

# Supplementary Material

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## SUPPLEMENTARY TABLES

**Supplementary Table 1.** Previous literature on the association between parental smoking in pregnancy and celiac disease (CD) in offspring.

Authors (year of publication)	Country	Design	Participants	Data sources		Selected covariates	Main findings
				CD n=number of children with CD	Smoking		
<b>Adlercreutz <i>et al.</i></b> (2014) <sup>A, 1</sup>	Sweden	National register-based study	768,395 children born in 1987-1993	The National Patient Register n=4008	The Swedish MBR: mom's smoking/non-smoking at 6-12 GW	-	25% of children with CD were exposed to maternal smoking in early pregnancy (1001/4008) as compared with 23% among those in the reference group (176,044/760,060) (OR 1.02; 95% CI 0.95-1.10).
<b>Aronsson <i>et al.</i></b> (2015) <sup>2</sup>	Sweden, Finland, Germany, United states	Multinational birth cohort	6436 children genetically at risk for CD	Repeated CD screening. n=773 with CD autoimmunity (consecutive positive tTG), of whom 307 had CD	Parental questionnaires completed at 3-4 months postpartum: mom's smoking/non-smoking any time in pregnancy	Presents unadjusted estimates. Genetic and dietary data are included in other parts of the study.	63 out of 773 children with CD autoimmunity and 28 out of 307 children with CD were exposed to maternal smoking in pregnancy (CD autoimmunity: HR 0.85, 95% CI 0.65-1.09; CD: HR 0.98, 95% CI 0.67-1.45).
<b>Emilsson <i>et al.</i></b> (2014) <sup>B, 3</sup>	Norway	National cohort	108,478 children born in 2000-2009. Earlier version of the Norwegian Mother and Child Cohort Study.	Parental questionnaires and the Norwegian Patient Registry n=650	Parental questionnaires administered at 18 GW and at 6 months postpartum: Mom's smoking/non-smoking at 18 GW; parental smoking/non-smoking pre-, post pregnancy	Maternal CD, type 1 diabetes, age at delivery, parity, education level, mode of delivery, birth weight, gestational age, child's attained age at end of study, breastfeeding duration, timing of gluten introduction.	6% (35/617) of children later developing CD were exposed to maternal smoking at 18 pregnancy weeks, compared with 8% (8430/101,413) of children without CD, corresponding to an adjusted OR of 0.66 (95% CI 0.44-0.97). Maternal and paternal smoking in the last three months of pregnancy yielded an adjusted OR of 0.86 [95% CI 0.68-1.08] and 0.88 [95% CI 0.77-1.00], respectively). Maternal and paternal smoking at child's age 4-6 months was associated with an adjusted OR of 0.85 (95% CI 0.71-1.03) and 0.84 (95% CI 0.73-0.96), respectively.

<b>Ludvigsson <i>et al.</i> (2005)</b> <sup>4</sup>	Sweden	Regional cohort	15,397 children born in 1997-1999. Part of the All Babies in Southeast Sweden Cohort	CD reported from regional pediatric departments. n=53	Parental questionnaires administered at birth and at child's age one year: mom's smoking any time in pregnancy, her daily number of cigarettes, ETS exposure 0-12 months	Maternal education level, pre-pregnancy body mass index, breastfeeding duration	17% of the children with CD were exposed to maternal smoking in pregnancy (9/53) as compared with 11% (1699/15,344) among children without CD (OR 1.64; 95% CI 0.80-3.37). Neither the number of cigarettes smoked during pregnancy nor maternal smoking in the child's first year of life was associated with childhood CD (both P-values>0.15).
<b>Namatovu <i>et al.</i> (2016)</b> <sup>5</sup>	Sweden	National register-based study	1,912,204 children born in 1991-2009	The National Swedish Childhood Celiac Disease Register n=6596	The Swedish MBR: mom's smoking/non-smoking at 6-12 GW	Maternal age at delivery, salary, parity, infections in pregnancy, gestational age, delivery mode, birth weight	Maternal smoking in pregnancy was found among 14% of children with CD (853/6596) as compared with 13% (240,677/1,912,204) among children without CD (OR 1.0; 95% CI 0.9-1.1).
<b>Roberts <i>et al.</i> (2009)</b> <sup>6</sup>	England	Regional register-based study	248,521 children born in 1970-1999 and included in the Oxford record linkage study database	CD diagnosed at inpatient or hospital-based day care admissions. n=90	Data abstracted from maternity records in the years 1973-1999: mom's smoking any time in pregnancy	Maternal CD, marital-status, age at delivery, parity, maternal occupation, delivery mode, gestational age, breastfeeding (yes/no), birth weight,	In bivariate analysis the cumulative CD incidence per 100,000 births was 56 (95% CI 33-87) in children exposed to maternal smoking in pregnancy vs. 26 (95% CI 18-38) among unexposed (P-value 0.01; P-value per cigarette smoked in pregnancy, 0.11). In the multivariate model maternal smoking was not significantly associated with CD (no risk estimates were reported).
<b>Sandberg-Bennich <i>et al.</i> (2002)</b> <sup>A, 7</sup>	Sweden	National register-based study	1,182,056 children born in 1987-1997	The National Patient Register n=3392	The Swedish MBR: mom's smoking/non-smoking at 6-12 GW	Maternal age at delivery, parity, year of birth	Maternal smoking in early pregnancy was significantly associated with offspring CD: OR 1.10; 95% CI 1.01-1.19
<b>Wingren <i>et al.</i> (2012)</b> <sup>A, 8</sup>	Sweden	National register-based study	681,954 children born in 1987-1993	The National Patient Register n=2641	The Swedish MBR: mom's smoking/non-smoking at 6-12 GW	Maternal age at delivery, year of birth, parity, neonatal comorbidity	Maternal smoking in early pregnancy was not significantly associated with offspring CD: Boys, HR 1.09; 95% CI 0.95-1.26; Girls, HR 1.06; 95% CI 0.95-1.19.

The listed papers were identified using a PubMed search on August 27, 2017, for (celiac disease[Title] OR coeliac disease[Title]) AND (pregnancy[Title/Abstract] OR perinatal[Title/Abstract] OR infant[Title/Abstract] OR offspring[Title/Abstract]).<sup>A</sup> Studies with largely overlapping study samples and data sources on CD and smoking status.<sup>B</sup> Partly overlapping study sample and outcome definitions as of the current study, but with the following distinctions; The previous study was restricted to self-reported data on smoking during and after pregnancy as recorded in the Norwegian Mother and Child Cohort Study (MoBa); exposure to pre-pregnancy smoking and environmental tobacco smoke were not examined and there were no data on smoking from the Norwegian Medical Birth Registry or of cotinine-determined smoking status. Compared with the current work, the previous study had a shorter follow-up for CD (eight versus eleven years of average follow-up) identifying almost half the number of CD cases compared with the present study. 95% CI, 95% confidence interval; CD, celiac disease; ETS, environmental tobacco smoke; GW, gestational weeks; HR, hazard ratio; OR, odds ratio; MFR, Medical Birth Register; tTG, tissue transglutaminase antibodies.

1. Adlercreutz EH, Wingren CJ, Vincente RP, Merlo J, Agardh D. Perinatal risk factors increase the risk of being affected by both type 1 diabetes and coeliac disease. *Acta Paediatr.* Feb 2015;104(2):178-184.
2. Aronsson CA, Lee HS, Liu E, et al. Age at gluten introduction and risk of celiac disease. *Pediatrics.* Feb 2015;135(2):239-245.
3. Emilsson L, Magnus M, Størdal K. Perinatal Risk Factors for Development of Celiac Disease in Children, Based on the Prospective Norwegian Mother and Child Cohort Study. *Clin Gastroenterol Hepatol* 2015; 13:921-7.
4. Ludvigsson JF, Ludvigsson J. Parental smoking and risk of coeliac disease in offspring. *Scand J Gastroenterol.* Mar 2005;40(3):336-342.
5. Namatovu F, Olsson C, Lindkvist M, et al. Maternal and perinatal conditions and the risk of developing celiac disease during childhood. *BMC Pediatr.* 2016;16(1):77.
6. Roberts SE, Williams JG, Meddings D, Davidson R, Goldacre MJ. Perinatal risk factors and coeliac disease in children and young adults: a record linkage study. *Aliment Pharmacol Ther.* Jan 2009;29(2):222-231.
7. Sandberg-Bennich S, Dahlquist G, Källén B. Coeliac disease is associated with intrauterine growth and neonatal infections. *Acta Paediatr.* 2002;91(1):30-33.
8. Wingren CJ, Agardh D, Merlo J. Revisiting the risk of celiac disease in children born small for gestational age: a sibling design perspective. *Scand J Gastroenterol.* Jun 2012;47(6):632-639.

**Supplementary Table 2.** Characteristics of children in the Norwegian Mother and Child Cohort Study (MoBa). Descriptive statistics based on complete-case data.

n (%)	All 94,019 (100)	Maternal smoking in pregnancy			
		No smoking 73,806 (79)	Smoking <18 preg. weeks 12,182 (13)	Smoking ≥18 preg. weeks 7453 (8)	Missing data 578
<b>Celiac disease, n (%)</b>	1035 (1.1)	848 (1.1)	132 (1.1)	52 (0.7)	3 (0.5)
Missing data, n	0	0	0	0	0
<b>Calendar year of birth, median (range)</b>	2005 (2000-2009)	2005 (2000-2009)	2005 (2000-2009)	2004 (2000-2009)	2005 (2000-2009)
Missing data, n	0	0	0	0	0
<b>Girls, n (%)</b>	45,879 (48.8)	36,035 (48.8)	5916 (48.6)	3655 (49.0)	273 (47.2)
Missing data, n	0	0	0	0	0
<b>Birth weight (gram), median (IQR)</b>	3600 (3250-3940)	3600 (3260-3940)	3636 (3290-3990)	3498 (3130-3830)	3605 (3230-3930)
Missing data, n	52	39	7	6	0
<b>Gestational age (weeks), median (IQR)</b>	40 (39-41)	40 (39-41)	40 (39-41)	40 (39-41)	40 (39-41)
Missing data, n	404	325	49	24	6
<b>Cesarean delivery, n (%)</b>	13,903 (14.8)	10,580 (14.3)	2001 (16.4)	1232 (16.5)	90 (15.6)
Missing data, n	0	0	0	0	0
<b>Duration of full breastfeeding, n (%)</b>					
<3 months	28,690 (33.8)	21,396 (31.8)	4268 (39.3)	2863 (45.0)	163 (33.1)
3-5 months	24,624 (29.0)	18,752 (27.9)	3476 (32.0)	2238 (35.2)	158 (32.1)
≥5 months	31,574 (37.2)	27,033 (40.2)	3111 (28.7)	1259 (19.8)	171 (34.8)
Missing data, n	9131	6625	1327	1093	86
<b>Child's infections age 0-6 months, median (IQR)</b>	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-3)
Missing data, n	10,671	7696	1595	1277	103
<b>Parity, n (%)</b>					
0 [first child]	42,708 (45.4)	32,483 (44.0)	6706 (55.0)	3285 (44.1)	234 (40.5)
1	33,255 (35.4)	26,815 (36.3)	3706 (30.4)	2507 (33.6)	227 (39.3)
≥2	18,056 (19.2)	14,508 (19.7)	1770 (14.5)	1661 (22.3)	117 (20.2)
Missing data, n	0	0	0	0	0
<b>Maternal age at delivery, median (IQR)</b>	30 (27-33)	31 (28-33)	29 (26-32)	29 (25-33)	30 (27-33)
Missing data, n	0	0	0	0	0
<b>Maternal education level, n (%)</b>					
≤9 years	7023 (7.5)	3714 (5.1)	1372 (11.3)	1884 (25.4)	53 (9.5)

10-12 years	27,407 (29.3)	18,982 (25.8)	4725 (38.9)	3511 (47.4)	189 (33.9)
≥13 years	59,158 (63.3)	50,788 (69.1)	6046 (49.8)	2009 (27.1)	315 (56.6)
Missing data, n	431	322	39	49	21
<b>Maternal occupation, n (%)</b>					
Sick leave/Studying	7459 (8.1)	5159 (7.1)	1249 (10.4)	996 (13.7)	55 (10.1)
Unemployed	5685 (6.2)	4079 (5.6)	691 (5.8)	880 (12.1)	35 (6.4)
Employed	79,056 (85.8)	63,221 (87.3)	10,013 (83.8)	5369 (74.1)	453 (83.4)
Missing data, n	1819	1347	229	208	35
<b>Maternal annual salary (NOK), n (%)</b>					
<200,000	26,428 (29.1)	18,757 (26.3)	4077 (34.6)	3435 (48.4)	159 (30.3)
200,000-399,999	53,794 (59.2)	43,493 (60.9)	6720 (57.1)	3269 (46.1)	312 (59.5)
≥400,000	10,613 (11.7)	9196 (12.9)	977 (8.3)	387 (5.5)	53 (10.1)
Missing data, n	3184	2360	408	362	54
<b>Maternal type 1 diabetes, n (%)</b>	528 (0.6)	398 (0.5)	69 (0.6)	58 (0.8)	3 (0.5)
Missing data, n	0	0	0	0	0
<b>Maternal celiac disease, n (%)</b>	1002 (1.1)	817 (1.1)	117 (1.0)	57 (0.8)	11 (1.9)
Missing data, n	0	0	0	0	0
<b>Maternal infections in pregnancy, median (IQR)</b>	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)
Missing data, n	0	0	0	0	0
<b>Paternal age at delivery, n (%)</b>					
≤29 years	25,491 (27.2)	18,333 (24.9)	4286 (35.3)	2700 (36.5)	172 (29.9)
30-34 years	36,494 (38.9)	29,493 (40.0)	4460 (36.7)	2343 (31.6)	198 (34.4)
≥35 years	31,792 (33.9)	25,822 (35.1)	3404 (28.0)	2361 (31.9)	205 (35.7)
Missing data, n	242	158	32	49	3
<b>Paternal education level, n (%)</b>					
≤9 years	9547 (10.5)	5833 (8.1)	1793 (15.2)	1857 (26.5)	64 (12.0)
10-12 years	36,701 (40.3)	26,970 (37.6)	5683 (48.3)	3811 (54.4)	237 (44.4)
≥13 years	44,781 (49.2)	38,919 (54.3)	4293 (36.5)	1336 (19.1)	233 (43.6)
Missing data, n	2990	2084	413	449	44
<b>Paternal occupation, n (%)</b>					
Sick leave/Studying	4905 (5.3)	3563 (4.9)	760 (6.4)	547 (7.7)	35 (6.5)
Unemployed	1623 (1.8)	1033 (1.4)	259 (2.2)	320 (4.5)	11 (2.1)
Employed	85,111 (92.9)	67,551 (93.6)	10,839 (91.4)	6231 (87.8)	490 (91.4)

Missing data, n	2380	1659	324	355	42
<b>Paternal annual salary (NOK), n (%)</b>					
<200,000	9475 (10.8)	6719 (9.7)	1515 (13.5)	1188 (18.2)	53 (10.5)
200,000-399,999	48,779 (55.7)	37,856 (54.6)	6566 (58.6)	4074 (62.4)	283 (56.0)
≥400,000	29,353 (33.5)	24,792 (35.7)	3120 (27.9)	1272 (19.5)	169 (33.5)
Missing data, n	6412	4439	981	919	73
<b>Paternal type 1 diabetes, n (%)</b>	609 (0.6)	472 (0.6)	87 (0.7)	49 (0.7)	1 (0.2)
Missing data, n	0	0	0	0	0
<b>Paternal celiac disease, n (%)</b>	312 (0.3)	257 (0.3)	28 (0.2)	24 (0.3)	3 (0.5)
Missing data, n	0	0	0	0	0
<b>Paternal smoking in pregnancy, n (%)</b>	18,915 (20.2)	9874 (13.4)	4299 (35.4)	4612 (62.2)	130 (48.3)
Missing data, n	555	185	26	35	309
<b>Parental cohabitation, n (%)</b>	90,647 (96.7)	71,968 (97.8)	11,512 (94.8)	6625 (89.4)	542 (96.4)
Missing data, n	302	206	34	46	16

Data from MoBa questionnaires, the Norwegian Patient Registry and the Medical Birth Registry of Norway. IQR, interquartile range; NOK, Norwegian krone, the national currency of Norway.

**Supplementary Table 3. Characteristics of children in register-based cohort. Descriptive statistics based on complete-case data.**

n (%)	All 536,861 (100)	Maternal smoking in pregnancy <sup>A</sup>			
		No smoking 384,807 (87)	Smoking 10 preg. weeks 21,618 (5)	Smoking 36 preg. weeks 35,868 (8)	Missing data 94,568
<b>Celiac disease, n (%)</b>	1919 (0.4)	1369 (0.4)	82 (0.4)	119 (0.3)	349 (0.4)
Missing data, n	0	0	0	0	0
<b>Calendar year of birth, median (range)</b>	2008 (2004-2012)	2008 (2004-2012)	2007 (2004-2012)	2008 (2004-2012)	2008 (2004-2012)
Missing data, n	0				0
<b>Girls, n (%)</b>	261,281 (48.7)	187,251 (48.7)	10,509 (48.6)	17,427 (48.6)	46,094 (48.7)
Missing data, n	0	0	0	0	0
<b>Birth weight (gram), median (IQR)</b>	3530 (3180-3880)	3554 (3206-3900)	3550 (3190-3900)	3360 (3000-3710)	3500 (3150-3850)
Missing data, n	259	174	12	19	54
<b>Gestational age (weeks), median (IQR)</b>	40 (39-41)	40 (39-41)	40 (39-41)	39 (38-40)	40 (38-41)
Missing data, n	3871	2675	192	362	642
<b>Cesarean delivery, n (%)</b>	90,021 (16.8)	63,086 (16.4)	3790 (17.5)	6037 (16.8)	17,108 (18.1)
Missing data, n	0	0	0	0	0
<b>Parity, n (%)</b>					
0 [first child]	226,233 (42.1)	158,022 (41.1)	12,201 (56.4)	14,460 (40.3)	41,550 (43.9)
1	191,677 (35.7)	140,844 (36.6)	6116 (28.3)	11,686 (32.6)	33,031 (34.9)
≥2	118,915 (22.2)	85,916 (22.3)	3300 (15.3)	9719 (27.1)	19,980 (21.1)
Missing data, n	36	25	1	3	7
<b>Maternal age at delivery, median (IQR)</b>	30 (26-33)	30 (26-33)	27 (23-32)	28 (23-32)	30 (27-34)
Missing data, n	19	10	0	0	9
<b>Maternal education level, n (%)</b>					
≤9 years	87,780 (17.0)	49,424 (13.4)	5977 (28.1)	15,812 (45.2)	16,567 (18.6)
10-12 years	153,795 (29.8)	106,859 (28.9)	8669 (40.8)	14,035 (40.1)	24,232 (27.2)
≥13 years	273,684 (53.1)	213,704 (57.8)	6596 (31.1)	5138 (14.7)	48,246 (54.2)
Missing data, n	21,602	14,820	376	883	5523
<b>Maternal diabetes, n (%)</b>					
Pre-gestational	3990 (0.7)	2785 (0.7)	166 (0.8)	311 (0.9)	728 (0.8)
Gestational	8433 (1.6)	6365 (1.7)	352 (1.6)	525 (1.5)	1191 (1.3)



Missing data, n	0	0	0	0	0
<b>Paternal age at delivery, median (IQR)</b>	<b>32 (29-37)</b>	<b>33 (29-37)</b>	<b>30 (26-35)</b>	<b>31 (26-36)</b>	<b>33 (29-37)</b>
Missing data, n	6559	3992	318	827	1422

Data from the Norwegian Patient Registry and the Medical Birth Registry of Norway. <sup>A</sup> Duration of smoking in pregnancy divided into mutually exclusive groups: no smoking, smoking up to 10 pregnancy weeks and continued smoking until 36 pregnancy weeks. Missing data are largely due to a lack of consent to record smoking data in the Medical Birth Registry of Norway. IQR, interquartile range

**Supplementary Table 4. Characteristics of nested case-control sample**

n (%)	Nested case-control sample	
	Celiac disease n=381	Random controls n=529
<b>HLA genotype, n (%)<sup>A</sup></b>		
Other genotypes (“low risk for celiac disease”)	5 (1.4)	159 (32.9)
DQ8 or DQ2 (“moderate risk”)	243 (68.8)	306 (63.2)
DQ2.5/DQ2 (“high risk”)	105 (29.7)	19 (3.9)
<b>No. of non-HLA risk alleles, median (IQR)<sup>B</sup></b>	44 (41-47)	42 (39-45)
<b>Calendar year of birth, median (range)</b>	2004 (2000-2009)	2005 (2000-2009)
<b>Girls, n (%)</b>	227 (59.6)	260 (49.1)
<b>Birth weight (gram), median (IQR)</b>	3570 (3280-3930)	3590 (3275-3970)
<b>Gestational age (weeks), median (IQR)</b>	40 (39-41)	40 (39-41)
<b>Cesarean delivery, n (%)</b>	43 (11.3)	54 (10.2)
<b>Duration of full breastfeeding, n (%)</b>		
<3 months	86 (25.8)	148 (33.1)
3-5 months	106 (31.8)	138 (30.9)
≥5 months	141 (42.3)	161 (36.0)
<b>Child’s infections age 0-6 months, median (IQR)</b>	1 (0-2)	1 (0-2)
<b>Parity, n (%)</b>		
0 [first child]	155 (40.7)	233 (44.0)
1	154 (40.4)	195 (36.9)
≥2	72 (18.9)	101 (19.1)
<b>Maternal age at delivery, median (IQR)</b>	30 (27-33)	30 (27-33)
<b>Maternal education level, n (%)</b>		
≤9 years	26 (7.1)	33 (6.7)
10-12 years	108 (29.6)	156 (31.8)
≥13 years	231 (63.3)	302 (61.5)
<b>Maternal occupation, n (%)</b>		
Sick leave/Studying	34 (9.4)	36 (7.3)
Unemployed	20 (5.5)	33 (6.7)
Employed	307 (85.0)	421 (85.9)
<b>Maternal annual salary (NOK), n (%)</b>		
<200,000	109 (31.1)	147 (30.7)
200,000-399,999	214 (61.0)	284 (59.3)
≥400,000	28 (8.0)	48 (10.0)
<b>Maternal type 1 diabetes, n (%)</b>	5 (1.3)	0 (0.0)
<b>Maternal celiac disease, n (%)</b>	45 (11.8)	2 (0.4)
<b>Maternal infections in pregnancy, median (IQR)</b>	1 (0-2)	1 (0-2)
<b>Paternal age at delivery, n (%)</b>		
≤29 years	103 (27.1)	157 (29.7)
30-34 years	158 (41.6)	190 (36.0)
≥35 years	119 (31.3)	181 (34.3)
<b>Paternal education level, n (%)</b>		
≤9 years	33 (9.4)	57 (11.9)
10-12 years	142 (40.3)	196 (41.0)
≥13 years	177 (50.3)	225 (47.1)
<b>Paternal occupation, n (%)</b>		
Sick leave/Studying	15 (4.2)	20 (4.1)
Unemployed	8 (2.2)	4 (0.8)
Employed	335 (93.6)	459 (95.0)

<b>Paternal annual salary (NOK), n (%)</b>		
<200,000	29 (8.3)	48 (10.3)
200,000-399,999	196 (56.3)	248 (53.2)
≥400,000	123 (35.3)	170 (36.5)
<b>Paternal type 1 diabetes, n (%)</b>	7 (1.8)	4 (0.8)
<b>Paternal celiac disease, n (%)</b>	19 (5.0)	0 (0.0)
<b>Paternal smoking in pregnancy, n (%)</b>	60 (16.3)	97 (19.6)
<b>Parental cohabitation, n (%)</b>	356 (97.5)	488 (98.4)

Data from Norwegian Mother and Child Cohort (MoBa), the Norwegian Patient Register and the Medical Birth Registry of Norway. <sup>A</sup> HLA, human leukocyte antigen; DQ2.5: *HLA-DQA1\*05:01-DQB1\*02:01*, DQ2: DQ2.5 or DQ2.2; DQ2.2: *HLA-DQA1\*02:01-DQB1\*02:02*; DQ8: *HLA-DQA1\*03-DQB1\*0302*. <sup>B</sup> Genetic risk score based on 44 non-HLA risk alleles linked to celiac disease. IQR, interquartile range; NOK, Norwegian krone, the national currency of Norway.

**Supplementary Table 5.** Complete-case analysis on the association of cord blood cotinine concentration and childhood celiac disease.

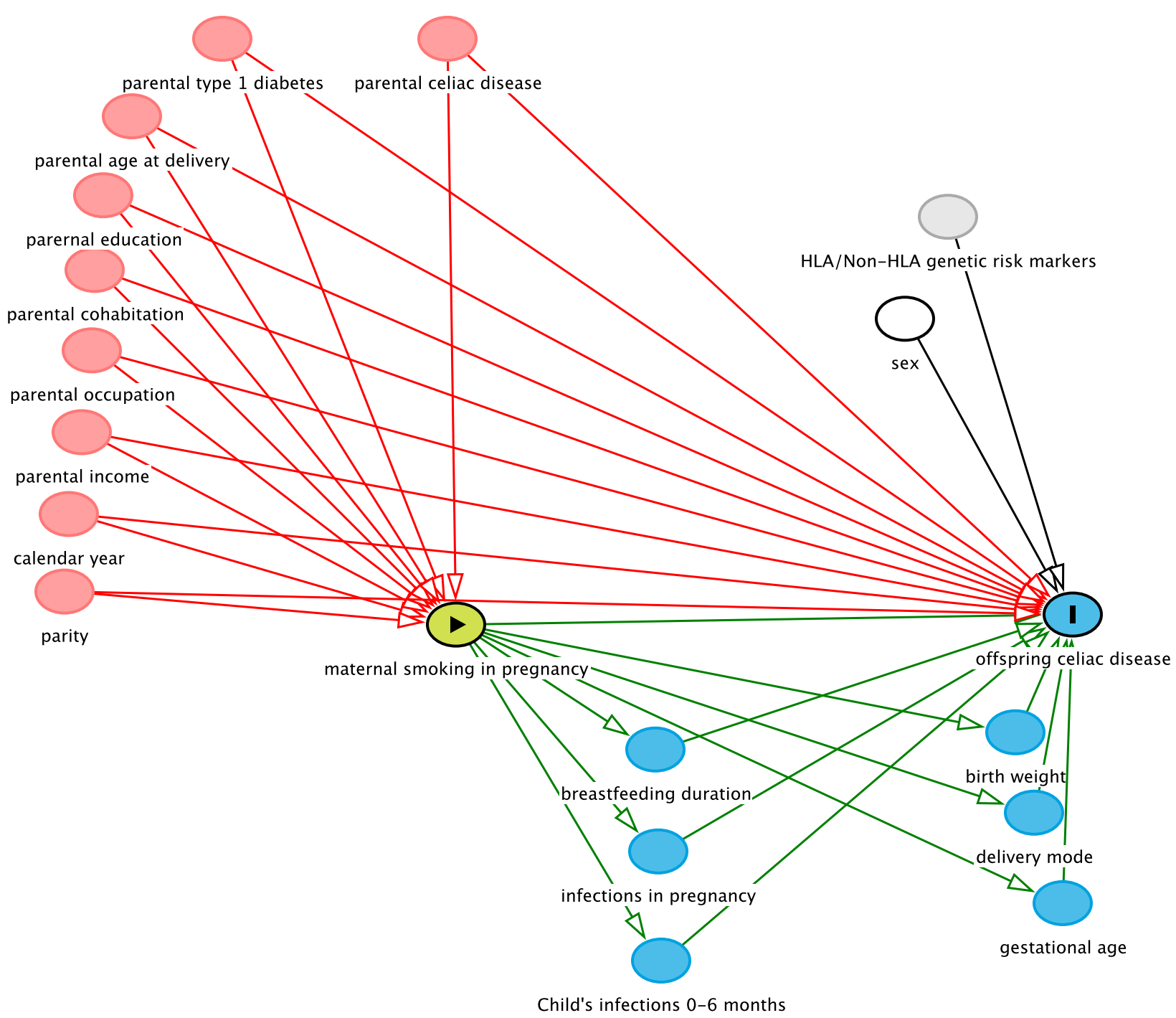
	Celiac disease n=381 (%)	Random controls n=529 (%)	Model I		Model II		Model III	
			aOR	95% CI	aOR	95% CI	aOR	95% CI
<b>Trichotomous cotinine groups</b> [“Maternal exposure level”]								
<i>Cotinine &lt;1.0 nmol/L</i> [“No smoke exposure”]	329 (86.4)	433 (81.9)		Ref.		Ref.		Ref.
<i>Cotinine 1.0-29.9 nmol/L</i> [“ETS/occasional smoking”]	32 (8.4)	49 (9.3)	0.84	0.53-1.33	0.89	0.55-1.42	1.01	0.58-1.73
<i>Cotinine ≥30.0 nmol/L</i> [“Daily smoking”]	20 (5.2)	47 (8.9)	0.54	0.31-0.95	0.57	0.33-1.04	0.64	0.31-1.31
<b>Per change in cotinine group</b> <sup>A</sup>			0.76	0.59-0.97	0.78	0.60-1.02	0.85	0.62-1.15
<i>Stratified by genetic risk</i> <sup>B</sup>								
Moderate-risk HLAs, n=549			0.79	0.57-1.08	0.80	0.57-1.13	0.73	0.47-1.14
High-risk HLAs, n=124			1.00	0.37-2.75	0.83	0.26-2.51	3.17	0.56-17.96

All analyses were adjusted for calendar year of birth and degree of hemolysis of cord blood samples (model I). Model II also included maternal education level, while Model III in addition to previous covariates also accounted for parental type 1 diabetes, celiac disease, income, occupation, cohabitation and paternal education level. The number of children varies between analyses because of missing data (model I: n=910; model II: n=856; model III: n=733). <sup>A</sup> Analysis of trend over categories of increasing cotinine concentrations. <sup>B</sup> Stratified analyses by the child’s human leukocyte antigen, HLA, genotype classified as conferring a moderate and high risk for celiac disease. Analyses adjusted for non-HLA genetic risk score. See Methods for details. The low-risk HLA group was excluded due to lack of events. 95% CI, 95% confidence interval; aOR, adjusted odds ratio; ETS, environmental tobacco smoke.

## SUPPLEMENTARY FIGURE LEGENDS

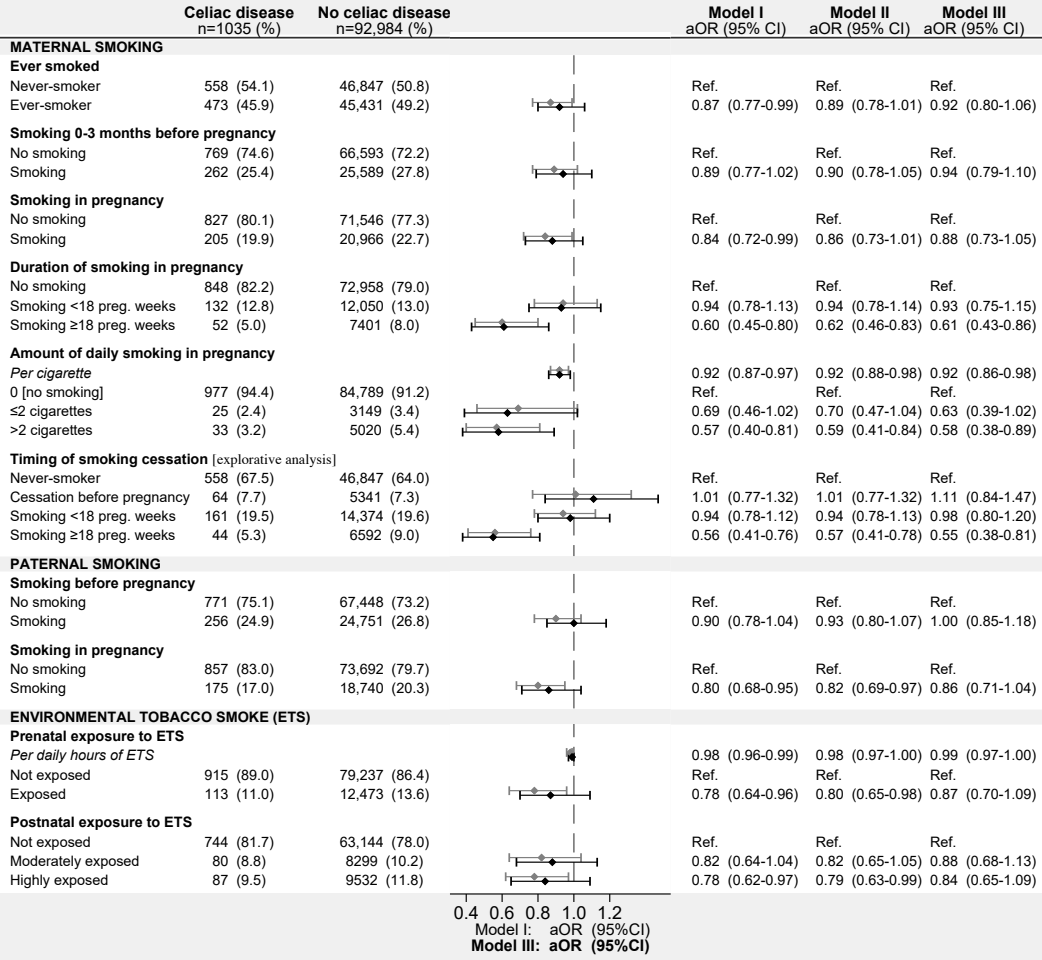
**Supplementary Figure 1.** Directed acyclic graph depicting the hypothesized relationships between maternal smoking in pregnancy and offspring celiac disease.

Confounding variables are coloured in red and mediating variables in blue. Biasing paths and causal paths are coloured in red and green, respectively. Child's sex is shown in white indicating predictor for celiac disease that was included as an adjustment variable despite not being associated with maternal smoking. CD-associated HLA and non-HLA genetic risk markers are shown in grey indicating unmeasured predictor for celiac disease as they were only measured in the nested case-control study. To ease the interpretation of the diagram, arrows between predictors and mediators (e.g. the arrow between sex and birth weight) and arrows between confounders and mediators (e.g. arrow between parental celiac disease and birthweight) have been omitted because these do not have any consequence for the selection of adjustment variables. All analyses were adjusted for calendar year of birth (model I) and further adjusted for maternal education level (model II). In MoBa and our nested case-control sample we were also able to adjust for parental type 1 diabetes, CD, income, occupation, cohabitation and paternal education level (model III). A sensitivity analysis considered the effect of additional adjustment for parental age at delivery, maternal infections in pregnancy, the child's infection frequency by age six months, sex, breastfeeding duration, parity, delivery mode, gestational age and birth weight. In our nested case-control study we were also able to adjust for HLA and non-HLA genetic risk markers for CD.



**Supplementary Figure 2.** Complete-case analyses of the association of parental smoking with childhood celiac disease in the MoBa cohort.

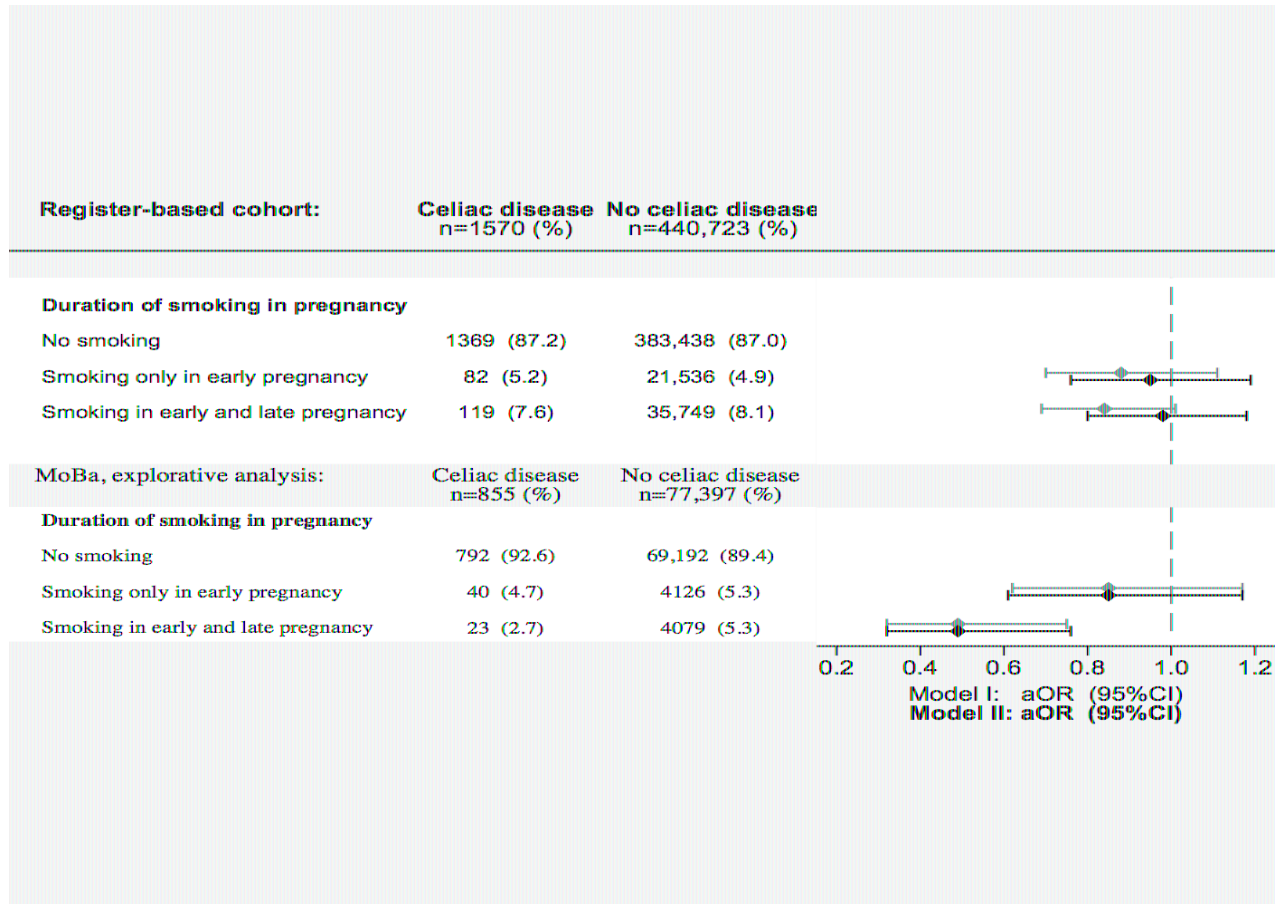
All analyses were adjusted for calendar year of birth (model I). Model II also included maternal education level, while Model III in addition to previous covariates also accounted for parental type 1 diabetes, celiac disease, income, occupation, cohabitation and paternal education level. The number of children varies between analyses because of missing data. 95% CI, 95% confidence interval; aOR, adjusted odds ratio.





**Supplementary Figure 3.** Complete-case analysis on the association of maternal smoking in pregnancy recorded in the Medical Birth Registry of Norway and celiac disease diagnosis in offspring.

Smoking recorded around 10 and 36 weeks of pregnancy. The primary analysis was based on a register-based cohort of Norwegian children born in 2004-2012. The explorative analysis examines the association among participants of the Norwegian Mother and Child (MoBa) cohort. Model I included calendar year of birth while model II was further adjusted for maternal education level, 95% CI, 95% confidence interval; aOR, adjusted odds ratio.



**Supplementary Figure 4.** *Sensitivity analysis on the effect of additional adjustments of parental and child characteristics recorded in the MoBa cohort.*

Model III includes calendar year of birth, parental education level, type 1 diabetes, CD, income, occupation and cohabitation. 95% CI, 95% confidence interval; aOR, adjusted odds ratio.

## Model III + additional covariate

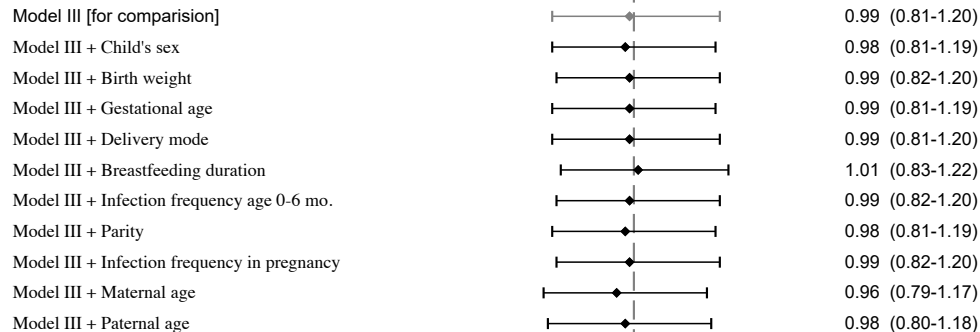
aOR (95% CI)

### Duration of smoking in pregnancy

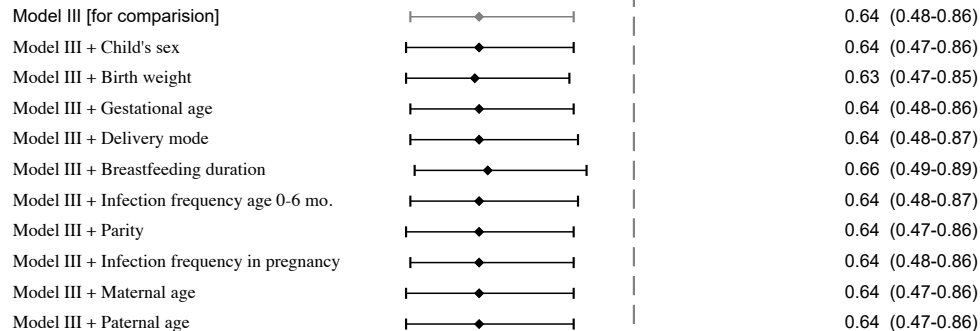
*No smoking*

Reference category

*Smoking <18 preg. weeks*



*Smoking ≥18 preg. weeks*



0.4 0.6 0.8 1.0 1.2

Model III [comparison]: aOR (95%CI)

Model III + covariate: aOR (95%CI)

## SUPPLEMENTARY METHODS

### *Recording of maternal smoking in the Medical Birth Registry of Norway*

The Medical Birth Registry of Norway (MBRN) is held by the Norwegian Institute of Health.<sup>1</sup> The registry contains information on essentially all births in Norway since 1967. Information on maternal smoking in pregnancy is available since 1999. Women may choose not to register smoking status in MBRN; in 16% of children born in 2004-2012 the mother declined to register smoking.

At the antenatal care clinics, the mother's current smoking status (or her declination for it to be registered) is documented in a medical record form ("Helsekort for gravide");<sup>2</sup> data are recorded at the time of the first antenatal visit (around 10 weeks of pregnancy, range 8-12 weeks) and at the last antenatal visit at 36 weeks of pregnancy. On both occasions, the mother's current smoking status is indicated by check boxes: "non smoker", "occasional smoker, not daily" or "daily smoker", and, if smoking daily, the number of cigarettes smoked per day.<sup>3</sup>

At the delivery units, maternal smoking status as recorded in the medical record form is transferred to a summarizing form sent to the MBRN, originally as paper forms that were computerized at the Norwegian Institute of Health. Since 2005, paper forms have been gradually replaced by an electronic transmission of information to the MBRN (by 2014, summarized paper forms were completely abandoned).<sup>3</sup> Minor differences exist between the recordings of maternal smoking in the paper-based and computer-based MBRN record systems;<sup>3</sup> while the original paper form recorded maternal smoking in "early" and "late" pregnancy, the electronic version requests maternal smoking in "first" and "last" trimester. Critically, however, both procedures defines "early"/"first trimester" as the mother's current smoking status as recorded at the time of the first antenatal visit (around 10 weeks of pregnancy) and "late"/"last trimester" as her current smoking status at the last antenatal visit at 36 weeks of pregnancy.

Since 1999, MBRN also provides information on maternal smoking before pregnancy (non-smoker, occasional and daily smoker). However, data on smoking during the pre-conception period suffer from a high degree of missingness (missing for 85% of children born in 2004-2012); for that reason, the current study did not examine smoking before pregnancy.

### References

1. Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand* 2000; 79:435-9.
2. Helsekort for gravide. 2018. Available from <https://helsedirektoratet.no/retningslinjer/helsekort-for-gravide-kontinuasjonsark-veileder-og-plastlomme>.
3. DATAKVALITET PÅ RØYKEDATA I MEDISINSK FØDSELSREGISTER. 2015. [Cited Folkehelseinstituttet, Avdeling for helseregistre.] Available from <https://www.fhi.no/globalassets/dokumenterfiler/helseregistre/mfr/2016---mfr-roykedata-.pdf>.

### *Details on genotyping of cord blood*

In our nested case-control analysis of cord blood cotinine we accounted for the child's human leukocyte antigen (HLA) genotype classified as conferring a high risk for celiac disease (CD) (homozygous for *DQA1\*05:01-DQB1\*02:01* [DQ2.5] or *DQ2.5/DQA1\*02:01-DQB1\*02:02* [DQ2.2]), moderate risk (*DQ2.5/X* or at least one of *DQ2.2* or *DQA1\*03-DQB1\*03:02* [DQ8]) and a low risk (any other genotype).<sup>1</sup> As previously described,<sup>2</sup> we computed a non-HLA genetic risk score for CD defined as the child's sum of 44 risk alleles that previously have been linked to CD at genome

wide significance.<sup>1,3</sup> Using DNA extracted from cord blood, genotyping was performed at the Core Facility for Genotyping at Oslo University Hospital (Oslo, Norway) on a Custom GoldenGate assay (Illumina, San Diego, CA). Genotypes for HLA were inferred from 66 tag single nucleotide polymorphisms using HLA:IMP\*02 software<sup>4</sup> and thereafter confirmed through allele-specific amplification (Gillespie's Diabetes and Metabolism lab at School of Clinical Sciences, Bristol University, UK).

## References

1. Trynka G, Hunt KA, Bockett NA, et al. Dense genotyping identifies and localizes multiple common and rare variant association signals in celiac disease. *Nat Genet.* Dec 2011;43(12):1193-1201.
2. Márild K, Vistnes M, Tapia G, et al. Midpregnancy and cord blood immunologic biomarkers, HLA genotype, and pediatric celiac disease. *J Allergy Clin Immunol.* May 2017;139(5):1696-1698.
3. Romanos J, Rosen A, Kumar V, et al. Improving coeliac disease risk prediction by testing non-HLA variants additional to HLA variants. *Gut.* Mar 2014;63(3):415-422.
4. Diltney A, Leslie S, Moutsianas L, et al. Multi-population classical HLA type imputation. *PLoS Comput Biol.* 2013;9(2):e1002877.

## Excerpts from MoBa-questionnaires used to assess parental smoking

The complete questionnaires are available at [www.fhi.no/moba](http://www.fhi.no/moba).

### Questionnaire administered at pregnancy week 18 (questions 87-96, 100, 104)

12

Living habits

87. Did your mother smoke when she was pregnant with you?  
 No  Yes  AA1348  
 Don't Know

88. Are you exposed to passive smoking at home?  
 No  Yes  AA1349

89. If yes, how many hours a day are you exposed to passive smoking?  
  hours per day AA1350  
 104: responses in questionnaire1b.doc and the Excel file don't match

90. Are you exposed to passive smoking at work?  
 No  Yes  AA1351

91. If yes, how many hours a day are you exposed to passive smoking?  
  hours per day AA1352

92. Did the baby's father smoke before you became pregnant?  
 No  Yes  AA1353

93. Does he smoke now?  
 No  AA1354  
 Yes

94. Have you ever smoked?  
 No (proceed to question 104)  AA1355  
 Yes

95. Do you smoke now (after you became pregnant)?  
 No  AA1356  
 Sometimes  AA1357 cigarettes per week  
 Daily  AA1358 cigarettes per day

96. Did you smoke during the last 3 months before you became pregnant this time?  
 No  AA1359  
 Sometimes  AA1360 cigarettes per week  
 Daily  AA1361 cigarettes per day

97. How old were you when you started to smoke on a daily basis?  
 AA1362 Years

98. Have you stopped smoking completely?  
 No  Yes  AA1363

99. If yes, how old were you when you stopped smoking?  
 AA1364 Years

100. If you stopped smoking after you became pregnant, in which week of pregnancy did you stop?  
 AA1365 week of pregnancy

101. How long after you get up in the morning until you light your first cigarette?  
 AA1366  
 5 minutes  
 6-29 minutes  
 30-60 minutes  
 More than one hour

102. Do you smoke when you are ill?  
 No  Yes  AA1367

103. Do you smoke more often during the first few hours after you wake up than you do during the rest of the day?  
 No  Yes  AA1368

104. If you have used other kinds of nicotine indicate which and when you used them.

	Before pregnancy	During pregnancy
Chewing tobacco/snuff	<input type="checkbox"/> AA1369	<input type="checkbox"/> AA1370
Nicotine chewing gum	<input type="checkbox"/> AA1371	<input type="checkbox"/> AA1372
Nicotine adhesive patch	<input type="checkbox"/> AA1373	<input type="checkbox"/> AA1374
Nicotine inhaler	<input type="checkbox"/> AA1375	<input type="checkbox"/> AA1376

105. What was your fluid consumption (number of cups/glasses) per day before and during pregnancy? (1 mug = 2 cups, 1 small plastic bottle (0.5 litre) = 4 cups, 1 large plastic bottle (1.5 litres) = 12 cups)

	Number of cups/glasses		Decaffeinated (Enter a cross)
	Before pregnancy	Now	
1 Filter coffee	<input type="text"/> AA1377	<input type="text"/> AA1378	<input type="text"/> AA1379
2 Instant coffee	<input type="text"/> AA1380	<input type="text"/> AA1381	<input type="text"/> AA1382
3 Boiled coffee	<input type="text"/> AA1383	<input type="text"/> AA1384	<input type="text"/> AA1385
4 Tea	<input type="text"/> AA1386	<input type="text"/> AA1387	<input type="text"/> AA1388
5 Herbal tea	<input type="text"/> AA1389	<input type="text"/> AA1390	<input type="text"/> AA1391
6 Coca Cola/Pepsi etc.	<input type="text"/> AA1392	<input type="text"/> AA1393	<input type="text"/> AA1394
7 Other fizzy drinks	<input type="text"/> AA1395	<input type="text"/> AA1396	<input type="text"/> AA1397
8 Diet Coca Cola/Pepsi	<input type="text"/> AA1398	<input type="text"/> AA1399	<input type="text"/> AA1400
9 Other diet fizzy drinks	<input type="text"/> AA1401	<input type="text"/> AA1402	<input type="text"/> AA1403
10 Tap water	<input type="text"/> AA1404	<input type="text"/> AA1405	
11 Bottled water	<input type="text"/> AA1406	<input type="text"/> AA1407	
	Before pregnancy	Now	Ecological (Enter a cross)
12 Juice/squash	<input type="text"/> AA1408	<input type="text"/> AA1409	<input type="text"/> AA1410
13 Diet juice/squash	<input type="text"/> AA1411	<input type="text"/> AA1412	<input type="text"/> AA1413
14 Milk (skim, low fat, whole)	<input type="text"/> AA1414	<input type="text"/> AA1415	<input type="text"/> AA1416
15 Yogurt, all types	<input type="text"/> AA1417	<input type="text"/> AA1418	<input type="text"/> AA1419
16 Yogurt/active Lactobacillus	<input type="text"/> AA1420	<input type="text"/> AA1421	<input type="text"/> AA1422
17 Other type of cultured milk - Kefir	<input type="text"/> AA1423	<input type="text"/> AA1424	<input type="text"/> AA1425
18 Other	<input type="text"/> AA1426	<input type="text"/> AA1427	<input type="text"/> AA1428

Questionnaire administered at around pregnancy week 30 (questions 98-102)

11

**91. If yes, which animals have you come into contact with and how often?**

	Daily	3-6 times a week	1-2 times a week	Less often
Dog .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cat .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Guinea pig/hamster/rabbit/rat, etc. ....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Canary or other caged birds .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hens and other poultry .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cow/sheep/goat .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Horse .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Pig .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**92. How many hours a day do you usually sleep now when you are pregnant?**

Over 10 hours

8-9 hours

6-7 hours

4-5 hours

Less than 4 hours

**93. Do you currently sleep on a waterbed or use an electric blanket?**

	Yes	No
Waterbed .....	<input type="checkbox"/>	<input type="checkbox"/>
Electric blanket .....	<input type="checkbox"/>	<input type="checkbox"/>

**94. Can you rest during the day (both at home and at work)?**

No

Yes

**95. Have you been in a sauna while you have been pregnant?**

No

1-5 times

6-10 times

More than 10 times

**96. Have you been in a solarium while you have been pregnant?**

No

1-5 times

6-10 times

More than 10 times

**97. Are you exposed to passive smoking either at home or at work? If yes, how many hours a day?**

	No	Yes	No. of hrs
Home .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Work .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**98. Do you smoke at present? If yes, how many cigarettes?**

No

Sometimes  Cigarettes per week

Daily  Cigarettes per day

**99. Does the baby's father smoke at present? If yes, how many cigarettes?**

No

Sometimes  Cigarettes per week

Daily  Cigarettes per day

**100. If one or both of you have stopped smoking during the pregnancy, in which week of pregnancy did you stop?**

You   Week of pregnancy

Baby's father   Week of pregnancy

**101. If you or the baby's father have smoked during the pregnancy, were there periods during which you or the baby's father did not smoke? (Fill in the weeks during pregnancy when you did not smoke.)**

	Weeks of pregnancy without smoking							
	0-4	5-8	9-12	13-16	17-20	21-24	25-28	29+
You	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Baby's father	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**102. Have you used other forms of nicotine after the 13th week of pregnancy?**

	No	Yes
Nicotine chewing gum .....	<input type="checkbox"/>	<input type="checkbox"/>
Nicotine patches .....	<input type="checkbox"/>	<input type="checkbox"/>
Nicotine inhaler .....	<input type="checkbox"/>	<input type="checkbox"/>
Chewing tobacco/snuff .....	<input type="checkbox"/>	<input type="checkbox"/>

**103. Have you used any of the following substances after the 13th week of pregnancy?**

	No	Yes
Hash .....	<input type="checkbox"/>	<input type="checkbox"/>
Amphetamine .....	<input type="checkbox"/>	<input type="checkbox"/>
Ecstasy .....	<input type="checkbox"/>	<input type="checkbox"/>
Cocaine .....	<input type="checkbox"/>	<input type="checkbox"/>
Heroin .....	<input type="checkbox"/>	<input type="checkbox"/>

**104. Have you ever used any of the following substances? (Fill in for each item.)**

	No	Previously	Last 6 months before pregnancy	During this pregnancy
Anabolic steroids .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Testosterone products .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Growth hormones (e.g. genotropin/somatropin) .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Questionnaire administered at child's age 6 months (question 81)**

13

**79. How often are you physically active at present? (Enter a cross in a box for each item.)**

	Never	1-3 times amonth	Once a week	Twice a week	Three times or more a week
1 Didn't smoke	<input type="checkbox"/> DD716				
2 Brisk walking	<input type="checkbox"/> DD717				
3 Running/jogging/orienteering	<input type="checkbox"/> DD718				
4 Cycling	<input type="checkbox"/> DD719				
5 Training studio/weight training	<input type="checkbox"/> DD720				
6 Special gymnastics/aerobics for pregnant women	<input type="checkbox"/> DD721				
7 Aerobics/gymnastics/dancing without running and jumping	<input type="checkbox"/> DD722				
8 Aerobics/gymnastics/dancing with running and jumping	<input type="checkbox"/> DD723				
9 Dancing (swing, rock, folk)	<input type="checkbox"/> DD724				
10 Skiing	<input type="checkbox"/> DD725				
11 Ball sport	<input type="checkbox"/> DD726				
12 Swimming	<input type="checkbox"/> DD727				
13 Riding	<input type="checkbox"/> DD728				
14 Other	<input type="checkbox"/> DD729				

**80. Currently how often are you physically active (during your spare time or at work) that you get out of breath or sweat?**

	Spare time	At work
Never	<input type="checkbox"/> DD730	<input type="checkbox"/> DD731
Less than once a week	<input type="checkbox"/>	<input type="checkbox"/>
Once a week	<input type="checkbox"/>	<input type="checkbox"/>
Twice a week	<input type="checkbox"/>	<input type="checkbox"/>
3-4 times a week	<input type="checkbox"/>	<input type="checkbox"/>
5 times or more a week	<input type="checkbox"/>	<input type="checkbox"/>

**81. What were your and your partner/husband's smoking habits during the last 3 months of your pregnancy and in the period after the birth? (Enter a cross in a box for each period.)**

	Yourself			Your partner/husband		
	Last 3 mths during pregnancy	0-3 mths after birth	4-6 mths after birth	Last 3 mths during pregnancy	0-3 mths after birth	4-6 mths after birth
Didn't smoke	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Smoked sometimes	<input type="checkbox"/> DD732	<input type="checkbox"/> DD733	<input type="checkbox"/> DD734	<input type="checkbox"/> DD735	<input type="checkbox"/> DD736	<input type="checkbox"/> DD737
Smoked every day	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If every day, number of cigarettes per day	<input type="checkbox"/> DD738	<input type="checkbox"/> DD739	<input type="checkbox"/> DD740	<input type="checkbox"/> DD741	<input type="checkbox"/> DD742	<input type="checkbox"/> DD743
If sometimes, number of cigarettes per week	<input type="checkbox"/> DD1114	<input type="checkbox"/> DD1115	<input type="checkbox"/> DD1116	<input type="checkbox"/> DD1117	<input type="checkbox"/> DD1118	<input type="checkbox"/> DD1119

**82. Is your child ever present in a room where someone smokes?**

No  DD744

Yes, sometimes

Yes, several times a week

Yes, every day

If every day, number of hours  DD745

**83. Did you take any of the following substances during the last 3 months of your pregnancy and after the birth? (Enter a cross in a box for each item.)**

	No	Yes, last 3 month of pregnancy	Yes after birth
Hanish	<input type="checkbox"/> DD746	<input type="checkbox"/> DD747	<input type="checkbox"/> DD748
Amphetamines	<input type="checkbox"/> DD749	<input type="checkbox"/> DD750	<input type="checkbox"/> DD751
Ecstasy	<input type="checkbox"/> DD752	<input type="checkbox"/> DD753	<input type="checkbox"/> DD754
Cocaine	<input type="checkbox"/> DD755	<input type="checkbox"/> DD756	<input type="checkbox"/> DD757
Heroin	<input type="checkbox"/> DD758	<input type="checkbox"/> DD759	<input type="checkbox"/> DD760
Other, specify:	<input type="checkbox"/> DD761	<input type="checkbox"/> DD762	<input type="checkbox"/> DD763
	<input type="checkbox"/> DD905	<input type="checkbox"/> DD764	