteral nutrition guidelines already suggest monitoring every two-four weeks [25].

The unique population of patients with severe eating disorders at ACUTE permits a different perspective with a population that has significantly lower body weight and more severe malnutrition compared to other facilities and in previous studies. Although zinc supplementation has been utilized in the treatment of patients with AN since at least 1979, we examined whether zinc levels in AN correlated with severe malnutrition, with particular subtypes of eating disorders, and what effect the refeeding process might have on zinc levels. Finally, we wonder whether low zinc levels could play a hypothetical role in treatment recidivism.

Methods

Study design and setting

This observational, single-center, cohort study was conducted at the ACUTE Center for Eating Disorders and Severe Malnutrition located at Denver Health Medical Center in Denver, Colorado. ACUTE is a 30-bed medical unit, which serves as a national referral center for patients with severe eating disorders requiring inpatient medical stabilization before becoming safe to step down to a lower level of care at residential ED treatment centers. Serum zinc levels were chosen based on the ease with which they are obtained (with a simple blood draw that can be added on to other necessary labs). The Colorado Multiple Institutional Review Board approved this study (protocol #21–2997) as an observational investigation.

Study participants

All patients at ACUTE between 18 and 65 years of age, diagnosed with AN-R, AN-BP, and ARFID, and with an initial %IBW [26] of less than 75% were screened for enrollment after admission. Potential case participants were excluded if the individuals were taking zinc supplementation upon admission or prior to admitting to the ACUTE unit, actively abusing substances, or in active substance withdrawal. Denver Health staff were recruited for the control cohort and were between 18 and 65 years of age, never diagnosed with an eating disorder, and had a body mass index between 18.5–24.9 kg/m^2. Controls were excluded from participation if the individuals were currently taking zinc supplements or multivitamins containing zinc, and if they had an active substance use disorder and or experiencing substance withdrawal. For the case cohort, a serum zinc blood sample was drawn after informed consent within four days of admission. A second zinc blood sample was drawn within 72 h prior to discharge. Control participants also completed two serum zinc labs, with the first after consent and the second two to three weeks later.

Statistical analysis

All inferential analyses were performed using general linear models. All models predicting change in zinc included admission zinc levels as predictors. By controlling for admission zinc levels, we are able to predict changes in zinc levels free from admission scores, which can bias change scores with artifacts such as regression to the mean. ED diagnosis was dummy coded such that the comparator was AN-R. By controlling for other factors in linear models, such as ED diagnosis, we are examining the impact of predictors "free from" or "holding constant" the influence of these controlled factors. All analyses were performed in R (version 4.3.1; R Core Team, 2023).

Results

This study enrolled a total of 100 cases and 23 controls. Within the 100 cases enrolled, eight were disqualified or withdrawn for admission shorter than seven days or for requiring conversion to involuntary treatment. Of the 92 remaining cases, 73 completed the serum zinc blood sample at admission and at discharge. Clinical and demographic features of the patients are shown in Table 1. Mean days between zinc serum levels for cases was 26.1 (SD = 13.7, Range: 5–77) and for controls, 20.9 (SD = 2.9, Range: 17–24). Mean age was 32.7 years (SD = 11.8, Range: 18–62) and the majority (87.8%) were Caucasian. Of the 92 cases, 47% had AN-R, 40% had AN-BP and 10% had ARFID. For cases, mean percent ideal body weight (%IBW) on admission was 59.8% (SD = 6.81, Range: 42.6–73.2) consistent with severe AN. By contrast, the mean %IBW was 105 (SD = 7.57, Range: 86.2–116) for controls.

Admission and changes in zinc levels between cases and controls

Admission/initial zinc levels (reference range 60–120 ug/dl) were significantly lower in cases (M = 63.28, SD = 14.56) compared to controls (M = 73.40, SD = 7.91; b = 10.12, t = 3.21, $p < 0.01$) (Fig. 1). For cases, 37 (40.2%) had abnormally low admission zinc levels (below 60 ug/dl), while for controls, one (4.3%) had an abnormal initial zinc level. When controlling for admission zinc levels, discharge zinc levels were significantly lower in cases (M = 58.76, SD = 12.40) than controls (M = 76.38, SD = 11.02; b = 13.97, t = 4.98, $p < 0.001$). For the 73 cases with discharge values, 41 (56.2%) had abnormally low discharge zinc levels, while for controls, one (4.3%) had an abnormal follow-up zinc level (Table 1).

Of the cases with low admission zinc values who also had discharge zinc values (N = 31, 83.8%), 10 cases (32.3%) had zinc levels that became normal during treatment. Of the cases with normal admission zinc values who also had discharge zinc values (N = 42, 76.4%), 20 cases (47.6%) became low during medical stabilization and weight gain. Of the 22 controls with normal initial zinc values, one control (4.5%) became low on follow up.

Admission zinc levels, admission %IBW, and ED diagnosis

Within cases, admission %IBW was not a significant predictor of admission zinc levels, though there was a trend for higher %IBW to be associated with higher admission zinc levels (b = 0.42, t = 1.90, p = 0.06). Admission zinc levels were significantly higher for patients with AN-R (M = 65.67, SD = 14.79) than patients with AN-BP (M = 59.43, SD = 12.88; b = 6.24, t = 2.05, p = 0.04). Although admission zinc levels were even higher for patients with ARFID (M = 68.34, SD = 18.74), they were not significantly different

Table 1 Demographic and Clinical Features

	Cases (N = 92)				Controls (N = 23)
	AN-BP (N = 40)	AN-R (N = 43)	ARFID (N = 9)	Overall cases (N = 92)	
Age					
Mean (SD)	34.6 (13.4)	29.8 (10.7)	35.8 (14.0)	32.5 (12.4)	33.8 (9.26)
Median [Min, Max]	30.5 [18.0, 61.0]	25.0 [18.0, 61.0]	30.0 [22.0, 62.0]	28.5 [18.0, 62.0]	32.0 [23.0, 54.0]
Gender					
Female	36 (90.0%)	38 (88.4%)	6 (66.7%)	80 (87.0%)	22 (95.7%)
Male	4 (10.0%)	5 (11.6%)	3 (33.3%)	12 (13.0%)	1 (4.3%)
Race					
Other	4 (10.0%)	3 (7.0%)	1 (11.1%)	8 (8.7%)	0 (0%)
White or Caucasian	36 (90.0%)	40 (93.0%)	8 (88.9%)	84 (91.3%)	17 (73.9%)
Asian/Indian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.3%)
Asian/Middle Eastern	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.3%)
Hispanic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (13.0%)
Korean/Norwegian	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.3%)
Eating disorder					
AN-BP	40 (100%)	0 (0%)	0 (0%)	40 (43.5%)	0 (0%)
AN-R	0 (0%)	43 (100%)	0 (0%)	43 (46.7%)	0 (0%)
ARFID	0 (0%)	0 (0%)	9 (100%)	9 (9.8%)	0 (0%)
None	0 (0%)	0 (0%)	0 (0%)	0 (0%)	23 (100%)
Admission/Initial %IBW					
Mean (SD)	60.9 (6.98)	59.6 (6.22)	55.8 (7.90)	59.8 (6.81)	105 (7.57)
Median [Min, Max]	60.3 [48.1, 73.2]	59.9 [47.7, 73.0]	54.5 [42.6, 67.8]	59.8 [42.6, 73.2]	105 [86.2, 116]
Admission/Initial BMI					
Mean (SD)	12.8 (1.45)	12.6 (1.46)	12.2 (2.32)	12.6 (1.55)	22.5 (1.61)
Median [Min, Max]	13.1 [9.80, 15.5]	12.5 [10.1, 16.0]	12.4 [8.51, 16.3]	12.5 [8.51, 16.3]	22.2 [18.5, 24.8]
Admission/Initial Zinc					
Mean (SD)	59.4 (12.9)	65.7 (14.8)	69.0 (17.6)	63.3 (14.6)	73.4 (7.92)
Median [Min, Max]	58.0 [36.0, 88.4]	65.3 [33.0, 99.0]	64.7 [48.2, 95.7]	63.9 [33.0, 99.0]	71.5 [59.9, 93.3]
Discharge %IBW					
Mean (SD)	74.7 (5.27)	71.2 (4.58)	77.4 (6.44)	73.3 (5.47)	
Median [Min, Max]	74.0 [63.6, 86.1]	71.9 [52.0, 77.9]	73.9 [70.5, 86.2]	72.60 (52.00, 82.60)	
Discharge BMI					
Mean (SD)	15.7 (1.25)	15.1 (1.18)	16.8 (1.64)	15.5 (1.35)	
Median [Min, Max]	15.7 [13.7,18.9]	15.1 [10.8, 17.8]	17.0 [14.4, 19.4]	15.20 (10.80, 19.4)	
Discharge/Second Zinc					
Mean (SD)	59.5 (12.1)	57.3 (13.5)	62.7 (7.43)	58.8 (12.4)	76.4 (11.0)
Median [Min, Max]	59.1 [38.6, 87.7]	58.4 [20.5, 83.4]	60.6 [53.2, 74.3]	59.1 [20.5, 87.7]	74.8 [54.5, 93.5]
Missing	9 (22.5%)	8 (18.6%)	2 (22.2%)	19 (20.7%)	0 (0%)
Days between Zinc draws					
Mean (SD)	20.7 (17.0)	19.1 (13.2)	28.2 (23.8)	20.7 (16.2)	20.9 (2.9)
Median [Min, Max]	19.5 [0, 54.0]	19.0 [0, 49.0]	29.0 [0, 77.0]	20.0 [0, 77.0]	21 [17, 27]

from levels in patients with AN-BP (b = 8.91, t = 1.60, p = 0.11). When controlling for differences on admission, changes in zinc levels were not significantly different between patients with AN-R (Δ = −7.33, SD = 14.79) and AN-BP (Δ = 0.24, SD = 12.88; b = −4.14, t = −1.46, p = 0.15), or between patients with ARFID (Δ = −8.51, SD = 18.74) and patients with AN-BP (b = −1.10, t = −0.23, p = 0.82).

Changes in zinc levels, admission %IBW, and ED diagnosis

Changes in zinc levels for cases were negative on average (M = −4.23, SD = 15.04), whereas changes in zinc

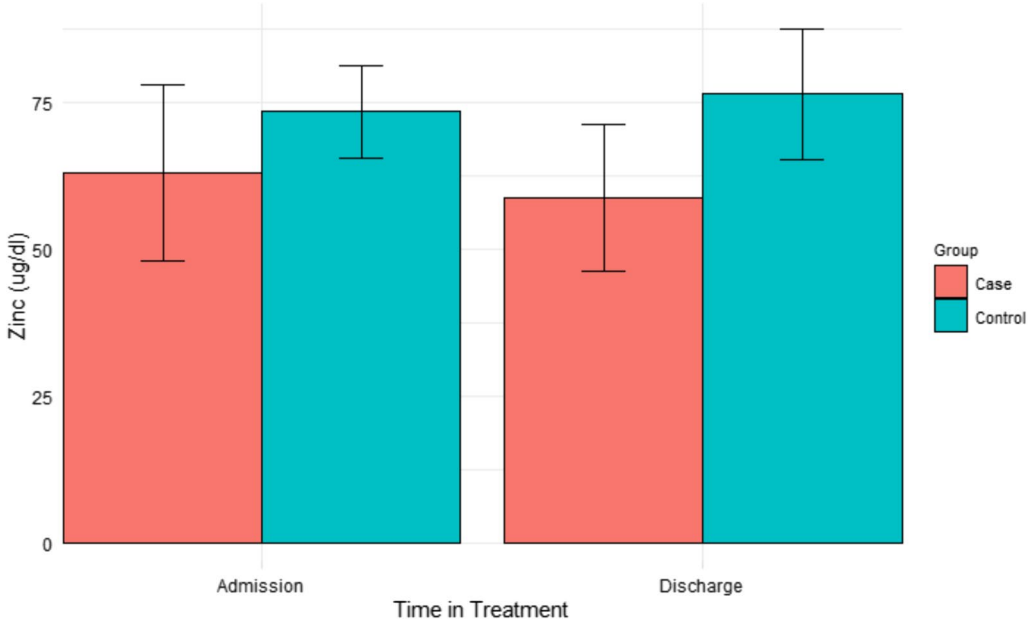

Fig. 1 Comparison of mean Zinc serum levels between cases and controls at time point one and time point two (admission and discharge for cases). Normal zinc level reference range is 60–120 mcg/dl. In cases, the mean zinc level at admission was 63.28 (SD = 14.56) compared to controls (initial blood draw) with a mean of 73.40 (SD = 7.91). This comparison was significant ($p < .01$). When controlling for admission zinc levels, discharge zinc levels were statistically significantly lower in cases (M = 58.76, SD = 12.40) than controls (M = 76.38, SD = 11.02; b = 13.97, t = 4.98, $p < .001$)

levels for controls were positive on average (M = 2.98, SD = 11.18). Within cases, lower admission %IBW was significantly associated with greater decreases in zinc levels (b = 0.40, t = 2.00, p = 0.04). However, after controlling for ED diagnosis among cases, %IBW was no longer a significant predictor of changes in zinc levels, though there was a trend for lower %IBW to be associated with greater decreases in zinc levels (b = 0.40, t = 1.90, p = 0.06). Within cases and controls, when controlling for admission/initial zinc levels and ED diagnosis status, admission %IBW also was not a significant predictor of changes in zinc levels (b = 0.18, t = 1.09, p = 0.28).

Discussion

As previously reported in the literature, zinc deficiency appears more prevalent among people with eating disorders. The proposed mechanisms suggested in the literature include under-consumption of zinc-containing foods among those with restricting behaviors and loss of zinc as a result of purging behaviors. The change in zinc in levels did not appear to vary after controlling for admission zinc between cases and controls and between eating disorder diagnoses, consistent with the interruption of these behaviors during treatment at ACUTE. Further, patients with AN-BP were the most likely to have low admission zinc, and those with ARFID had the highest levels of admission zinc, again consistent with mechanisms proposed by Kanayama [5] and Zepf [6]. IBW was correlated with admission zinc only until ED diagnosis was accounted for, making diagnosis appear to be a stronger predictive factor than low IBW, though these were not tested head-to-head. Interestingly, the degree of malnutrition did not appear to affect admission zinc within eating disorder diagnoses, further emphasizing the role of binging and purging behaviors. Additional investigation could help specifically elucidate zinc-detrimental behaviors and therefore identify those who may benefit from prompt treatment.

Standard refeeding protocols on the ACUTE unit, which are aggressive and complied with, appeared often insufficient to normalize zinc deficiency in cases. Also mean zinc levels dropped in a significant manner in cases from the time of admission to discharge among all eating disorder diagnoses, suggesting the possibility of a newly described entity which we will term "refeeding hypozincemia." Bakan and Birminghams' previous studies have utilized zinc supplementation to augment weight gain, potentially consistent with zinc's pervasive anabolic roles throughout the body. Further study with controlled calorie intake to investigate zinc supplementation's effect on weight gain or rate of weight gain may be helpful to guide future treatment protocols. The recidivism rate among people suffering from eating disorders after formal treatment programs is bleak. Zinc's role in taste, appetite, and

quality of life should be further investigated as a possible treatment intervention to help patients achieve longer-lasting remission from their eating disorders. Formal taste testing while in different stages of refeeding could be valuable in this regard.

Strengths and limitations

Strengths of this study include the examination of a unique cohort with extreme forms of eating and feeding disorders with severely low body weight. Additionally, the diets, calories, and weight gain for each patient were controlled within the setting of hospitalization as well as the cessation of eating disorder behaviors with one-on-one sitters which allows cleaner interpretation of serum zinc levels. Limitations include the uneven distribution of the patients by ED subtype which limits the power of comparisons particularly in patients with ARFID. Additionally, these patients were seeking or referred for care, and thus there may be referral bias not limited to demographics of race, gender, and financial privilege. Finally, limitations of zinc testing including varying levels by time of day and the extent of the relationship between symptoms of zinc deficiency such as impaired taste and the level itself is uncertain.

Conclusions

Overall, we were hoping that the fall in serum zinc levels with refeeding would have been more prevalent and that zinc levels would have more consistently correlated with admission BMI. But, per a recent opinion piece entitled "Seeing the Positive in Negative Studies," [27], there is also importance in identifying less than fully positive findings in order to inform health interventions or not. This paper, which arguably is the first to involve an extremely ill cohort of patients with severe eating disorders regarding zinc, does not provide ample confirmatory evidence to change clinical practice. However, there are hints that exhort us to look further into this question with a more rigorous trial, including assessment of taste and smell, given that impairment in these senses could certainly interfere with ongoing weight restoration once patients leave eating disorder treatment programs and transition back home. One wonders if the "refeeding hypozincemia" observed continues to worsen after patients discharge from ACUTE to residential treatment programs and becomes even more severe after they are back home. Perhaps serial zinc level determinations should be obtained, and supplemental zinc provided to those whose levels are found to be low. In addition, there needs to be formal taste testing which is correlated with serum zinc levels. The opportunity to learn more about zinc, taste, and maintaining sustained recovery in patients with eating disorders is compelling, given the reduced appetite induced by zinc deficiency, the potential for ongoing food restriction, and the risk of recidivism of their eating disorders.

What is already known on this subject?

Severe eating disorders lead to multiple nutrient deficiencies, including zinc. Given zinc's pervasive roles in metabolism throughout the body, common symptoms of deficiency including impaired taste and smell, decreased appetite, and depression, zinc may be relevant to the high relapse and recidivism rate among those suffering from severe ED.

What this study adds?

This study examines serum zinc levels in a unique cohort of people with severe malnutrition during the initial refeeding process. The decrease in zinc levels suggests "refeeding hypozincemia" which may present a new role for zinc supplementation to reduce relapse, given zinc's role in taste, appetite, and quality of life.

Author contributions

Authors contribution statement: All authors contributed to the study conception and design except Kara Leach who joined project later. Material preparation, data collection, and analysis were performed by Marina Foster, Judy Oakes, and Dan Blalock. The first draft of the manuscript was written by Kara Leach, and all authors except for Melanie Hebert commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

There are no funding sources to disclose.

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board and adhered to the guidelines set forth by the Office of Human Research Protection that is supported by U.S. Department of Health and Human Services. Institutional Review Board approval and informed consent were waived due to the use of retrospective and de-identified data. This study adhered to the guidelines set forth by the Office of Human Research Protection that is supported by U.S. Department of Health and Human Services.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Competing interests

The authors declare no competing interests.

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Received: 2 October 2024 Accepted: 21 January 2025
Published online: 04 February 2025

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