

## Online Supplement:

This appendix has been provided by the authors to give additional information about their work.

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## Gluten intake in early childhood and risk of celiac disease: A nationwide cohort study.

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Supplementary Table 1: Characteristics of MoBa participants included and excluded from the analyses.

	Included n=67,608 (%)	Excluded n=45,445 (%)
<b>Maternal</b>		
<b>Maternal age</b>		
<25	6,243 (9)	6,904 (15)
25-34	49,272 (73)	30,815 (68)
≥35	12,093 (18)	7,726 (17)
<b>Parity</b>		
0	31,826 (47)	17,979 (40)
1	23,347 (35)	17,260 (38)
≥2	12,435 (18)	10,206 (22)
<b>C. section</b>	9,889 (15)	7,236 (16)
<b>Education <sup>a</sup></b>		
≤12 years	22,595 (34)	15,738 (45)
12-15 years	28,525 (42)	12,439 (36)
≥16 years	16,225 (24)	6,482 (19)
<b>Smoking <sup>b</sup></b>		
No	62,033 (92)	29,141 (86)
Occasionally	1,094 (2)	854 (3)
Yes	4,145 (6)	3,863 (11)
<b>Celiac disease</b>	704 (1)	523 (1)
<b>Pre-pregnancy body mass index <sup>c</sup></b>		
<20	8,206 (12)	4,468 (13)
20-25	37,417 (57)	18,291 (54)
25-29.99	14,390 (22)	7,406 (22)
≥30	6,063 (9)	3,489 (10)
<b>Paternal</b>		
<b>Celiac disease</b>	231 (0.3)	120 (0.3)
<b>Child</b>		
<b>Female sex (%)</b>	33,041 (49)	22,079 (49)
<b>Birth weight, g</b>		
<2500	2,598 (4)	2,133 (5)
2500-3499	25,878 (38)	17,259 (38)
3500-4499	36,230 (54)	23,993 (53)
>4500	2,901 (4)	2,039 (4)
<b>Prematurity (&lt;37 weeks)</b>	4,006 (6)	3,059 (7)
<b>Breastfeeding duration <sup>d</sup></b>		
≤6 months	13,558 (20)	1,130 (19)
6-12 months	28,073 (42)	2,469 (42)
≥12 months	25,977 (38)	2,261 (39)
<b>Age at gluten introduction <sup>e</sup></b>		
≤3 months	445 (1)	284 (1)
4-5 months	15,195 (22)	6,276 (29)
≥6 months	51,968 (77)	15,400 (70)
<b>Celiac disease from the patient register</b>	733 (1.1)	473 (1.0)

<sup>a</sup> missing education for 10,786 of excluded and 263 of included

<sup>b</sup> missing smoking for 11,587 of excluded and 336 of included

<sup>c</sup> missing BMI for 11,791 of excluded and 1,532 of included

<sup>d</sup> missing for 39,585 of the excluded

<sup>e</sup> missing for 23,485 of the excluded

Supplementary Table 2: Association of gluten amount at 18 months and celiac disease excluding children with reported restricted wheat intake due to suspected allergy at age 18 months.<sup>a</sup>

	Unadjusted relative risk	Adjusted relative risk Model 1 <sup>b</sup>	Adjusted relative risk Model 2 <sup>c</sup>
<b>Change in risk of celiac disease per standard deviation increase (3.6 g/d)</b>			
	1.11 (1.04-1.19)	1.10 (1.03-1.18)	1.10 (1.03-1.18)
<b>Quartile of gluten intake</b>			
<b>1<sup>st</sup> (&lt;6.22 g/d)</b>	1 (ref.)	1 (ref.)	1 (ref.)
<b>2<sup>nd</sup> (6.22-8.16 g/d)</b>	0.96 (0.77-1.19)	0.97 (0.78-1.20)	0.95 (0.77-1.19)
<b>3<sup>rd</sup> (8.16-10.68 g/d)</b>	1.19 (0.97-1.46)	1.19 (0.97-1.46)	1.17 (0.96-1.44)
<b>4<sup>th</sup> (10.68 g/d)</b>	1.33 (1.09-1.63)	1.29 (1.06-1.58)	1.27 (1.04-1.55)

<sup>a</sup> 234 reported restricted wheat intake at 18 months due to intolerance (not celiac disease), and were excluded from the analysis.

<sup>b</sup> Model 1 adjusted for age of gluten introduction and duration of breastfeeding, parental celiac disease, child's age and sex.

<sup>c</sup> Model 2 is additionally adjusted for maternal age and parity, education, smoking, caesarean section, child's birth weight and prematurity.

Supplementary Table 3: Risk of celiac disease by combination of age at introduction and amount of gluten at 18 months.

	Celiac disease, n (%)		Unadjusted relative risk	Adjusted relative risk Model 1 <sup>a</sup>	Adjusted relative risk Model 2 <sup>b</sup>
	No n=66,430	Yes n=733			
<b>Group 1</b>	7,827 (12)	55 (8)	1 (ref.)	1 (ref.)	1 (ref.)
<b>Group 2</b>	7,246 (11)	67 (9)	1.31 (0.92-1.87)	1.32 (0.93-1.88)	1.33 (0.93-1.90)
<b>Group 3</b>	25,322 (28)	264 (36)	1.48 (1.11-1.97)	1.38 (1.03-1.84)	1.38 (1.03-1.84)
<b>Group 4</b>	26,035 (39)	347 (47)	1.88 (1.42-2.50)	1.73 (1.30-2.30)	1.71 (1.28-2.28)

Group 1: Started gluten 4-5.9 months, amount <50<sup>th</sup> centile at 18 months

Group 2: Started gluten 4-5.9 months, amount >50<sup>th</sup> centile at 18 months

Group 3: Started gluten ≥ 6 months, amount <50<sup>th</sup> centile at 18 months

Group 4: Started gluten ≥ 6 months, amount >50<sup>th</sup> centile at 18 months

<sup>a</sup> Model 1 adjusted for duration of breastfeeding, parental celiac disease, child's age and sex

<sup>b</sup> Model 2 adjusted for duration of breastfeeding, parental celiac disease, child's age and sex, maternal age and parity, education, smoking, caesarean section, child's birth weight and prematurity.

Supplementary Table 4: Association of gluten amount at 18 months and celiac disease additionally adjusted for pre-pregnant BMI and childhood infections.<sup>a</sup>

	Unadjusted relative risk	Adjusted relative risk including pre- pregnant BMI	Adjusted relative risk including number of infections <18 months age
<b>Change in risk of celiac disease per standard deviation increase (3.6 g/d)</b>			
	1.11 (1.04-1.19)	1.10 (1.02-1.17)	1.09 (1.02-1.17)
<b>Quartile of gluten intake</b>			
<b>1<sup>st</sup> (&lt;6.22 g/d)</b>	1 (ref.)	1 (ref.)	1 (ref.)
<b>2<sup>nd</sup> (6.22-8.16 g/d)</b>	0.97 (0.78-1.21)	0.97 (0.78-1.21)	0.95 (0.77-1.18)
<b>3<sup>rd</sup> (8.16-10.68 g/d)</b>	1.19 (0.97-1.47)	1.18 (0.96-1.45)	1.17 (0.95-1.43)
<b>4<sup>th</sup> (10.68 g/d)</b>	1.33 (1.08-1.62)	1.26 (1.03-1.55)	1.25 (1.02-1.53)

Adjusted for age of gluten introduction and duration of breastfeeding, parental celiac disease, child's age and sex, maternal age and parity, education, smoking, caesarean section, child's birth weight and prematurity in addition to the covariate in the table.

<sup>a</sup> Maternal BMI and/or infections during 0-18 months were incomplete for 1540 of the participants.

Supplementary Table 5: Association of gluten amount at 18 months and celiac disease with exclusion of children with parental celiac disease. <sup>a</sup>

	Unadjusted relative risk	Adjusted relative risk Model 1 <sup>b</sup>	Adjusted relative risk Model 2 <sup>c</sup>
<b>Change in risk of celiac disease per standard deviation increase (3.6 g/d)</b>	1.13 (1.05-1.21)	1.13 (1.05-1.21)	1.13 (1.05-1.21)
<b>Quartile of gluten intake</b>			
1 <sup>st</sup> (<6.22 g/d)	1 (ref.)	1 (ref.)	1 (ref.)
2 <sup>nd</sup> (6.22-8.16 g/d)	1.03 (0.81-1.31)	1.03 (0.81-1.31)	1.02 (0.80-1.30)
3 <sup>rd</sup> (8.16-10.68 g/d)	1.23 (0.98-1.54)	1.22 (0.97-1.54)	1.20 (0.96-1.52)
4 <sup>th</sup> (10.68 g/d)	1.41 (1.13-1.75)	1.40 (1.12-1.75)	1.38 (1.10-1.72)

<sup>a</sup> 698 were excluded due to maternal celiac disease, 225 due to paternal celiac disease, and 6 due to celiac disease in both parents.

<sup>b</sup> Model 1 adjusted for age of gluten introduction and duration of breastfeeding, child's age and sex.

<sup>c</sup> Model 2 is additionally adjusted for maternal age and parity, education, smoking, caesarean section, child's birth weight and prematurity.

Supplementary Table 6: Association of gluten amount at 18 months and celiac disease excluding cases without confirmation from a previous validation study.<sup>a</sup>

	Celiac disease, n (%)		Unadjusted relative risk	Adjusted relative risk Model 1 <sup>a</sup>	Adjusted relative risk Model 2 <sup>b</sup>
	No	Yes			
Per SD increase in gluten intake					
	n=66,870	n=316	1.09 (0.98-1.21)	1.08 (0.98-1.19)	1.08 (0.98-1.19)
Per quartile of gluten intake					
1 <sup>st</sup> quartile	16,679 (25)	68 (22)	1 (ref.)	1 (ref.)	1 (ref.)
2 <sup>nd</sup> quartile	16,740 (25)	72 (23)	1.05 (0.76-1.47)	1.06 (0.76-1.48)	1.05 (0.75-1.46)
3 <sup>rd</sup> quartile	16,724 (25)	81 (26)	1.19 (0.86-1.64)	1.20 (0.87-1.65)	1.18 (0.85-1.63)
4 <sup>th</sup> quartile	16,727 (25)	95 (30)	1.39 (1.02-1.90)	1.36 (1.00-1.86)	1.34 (0.99-1.83)

<sup>a</sup> 422 were excluded due to missing details from the diagnostic process, mainly due to a diagnosis of celiac disease more recent than the validation process.

<sup>b</sup> Model 1 adjusted for age of gluten introduction and duration of breastfeeding, child's age and sex.

<sup>c</sup> Model 2 is additionally adjusted for maternal age and parity, education, smoking, caesarean section, child's birth weight and prematurity.

Supplementary Table 7: Hazard ratio for celiac disease in cases with estimated age at diagnosis (n=703) and cohort controls by SD increase in gluten intake at 18 months, by quartile and by age of gluten introduction.

	Celiac disease, n (%)		Unadjusted hazard ratio	Adjusted hazard ratio <sup>a</sup>	p-value
	No	Yes			
Per SD increase in gluten intake					
	n=66,430	n=703	1.12 (1.05-1.21)	1.12 (1.04-1.20)	0.002
Per quartile increase in gluten intake					
1 <sup>st</sup> quartile	16,679 (25)	156 (22)	1 (ref.)	1 (ref.)	
2 <sup>nd</sup> quartile	16,740 (25)	149 (21)	0.96 (0.77-1.20)	0.97 (0.77-1.21)	0.76
3 <sup>rd</sup> quartile	16,724 (25)	185 (26)	1.19 (0.96-1.47)	1.19 (0.96-1.48)	0.11
4 <sup>th</sup> quartile	16,727 (25)	213 (30)	1.37 (1.12-1.69)	1.34 (1.09-1.64)	0.006
Age at gluten introduction					
< 4 months	440 (0.7)	5 (0.7)	1.48 (0.60- 3.63)	1.60 (0.64-4.95)	0.31
4-6 months	15,073 (23)	112 (16)	1 (ref.)	1 (ref.)	
≥ 6 months	51,357 (77)	586 (83)	1.64 (1.34- 2.01)	1.49 (1.22-1.83)	<0.001

<sup>a</sup> Adjusted for sex, parental celiac disease, duration of breastfeeding - and reciprocally for age of gluten introduction and amount of gluten at 18 months.



Supplementary Figure 1: Excerpts of questionnaires at child age 6 (a) and 18 months (b).

a.

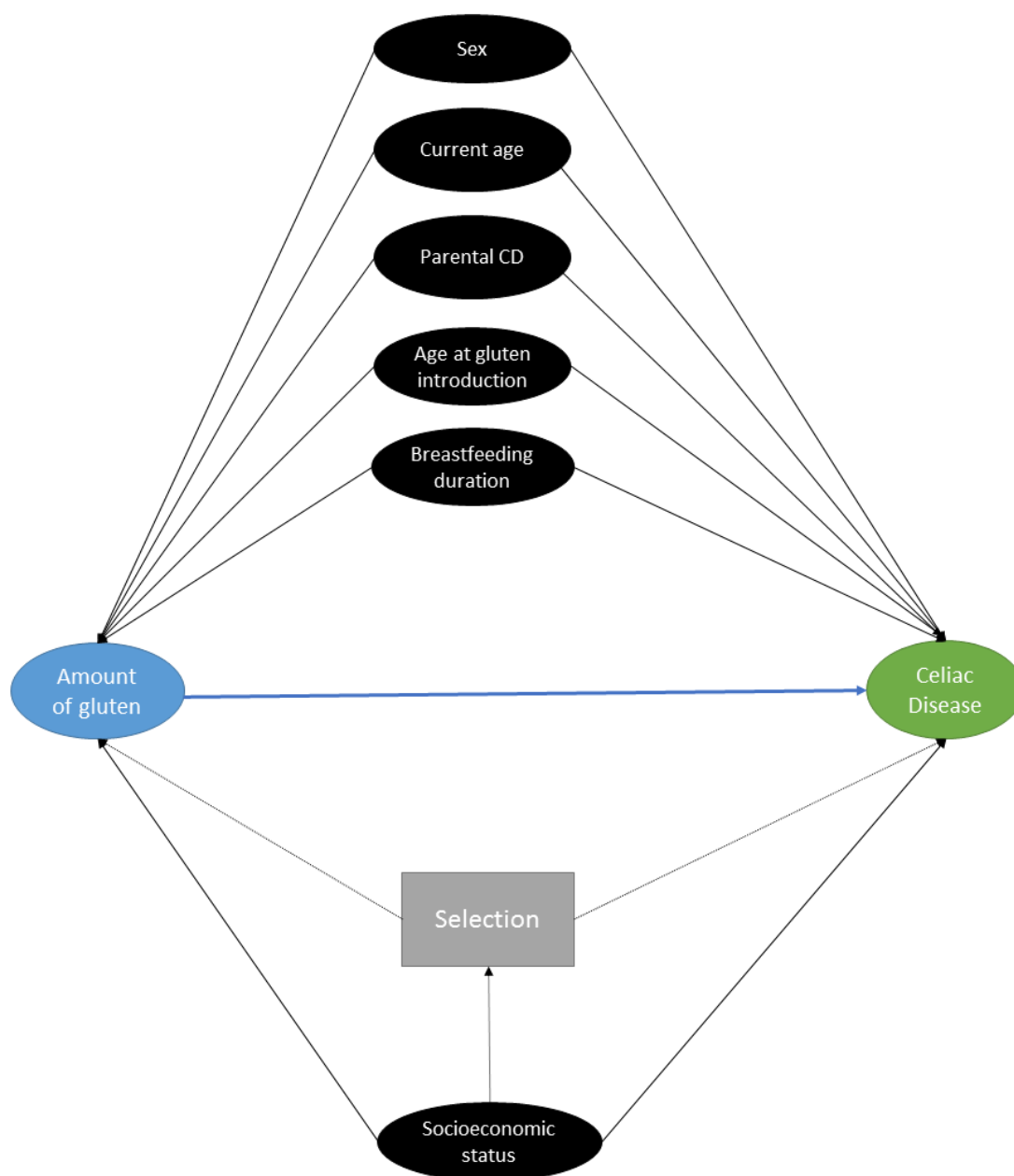
18. How often does your child eat the following food at the moment, and how old was your child when you started giving him/her this food?					
+	How often do you give this to your child?				How old was your child when you gave him/her this food for the first time?
	Never/ seldom	1-3 times a week	4-6 times a week	At least once a day	
<b>Instant porridge</b>					
1. Rice porridge, maize porridge .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
2. Oatmeal porridge, different types .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
3. Wheat porridge, all types, rusk porridge	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
<b>Home-made porridge using:</b>					
4. Wheat flour (rough/line), rusk, semolina, oats	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
5. Iron-enriched wheat flour .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
6. Helios baby flour .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
7. Millet .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
<b>Processed dinner in a jar:</b>					
8. Vegetables .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
9. Vegetables and meat .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
<b>Home-made dinner:</b>					
10. Potato/vegetable puree .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
11. Meat and vegetables/potatoes .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
12. Fish and vegetables/potatoes .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
13. Other type of home-made dinner .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
<b>Snack/dessert:</b>					
14. Home-made fruit puree .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
15. Fruit/berry puree in a jar .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
16. Rusks/biscuits/bread .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months
17. Other, specify: .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="text"/> months

b.

4. How often do you give your child the following to eat now that he/she is 18 months old? Select the frequency which is most applicable on average.  
(Enter a cross in a box for each item.)

[illegible]

Supplementary Figure 2: Directed Acyclic Graph (DAG) indicating exposure, outcome and potential confounders.



CD: Celiac disease.

The lower part of the diagram indicates the potential selection bias by socioeconomic status from participants lost to follow-up and those not consenting to participate. In the analyses of complete cases, socioeconomic status (maternal education) was adjusted for without appreciable change in the estimates.