Clinical Nutrition ESPEN 62 (2024) 22–27

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Maternal gluten, cereal, and dietary fiber intake during pregnancy and lactation and the risk of islet autoimmunity and type 1 diabetes in the child

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ARTICLE INFO

Article history:
Received 20 February 2024
Accepted 8 May 2024

Keywords:
Pregnancy
Prenatal exposure delayed effects
Dietary intake
Gluten
Diabetes mellitus, Type 1
Cohort study

SUMMARY

Background & aims: Maternal gluten intake in relation to child's risk of type 1 diabetes has been studied in few prospective studies considering the diet during pregnancy but none during lactation. Our aim was to study whether gluten, cereals, or dietary fiber in maternal diet during pregnancy and lactation is associated with the risk of islet autoimmunity or type 1 diabetes in the offspring.

Methods: We included 4943 children with genetic susceptibility to type 1 diabetes from the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) Study, born between 1996 and 2004. Maternal intake of gluten, different types of cereals, and dietary fiber were derived from a semi-quantitative validated food frequency questionnaire covering the eighth month of pregnancy and the third month of lactation. Children were monitored for islet autoantibodies up to age of 15 years and type 1 diabetes until year 2017. Risk of islet autoimmunity and clinical type 1 diabetes were estimated using Cox regression model, adjusted for energy intake, child's sex, HLA genotype, and familial diabetes.

Results: Altogether 312 children (6.4%) developed islet autoimmunity at median age of 3.5 (IQR 1.7, 6.6) years and 178 children (3.6%) developed type 1 diabetes at median age of 7.1 (IQR 4.3, 10.6) years. Gluten intake during pregnancy was not associated with islet autoimmunity (HR 0.96; 95% CI 0.68, 1.35), per 1 g/MJ increase in intake nor type 1 diabetes (HR 0.96; 95% CI 0.62, 1.50) in the offspring. Higher barley consumption during lactation was associated with increased risk of type 1 diabetes (HR 3.25; 95% CI 1.21, 8.70) per 1 g/MJ increase in intake. Maternal intake of other cereals or dietary fiber was not associated with the offspring outcomes.

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https://doi.org/10.1016/j.clnesp.2024.05.001

Conclusions: We observed no association between maternal intake of gluten, most consumed cereals, or dietary fiber during pregnancy or lactation and the risk of islet autoimmunity or type 1 diabetes in children from a high-risk population.

1. Introduction

Exposure to dietary gluten during pregnancy has been suggested to be a potential risk factor for type 1 diabetes in the offspring based on some animal studies [1] and the Danish National Birth Cohort study, in which a higher maternal gluten intake during pregnancy was associated with an increased risk of type 1 diabetes in the offspring [2]. However, a similar Norwegian prospective general population-based study found no such association [3]. In studies including children with genetic or familial susceptibility to type 1 diabetes, maternal consumption of gluten containing foods or cereals and non-gluten cereals during pregnancy has not been associated with islet autoimmunity or type 1 diabetes in the offspring [4–6]. In the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study, we observed that higher childhood intake of gluten, as well as oats, gluten-containing cereals, wheat, rye, and dietary fiber was associated with an increased risk of islet autoimmunity and/or type 1 diabetes [7]. This suggests that other factors in cereals in addition to gluten may play a role in the development of type 1 diabetes.

Cereals include components that may directly or indirectly promote the activation of autoimmune processes, observed as circulating islet autoantibodies (islet autoimmunity) and later development of type 1 diabetes. For example, gliadin, the wheat gluten protein has been detected in human milk along with other food peptides [8,9], and maternal gluten intake during lactation could therefore affect the child's risk of type 1 diabetes by direct antigen effects of gluten in breast milk. Gluten exposure during pregnancy could affect the risk of type 1 diabetes in the offspring e.g. by modifying the inflammatory milieu of the mother and the fetus [2]. Dietary fiber intake during pregnancy and lactation could affect the risk of type 1 diabetes in the offspring e.g. by modifying maternal gut microbiota [10], followed by human milk microbiota [11], child's microbiota [12], and child's immunological responses to the environment. Additionally, mycotoxins [13] and heavy metals [14] are potential prenatal cereal consumption-related exposures that could be transmitted from the mother to the child and affect the child's risk of type 1 diabetes.

The associations between maternal cereal consumption during pregnancy and the risk of islet autoimmunity has been partly reported before in the DIPP study: there was no association between consumption of cereal products, wheat, rye and rice with the risk islet autoimmunity [6]. The present study with higher number of participants than the previous report, adds to the knowledge by including the exposures of maternal gluten and dietary fiber intake during pregnancy, as well as the type 1 diabetes outcome. Further, maternal gluten, cereal, and dietary fiber intake during lactation in relation to the risk of islet autoimmunity and clinical type 1 diabetes has not been reported in DIPP before, nor in other human studies, to our knowledge.

Our aim was to study the associations between maternal intake of gluten, cereals, and dietary fiber during pregnancy and lactation and the risk of islet autoimmunity and type 1 diabetes in children participating in the DIPP study. The hypothesis was that higher maternal gluten intake is associated with an increased risk of islet autoimmunity and type 1 diabetes in the child.

2. Materials & methods

2.1. Study design

We used data from the DIPP study, a large population-based birth cohort study of children with HLA-DQB1-conferred susceptibility to type 1 diabetes [15]. The children participated in the follow-up visits, including blood sampling, and scheduled for 3, 6, 12, 18 and 24 months of age, and annually thereafter, until the age of 15 years or the diagnosis of type 1 diabetes.

Of the 54 350 screened children, 7782 infants born in Tampere and Oulu University Hospitals between September 1996 and September 2004 were invited to the dietary study within DIPP. Inclusion criteria for the present report was having maternal food frequency questionnaire (FFQ) data for pregnancy or lactation diet. There were 4943 (63.5%) and 2944 (37.8) children with information on maternal diet during pregnancy and lactation, respectively (Supplementary Fig. 1). Pregnancy and lactation cohorts had slightly different number of participants for islet autoimmunity vs. type 1 diabetes outcomes based on the availability of outcome data (Supplementary Fig. 1). Parents gave their written informed consent for genetic testing of the newborn and for participation in the follow-up. The study adheres to the Declaration of Helsinki, and the local ethics committees approved the study protocol.

2.2. Exposure variables

The studied exposures were maternal intake of the following cereals and food components during pregnancy and lactation: gluten, oats, rice, gluten-containing cereals, wheat, rye, barley, total dietary fiber, and dietary fiber fractions. The mothers completed a validated 181-item semi-quantitative FFQ concerning their habitual diet during one month, the 8th month of pregnancy, which is the last month preceding the maternity leave in Finland [16]. The questionnaire was mailed to the mothers after delivery and checked at the 3-month visit. Maternal diet during lactation was inquired from mothers who were still partly or fully breastfeeding at the 3-month study visit and the FFQ covered the preceding month prior to the child's 3-month visit. The mothers received this questionnaire at the 3-month visit and returned it at the 6-month visit. The questionnaire was checked by a study nurse when returned. The FFQ contained questions on the frequency and amounts of foods consumed. Information was also requested concerning special diets, as well as the use of dietary supplements. FFQ is an established and appropriate method to assess diet in epidemiologic settings, including studies among pregnant women [16]. A strength of FFQ in comparison to short-term food-records is that FFQ allows estimation of habitual diet over a longer period of time [16].

Based on the FFQs and the regularly updated national food composition database Fineli (National Institute for Health and Welfare, Finland) we calculated the energy intake, as well as the amounts (dry weights in grams) of wheat, barley, and rye separately and grouped as gluten-containing cereals, as well as the amounts of oats and rice. The amount of gluten in wheat, rye, and barley was calculated by multiplying the amount of protein with 0.8

for wheat, 0.65 for rye, and 0.5 for barley [7]. Total dietary fiber and three dietary fiber fractions (insoluble dietary fiber, IDF; dietary fiber soluble in water but insoluble in 78% aqueous ethanol, SDFP; and dietary fiber soluble in water and soluble in 78% aqueous ethanol, SDFS) were calculated from all foods (not just cereals) based on recently updated Fineli food composition database [17].

2.3. Outcomes

The study outcomes were 1) islet autoimmunity defined as repeated positivity for islet cell antibodies (ICA) and at least one biochemical autoantibody or having type 1 diabetes, and 2) type 1 diabetes. ICA was screened at each study visit at 3 to 12-month intervals as described before [18]. If a participant tested positive for ICA, all available samples from the subject in question were analyzed for insulin autoantibodies (IAA), glutamic acid decarboxylase autoantibodies (GADA) and islet antigen-2 autoantibodies (IA-2A). Date of diagnosis of type 1 diabetes was obtained from the Finnish Pediatric Diabetes Register and the University Hospitals in May 2017 (Oulu) and in October 2017 (Tampere). Children not identified as having type 1 diabetes were considered free from type 1 diabetes.

2.4. Other variables

Genotypes HLA-DQB1*02/*0302 represented “high” and HLA-DQB1 *0302/x “moderate” risk for type 1 diabetes. (x indicates alleles other than DQB1 *02, *0301 or *0602/3). Since April 1997 DQB1*0602/3 probe recognizing both DQB1*06:02 and DQB1*06:03 alleles was replaced by a probe specific for DQB1*06:02. Information on child sex (male, female), any type of familial diabetes (yes, no), maternal age at the time of child's birth, maternal education (none or vocational, secondary vocational, university studies or degree), and smoking during pregnancy (yes, no) were collected from the parents after the delivery using a structured questionnaire. Maternal special diet was asked with a separate question in the FFQ form. Cereal-related special diet included special diets related to celiac disease, allergy to wheat, rye, barley and/or oats, and avoidance of cereals for another reason (including child's suspected allergy).

2.5. Statistical analysis

Cox proportional hazards regression analysis was used to study the association of maternal cereal intake during pregnancy and lactation with the development of islet autoimmunity and type 1 diabetes.

For islet autoimmunity, the onset time was set as midpoint between the collection time of the last negative and first positive (positive for ICA and at least one other autoantibody) sample. For islet autoimmunity outcome, participants were followed until the onset time or until the time of the last islet autoimmunity-negative measurement up to 15 years. For type 1 diabetes outcome, children were followed up until the diagnosis date and the children without type 1 diabetes were right-censored for the date of type 1 diabetes data was derived in 2017.

The association of categorized exposure variables with the outcomes showed no indication of significant non-linear association so we used exposures as continuous variables in the models. We adjusted the models for energy intake, child's sex, HLA genotype, and familial diabetes. For energy-adjustment we divided the food or nutrient intake in grams or 0.25 g by total energy intake in MJs, and additionally added the energy in the model as covariate [19]. The following variables were also used as covariates in the model but were not included in the final model as they did not clearly affect the estimates: maternal age, maternal education, and smoking during pregnancy.

To investigate whether the exposure related risk of islet autoimmunity and type 1 diabetes changed over the follow-up time, we added time dependent interaction term between exposure and logarithm of the follow-up time to the model and considered a p value < 0.05 for interaction as a sign of interaction. In addition, we explored whether sex and HLA genotype modified the association between each exposure and outcome by adding relevant interaction terms and presented stratified associations for those with a p value for interaction <0.05.

Analyses were performed using SAS Enterprise Guide 8.3 (SAS Institute Inc., Cary, North Carolina, USA).

3. Results

Participant characteristics are shown in Table 1. Participants who were excluded due to missing exposure information developed type 1 diabetes less often (55/2839, 1.9%) than those who were included in the analyses (178/4943, 3.6%).

During the follow-up 312 children (6.4%) developed islet autoimmunity at a median age of 3.5 (IQR 1.7–6.6) years and 178 children (3.6%) developed type 1 diabetes at a median age of 7.1 (IQR 4.3–10.6) years. The median follow-up time was 9.4 (IQR 3.0.-14.0) years in the islet autoimmunity cohort and 16.4 (14.5, 18.1) years in the type 1 diabetes cohort. The drop-out rates among the 4887 children in the pregnancy - islet autoimmunity cohort at 1- and 5-year autoantibody follow-up were 5.7% (279 children) and 30% (1415 children), respectively.

Mean maternal gluten intake was 14.9 (SD 5.5) g/day during pregnancy and 13.5 (5.1) g/day during lactation (Supplementary Table 1). Wheat was the most consumed cereal during pregnancy with a mean of 108.7 g daily consumption followed by rye (61.5 g), rice (14.1 g), oats (8.4 g), and barley (1.9 g). Cereal consumption during lactation showed a similar pattern but mean intakes were approximately 10% lower than during pregnancy (Supplementary Table 1).

Maternal cereal, gluten, and dietary fiber intake during pregnancy was not associated with the risk of the islet autoimmunity or type 1 diabetes in the offspring (Table 2). For example, HR; 95% CI for islet autoimmunity for 1 g/MJ increase in gluten intake was 0.96; 0.68, 1.35, $p = 0.82$.

Higher maternal barley consumption during lactation was associated with increased risk of type 1 diabetes in the child (HR 3.25; 95% CI 1.21, 8.70, per 1 g/MJ increase in barley intake, $p = 0.02$). Similar but weaker association was seen for islet autoimmunity (HR 2.17; 95% CI 0.99, 4.76, $p = 0.05$). Consumption of other cereals, gluten or dietary fiber intake during lactation was not associated with the outcomes (Table 3).

Exclusion of children with maternal cereal-related special diet did not change the results. E.g., to compare with the above-presented estimates HR for islet autoimmunity for 1 g/MJ increase in pregnancy gluten intake was 0.99; 95% CI 0.70, 1.41, $p = 0.98$ after exclusion of those with a special diet. Respectively, higher maternal barley consumption during lactation was still associated with increased risk of type 1 diabetes in the child (HR 3.45; 95% CI 1.30, 9.20, $p = 0.01$).

We observed no indication of interaction between intake of gluten, cereals, or dietary fiber during pregnancy or lactation and sex, HLA genotype, or follow-up time with islet autoimmunity or type 1 diabetes with a few exceptions: Higher maternal intake of oats during lactation was associated with an increased risk of islet autoimmunity (HR 1.26; 95% CI 1.06, 1.50) and type 1 diabetes (1.34; 1.11, 1.62) among males but a decreased risk for islet autoimmunity (0.71; 0.51, 1.00) and type 1 diabetes (0.58; 0.35, 0.95) among

Table 1
Child characteristics for all participants in the pregnancy cohorts to study islet autoimmunity and the type 1 diabetes.

Characteristics	Pregnancy cohort - islet autoimmunity (n = 4887)	Islet autoimmunity (n = 312)	Pregnancy cohort - type 1 diabetes (n = 4943)	Type 1 diabetes (n = 178)
	n (%)	n (%)	n (%)	n (%)
Sex				
Male	2579 (52.8)	189 (60.6)	2605 (52.7)	105 (59.0)
Female	2308 (47.2)	123 (39.4)	2338 (47.3)	73 (41.0)
HLA-DQB1-conferred risk				
High	961 (19.7)	109 (34.9)	971 (19.6)	66 (37.1)
Moderate	3926 (80.3)	203 (65.1)	3972 (80.4)	112 (62.9)
Familial diabetes				
Yes	285 (5.8)	37 (11.9)	287 (5.8)	26 (14.6)
No	4421 (90.5)	268 (85.9)	4470 (90.4)	148 (89.1)
Missing	181 (3.7)	7 (2.2)	186 (3.8)	4 (2.2)

Table 2
Associations of maternal cereal, gluten, and dietary fiber intake during pregnancy with the risk of islet autoimmunity and type 1 diabetes in the offspring.

	Islet Autoimmunity	p-value	Type 1 diabetes	p-value
	n = 4706 (305)		n = 4757 (174)	
	Adj. HR (95% CI)		Adj. HR (95% CI)	
Oats, g/MJ	0.91 (0.78, 1.06)	0.21	0.91 (0.74, 1.11)	0.36
Rice, g/MJ	1.10 (0.98, 1.23)	0.12	1.02 (0.88, 1.20)	0.76
Gluten-containing cereals, g/MJ	1.00 (0.97, 1.03)	0.89	1.00 (0.96, 1.03)	0.92
Wheat, g/MJ	0.99 (0.96, 1.03)	0.75	0.99 (0.95, 1.04)	0.81
Rye, g/MJ	1.00 (0.97, 1.03)	0.92	1.00 (0.96, 1.04)	0.95
Barley, g/MJ	1.29 (0.59, 2.82)	0.52	1.48 (0.54, 4.08)	0.45
Gluten, g/MJ	0.96 (0.68, 1.35)	0.82	0.96 (0.62, 1.50)	0.87
Total dietary fiber, 0.25 g/MJ	1.01 (0.97, 1.04)	0.67	1.01 (0.97, 1.06)	0.67
Insoluble fiber, 0.25 g/MJ	1.01 (0.96, 1.06)	0.71	1.01 (0.95, 1.08)	0.70
Soluble fiber SDFP, 0.25 g/MJ	1.09 (0.92, 1.28)	0.32	1.07 (0.87, 1.33)	0.52
Soluble fiber SDFS, 0.25 g/MJ	0.99 (0.83, 1.18)	0.92	1.03 (0.82, 1.28)	0.83

HR's are from Cox regression model per g/MJ, 0.25 g/MJ increase in the intake adjusted for energy intake, sex, HLA genotype and familial diabetes.
SDFP, dietary fiber soluble in water but insoluble in 78% aqueous ethanol; SDFS, dietary fiber soluble in water and soluble in 78% aqueous ethanol.

Table 3
Associations of maternal cereal, gluten, and dietary fiber intake during lactation with the risk of islet autoimmunity and type 1 diabetes in the offspring.

	Islet Autoimmunity	p-value	Type 1 diabetes	p-value
	n = 2862 (188)		n = 2865 (107)	
	Adj. HR (95% CI)		Adj. HR (95% CI)	
Oats, g/MJ	1.06 (0.90, 1.24)	0.50	1.08 (0.89, 1.32)	0.42
Rice, g/MJ	1.04 (0.90, 1.20)	0.60	1.03 (0.85, 1.25)	0.75
Gluten-containing cereals, g/MJ	0.99 (0.96, 1.03)	0.70	0.99 (0.95, 1.04)	0.76
Wheat, g/MJ	0.99 (0.95, 1.04)	0.72	1.01 (0.96, 1.07)	0.67
Rye, g/MJ	1.00 (0.96, 1.04)	0.84	0.98 (0.93, 1.03)	0.42
Barley, g/MJ	2.17 (0.99, 4.76)	0.05	3.25 (1.21, 8.70)	0.02
Gluten, g/MJ	0.91 (0.61, 1.37)	0.66	0.97 (0.56, 1.66)	0.91
Total dietary fiber, 0.25 g/MJ	1.01 (0.97, 1.06)	0.55	1.00 (0.94, 1.06)	0.99
Insoluble fiber, 0.25 g/MJ	1.04 (0.96, 1.11)	0.35	1.01 (0.92, 1.12)	0.77
Soluble fiber SDFP, 0.25 g/MJ	1.05 (0.85, 1.30)	0.63	0.99 (0.75, 1.32)	0.96
Soluble fiber SDFS, 0.25 g/MJ	0.98 (0.80, 1.20)	0.83	0.92 (0.70, 1.22)	0.57

HR's are from Cox regression model per g/MJ or 0.25 g/MJ increase in the intake adjusted for energy intake, sex, HLA genotype and familial diabetes.
SDFP, dietary fiber soluble in water but insoluble in 78% aqueous ethanol; SDFS, dietary fiber soluble in water and soluble in 78% aqueous ethanol.

females. In addition, a higher maternal intake of barley during lactation was associated with an increased risk of islet autoimmunity in males (5.36; 2.00, 14.35) but not females (0.58; 0.35, 0.95).

4. Discussion

This prospective study among genetically susceptible children found no association between maternal gluten exposure during pregnancy and lactation and the risk of islet autoimmunity or type 1 diabetes in the offspring. The most consumed cereals and dietary fiber showed no association with type 1 diabetes outcomes either. However, higher maternal barley consumption during lactation was associated with increased risk of type 1 diabetes in the offspring.

Strengths of this study include a large study population and prospective setting, having information about maternal diet both during pregnancy and lactation, and being able to study two type 1 diabetes related outcomes: islet autoimmunity and clinical diabetes. Further, we were able to study several components of cereals and related factors, such as various cereal types, gluten, and dietary fiber fractions. Finally, we were able to adjust the analyses for relevant potential confounders.

A limitation for all observational studies is that we cannot exclude the possibility of unmeasured confounders that could have influenced the results. The FFQ as a dietary assessment method has limitations too. Although the FFQ we used is validated [16], all FFQs are prone to imprecisions in the estimated food and nutrient intakes both due to the questionnaires as such, and due to the recipes used in the calculation of specific components in the diet. In the present study, the daily gluten intake during pregnancy (14.9 g) was comparable to, but slightly higher than, what was reported in Danish 13.0 g [2] and Norwegian 13.6 g [3] populations using their country-specific FFQs.

The participants were selected based on their HLA-conferred genetic susceptibility for type 1 diabetes and the findings are not necessarily generalizable to the general population. Further, children with maternal FFQ data had a higher incidence of type diabetes than children without maternal FFQ data suggesting that higher risk families may be more active in participation than those with lower risk of type 1 diabetes. The maternal diet during lactation was studied only among mothers who were still breastfeeding their child at the 3-month visit. Therefore, this might be a slightly selected study population and not representative to all mothers who had been breastfeeding.

Our results do not support the hypothesis, nor the findings from some animal studies [1] and one human study [2] that higher gluten intake during pregnancy would increase the risk of type 1 diabetes in the offspring. However, our results are in line with other prospective observational human studies that found no association between gluten or gluten-containing cereal consumption during pregnancy and offspring islet autoimmunity or type 1 diabetes [3–5], and a recent animal study that failed to replicate their previous finding [20].

To our knowledge, this was the first human study to explore the relationship between maternal gluten, cereal, and dietary fiber intake during lactation and the risk of islet autoimmunity or type 1 diabetes in the child. The only association we observed was that higher barley intake during lactation was associated with increased risk of type 1 diabetes in the offspring. The average barley consumption among the mothers was very low compared to other cereals, however, most mothers had small amounts of barley in their diets. The presented risk estimates were per 1 g/MJ increase in intake, which for barley, represents quite large contrast relative to the average consumption in the cohort. Barley consumption was calculated from various foods: e.g. breads, and breakfast cereals (hot porridges, cold cereals). As we cannot think of a rationale for barley being harmful, while other gluten containing cereals not being harmful, our observation could be confounded by an unknown factor. However, we were able to adjust for maternal education, age, and smoking, and only minor changes in the estimates were observed.

We observed some interactions between maternal lactation cereal consumption and child sex. In general, male children had a higher risk of islet autoimmunity related to higher maternal oats or barley consumption than female. The significance of this finding is not known. However, it would be meaningful to explore whether sex modifies the associations between other risk factors and the risk of type 1 diabetes.

5. Conclusion

This study suggests that there is no association between maternal intake of gluten, most common cereals, and dietary fiber during pregnancy or lactation and risk of islet autoimmunity or type 1 diabetes in children from a high-risk population.

Funding statement

Supported by the Research Council of Finland (grants 63 672, 68 292, 79 685, 79 686, 80 846, 114 666, 126 813, 129 492, 139 391, 201 988, 210 632, 250 114, 276 475, 308 066, 339 922); European Foundation for the Study of Diabetes award supported by EFSD/JDRF/Lilly; the Diabetes Research Foundation; the Juho Vainio Foundation; Competitive Research Funding of the Turku and Oulu University Hospitals; the Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital (grants 9E082, 9F089, 9G087, 9H092, 9J147, 9K149, 9L042, 9L117, 9M036, 9M114, 9N086, 9P057, 9R055, 9S074, 9T072, 9U065, 9V072, 9X062, 9AA084, 9AB083); the Juvenile Diabetes Research Foundation (grants 4-1998-274, 4-1999-731, 4-2001-435, 1-SRA-2016-342-M-R, 1-SRA-2019-732-M-B, and 3-SRA-2020-955-S-B); the Novo Nordisk Foundation; the European Union Biomed 2 Program (BMH4-CT98-3314). This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 874864 HEDIMED.

Supporting sources had no involvement or restrictions regarding publication.

Author contributions

The authors' responsibilities were as follows: Conceptualization: LH, NALB, SMV; Formal analysis: HMT, Data Curation: HMT, HT: Writing - Original Draft: LH, NALB, SMV; Writing - Review & Editing: all authors; Supervision: SMV, Funding acquisition: HH, JT, JI, MK, RV, NALB, SMV.

Data statement

The data is not shared due to the sensitive nature of the data and the existing legislation.

Declaration of competing interest

Authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2024.05.001.

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