Association between Obesity predisposing Genes, Energy intake and Adiposity in Early Life: preliminary results from CHILD and START cohorts

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Plan

- Introduction
  - Childhood overweight and obesity
  - Anthropometric measures in children
  - Adiposity development is influenced by many factors
  - Genes related to adiposity traits in adults
  - GWAS Meta-analysis of BMI accross early life
- Hypothesis and tasks
- Methods
  - Population : CHILD & START
  - Z-scores calculation
  - GRS calculation
  - Statistical analyses
- Results
  - At birth for CHILD and START
  - During the follow-up for CHILD and START
- Discussion
- Next steps
- Conclusion

INTRODUCTION

Childhood overweight and obesity

- Worldwide public health challenge

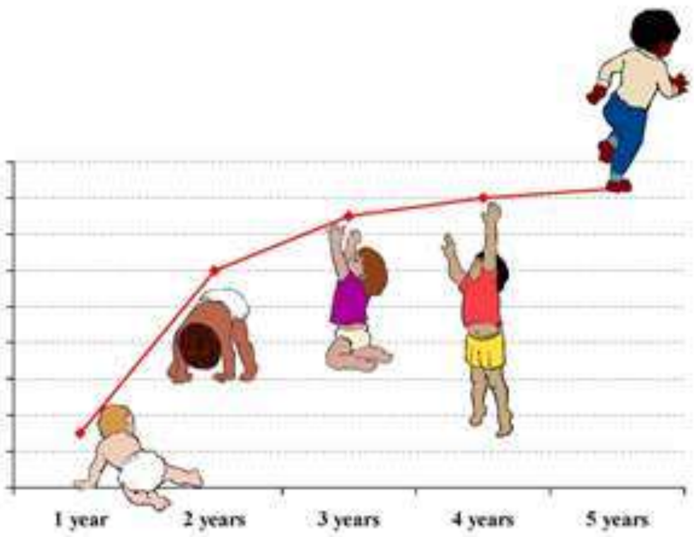
- Affecting Westernized countries as well as low- and middle-income countries, particularly in urban area

- Prevalence is increasing at alarming rate
  - In 2013, the number of overweight and obese children under 5 y-old, was estimated at 42 million by the WHO
    - 31 million of these children living in developing countries

- Up to 60% of overweight and obese children are likely to stay obese into adulthood and also more likely to develop metabolic and cardiovascular diseases at a younger age.

Anthropometric measures in children

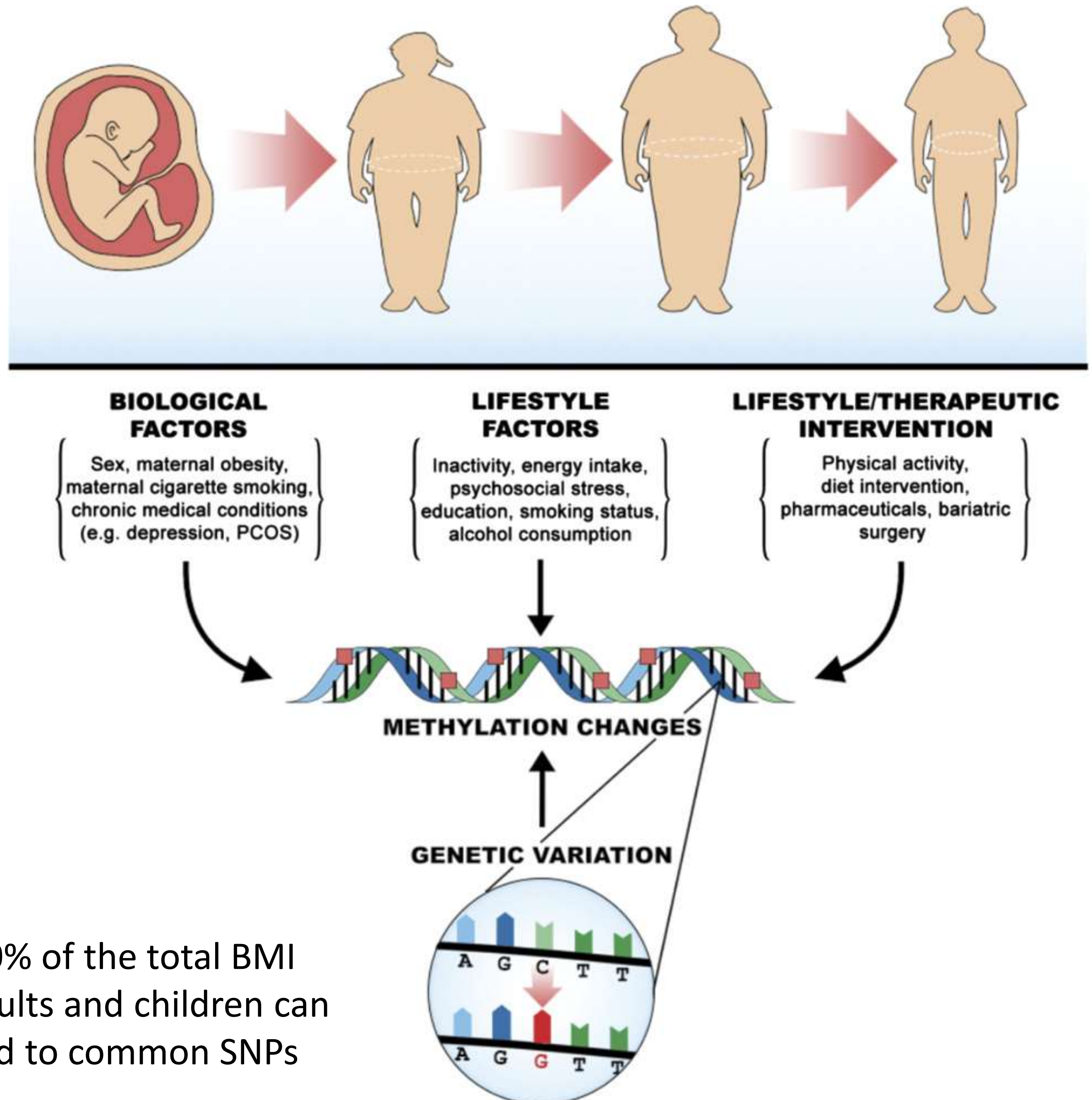
- Concerns in measuring adiposity in children because of their growth
- Depending on the age, different methods to measure body's healthy weight are available (IOTF, WHO, CDC)



- **For children aged 0-5 years :** the WHO Child Growth Standards are the most recommended (release on April 2006)
  - Based on a multiethnic sample
  - Growth standards (Z-scores) for infants and young children up to 5 y-old, for weight, length, weight-for-length/height, body mass index, skinfolds (triceps and subscapular)

Source : WHO - website

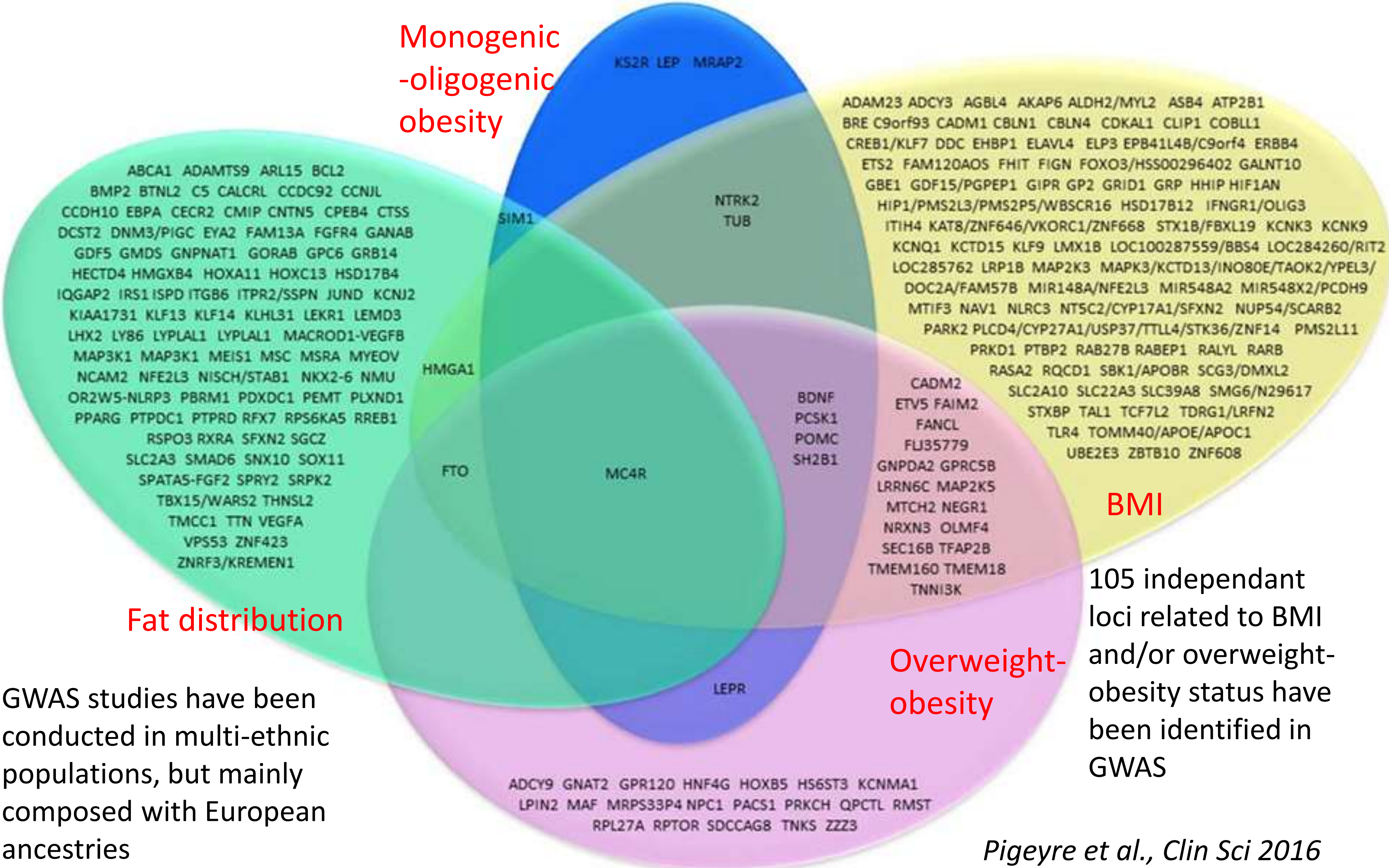
Adiposity development is influenced by many factors



Up to 27–30% of the total BMI variance in adults and children can be attributed to common SNPs

Reddon et al., Clin Sci, 2016

Genes related to adiposity traits in adults



105 independant loci related to BMI and/or overweight-obesity status have been identified in GWAS

GWAS studies have been conducted in multi-ethnic populations, but mainly composed with European ancestries

Pigeyre et al., Clin Sci 2016

A genome-wide association study of body mass index across early life and childhood

- GWAS meta-analysis of BMI trajectories from 1 to 17 years of age in 9377 children (77 967 measurements) from the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Western Australian Pregnancy Cohort (Raine) Study
- Genome-wide significant loci were examined in a further 3918 individuals (48 530 measurements) from Northern Finland
- Identification of a novel SNP, downstream from the *FAM120AOS* gene on chr9
- Replication of several known adult BMI-associated loci (*FTO* , *MC4R* and *ADCY3*) and one childhood obesity locus (*OLFM4*)

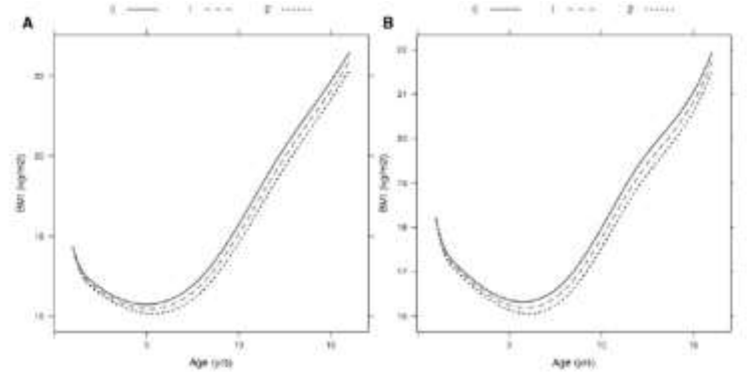


Figure 1. Population average trajectories for females (A) and males (B) from the ALSPAC cohort with 0, 1 or 2 copies of the C allele at the *FAM120AOS*, rs944990, locus.

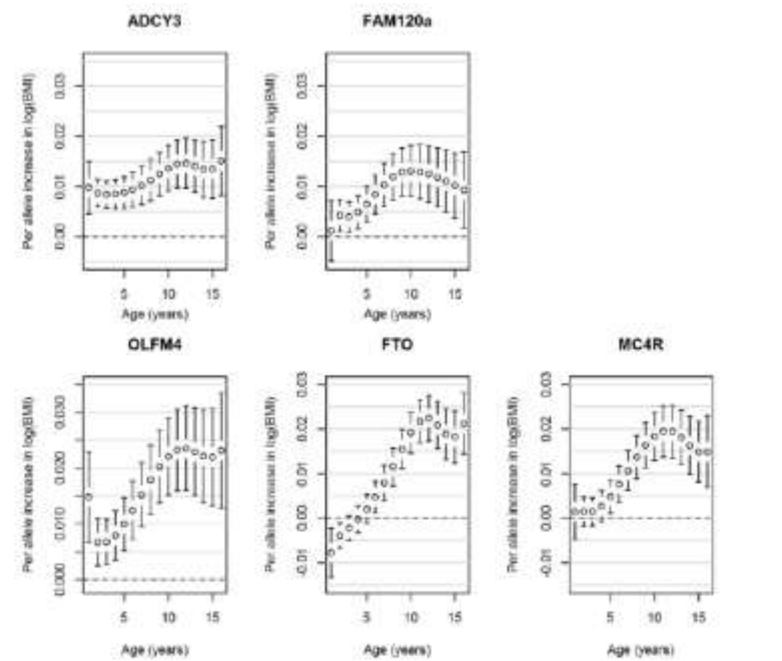


Figure 2. Associations from the ALSPAC cohort between the genome-wide significant SNPs and BMI from age one to 16 years. Error bars represent the regression coefficient of BMI on the natural log scale and 95% confidence intervals derived from the longitudinal additive genetic models. The SNPs are aligned to the minor allele.

Warrington et al, IEA, 2015

Hypothesis

- Many SNPs identified in adults and replicated in children, are involved in the central nervous system's control of appetite, suggesting that these SNPs predispose individuals for obesity by modulating energy intake.

- Causality between energy intake and obesity cannot be established from cross-sectional studies.
- This relationship can also be explained by the fact that obese individuals require more energy intake to support their higher BMI.

- **Objective:** To investigate the temporal association of identified obesity-predisposing genetic variants (included in a genetic risk score) with adiposity phenotypes and "energy intake" in children through longitudinal study.

Tasks

1/ **To assess the association between obesity genetic risk score (GRS) and the evolution of adiposity in children from birth to five years-old**

2/ To assess the association between obesity-GRS and the evolution of energy intake of children from birth to five years-old

3/ To investigate the more likely causal model linking predisposing SNPs, diet and BMI (mediation, independence, moderation)

METHODS

AUDIT, RESEARCH AND GUIDELINE UPDATE

The Canadian Healthy Infant Longitudinal Development (CHILD) Study: examining developmental origins of allergy and asthma

- Aims : 3542 infants, recruited between 2008-2012, in four communities across Canada, and followed for 5 years
  - To examine the developmental origins of allergy and asthma
- Repeated clinical assessments and environmental, psychological, nutrition and health questionnaires
- Follow-up and genotyping still in progress
- Preliminary analyses performed on a sample of 462 infants with a genotype, and followed for 20% of them, until 5 years

Subbarao P et al, Thorax 2015

STUDY PROTOCOL Open Access

Rationale and design of South Asian Birth Cohort (START): a Canada-India collaborative study

BMC Public Health

- Aims : 750 South Asian mother-infant pairs, recruited equally in rural India, urban India and Canada and followed for 3 years
  - To understand the early development of adiposity among South Asians
  - Detailed information on health behaviors including diet and physical activity, and blood samples for metabolic parameters and DNA are collected from pregnant women
  - Cord blood and newborn anthropometric indices at delivery
- Mother and offspring followed prospectively annually for 3 years

– growth trajectory, adiposity and health behavior records

– Recruitment, follow-up and genotyping still in progress

- **Preliminary analysis performed on a sample of 454 infants, with a genotype and followed for 50 % of them, up to 2 y-old**

Anand et al, BMC Public Health 2013

Method for Z-scores calculation

- Use of a specific R package, including the referent growth curves from WHO (updated in 2006)

- Z-score = standard deviation from the mean, according to the gender and the age

- Calculation of the indicators of the WHO growth standards
  - length/height-for-age,
  - weight-for-age,
  - weight-for-length or weight-for-height,
  - body mass index-for-age,
  - triceps skinfold-for-age
  - subscapular skinfold-for-age

Source : WHO website

Genetic risk score calculation

- Whole-genome SNP genotyping of samples by the HumanCoreExome (Nov 2015)

- Up to date list of SNPs that reach genome-wide significance (P<5x10-8) with BMI or obesity status in children and adults, using three different strategies (last update on May 25, 2016)
  - the National Human Genome Research Institute (NHGRI) GWAS Catalog www.genome.gov/gwastudies/
  - the HuGE Navigator GWAS Integrator www.hugenavigator.net/HuGENavigator/gWAHitStartPage.do
  - the PubMed database www.ncbi.nlm.nih.gov/pubmed

- SNP information (risk alleles) is extracted from published data
- Each SNP genotype is coded as 0, 1, or 2 according to the number of risk alleles.
- Unweighted GRS is calculated by summing the increasing risk alleles of the SNPs
- “Imputation” for missing genotypic by using the mean of number of increasing risk alleles

															GIANT Consortium			
					CHILD (n=462)					START (n=454)					All_ancestries		European_ancestries	
Gene	Chr	Snps	Effect_allele	Other_allele	HZ_OA	HT	HZ_EA	Total	Missing	HZ_OA	HT	HZ_EA	Total	Missing	beta	p_value	beta	p_value
ADCY3/POMC	2	rs11676272	G	A	53	100	57	210	244	46	56	33	135	327	0.0328	4.68E-24	0.0322	1.12E-21
ADCY3/POMC	2	rs6545814	A	G	97	229	127	453	1	87	223	147	457	5	-0.0302	4.91E-17	-0.0303	2.63E-16
ADCY9	16	rs879620	C	T	35	109	65	209	245	29	64	38	131	331	-0.0244	3.94E-10	-0.0244	1.06E-09
AGBL4	1	rs657452	A	G	103	222	129	454	0	146	217	98	461	1	0.0227	2.12E-13	0.0227	5.48E-13
BDNF	11	rs10835210	C	A	193	204	56	453	1	244	182	31	457	5	0.0024	0.4338	0.0021	0.5019
BDNF	11	rs2030323	C	A	24	178	252	454	0	23	159	279	461	1	0.0408	2.09E-29	0.0407	2.04E-27
BDNF	11	rs6265	C	T	12	129	312	453	1	22	145	292	459	3	0.0428	2.43E-29	0.0424	2.99E-27
CADM1	11	rs12286929	G	A	137	247	70	454	0	124	241	94	459	3	0.0211	5.44E-13	0.0217	1.31E-12
CBLN1	16	rs2080454	A	C	31	199	223	453	1	70	210	179	459	3	-0.0171	8.60E-09	-0.0168	6.55E-08
CDKAL1	6	rs9356744	C	T	237	179	38	454	0	205	210	45	460	2	-0.0087	0.006195	-0.0084	0.01139
CREB1/KLF7	2	rs17203016	G	A	325	119	9	453	1	322	127	10	459	3	0.0211	3.41E-08	0.021	8.15E-08
DDC	7	rs4947644	C	T	170	216	68	454	0	115	235	106	456	6	-0.0129	0.0003392	-0.0129	0.0004894
ELAVL4	1	rs11583200	C	T	105	221	126	452	2	130	217	112	459	3	0.0174	6.00E-09	0.0177	1.48E-08
ERBB4	2	rs7599312	G	A	21	155	267	443	11	26	167	265	458	4	0.0214	4.73E-11	0.022	1.17E-10
ETS2	21	rs2836754	C	T	213	205	34	452	2	127	188	139	454	8	0.0169	1.61E-08	0.0164	4.16E-07
FAIM2	12	rs7138803	G	A	71	217	166	454	0	62	220	175	457	5	-0.032	5.12E-26	-0.0315	8.15E-24
FAM120AOS	9	rs944990	C	T	10	124	320	454	0	32	176	251	459	3	0.0023	0.5748	0.0028	0.505
FANCL	2	rs1016287	T	C	265	155	32	452	2	233	184	41	458	4	0.0228	4.36E-12	0.0229	2.25E-11
FANCL	2	rs12617233	C	T	51	216	187	454	0	86	216	157	459	3	0.0183	7.58E-07	0.0188	7.52E-07
FANCL	2	rs4671328	T	G	81	106	22	209	245	40	65	25	130	332	0.0214	2.77E-09	0.0215	6.22E-09
FTO	16	rs12149832	A	G	103	218	51	372	82	149	213	63	425	37	0.0737	1.43E-133	0.0746	3.51E-127
FTO	16	rs9936385	C	T	212	201	41	454	0	185	213	60	458	4	0.0763	4.37E-145	0.0795	2.73E-144
FTO	16	rs9940128	A	G	145	239	70	454	0	159	224	73	456	6	0.076	6.54E-144	0.0792	3.45E-143
GDF15/PGPEP1	19	rs17724992	A	G	100	219	134	453	1	51	187	222	460	2	0.0196	7.79E-09	0.0194	3.42E-08
GIPR/QPCTL	19	rs11671664	G	A	182	218	54	454	0	268	167	23	458	4	0.025	4.45E-07	0.0277	1.45E-07
GIPR/QPCTL	19	rs2287019	C	T	11	108	335	454	0	13	135	309	457	5	0.0354	1.68E-18	0.036	4.59E-18
GNPDA2	4	rs13130484	C	T	66	214	174	454	0	90	187	182	459	3	-0.0398	8.01E-41	-0.0401	4.24E-38
GPRC5B	16	rs12597579	T	C	389	61	3	453	1	385	72	1	458	4	-0.039	1.07E-18	-0.0396	1.34E-17
HIP1/PMS2L3/PMS2P5/WBSCR16	7	rs1167827	A	G	155	217	81	453	1	135	215	106	456	6	-0.02	1.98E-10	-0.0202	6.33E-10
HNF4G	8	rs4735692	A	G	151	209	93	453	1	97	221	142	460	2	0.0242	6.13E-11	0.0238	3.77E-10
HOXB5	17	rs9299	T	C	69	200	184	453	1	67	235	156	458	4	0.014	0.000331	0.0142	0.0003852
HSD17B12	11	rs2176598	T	C	295	142	17	454	0	252	184	25	461	1	0.0185	3.47E-08	0.0198	2.97E-08
KCNK3	2	rs11126666	G	A	102	215	136	453	1	180	199	79	458	4	-0.0201	1.32E-09	-0.0207	1.33E-09
KCNK9	8	rs2471083	T	C	197	208	48	453	1	215	204	40	459	3	-6.00E-04	0.8837	-0.0011	0.7934
KCTD15	19	rs11084753	A	G	158	203	84	445	9	177	205	67	449	13	-0.0151	2.51E-06	-0.0165	7.41E-07
KLF9	9	rs11142387	C	A	62	196	195	453	1	101	225	132	458	4	0.0076	0.03997	0.0078	0.04011
LOC284260/RIT2	18	rs7239883	G	A	240	174	39	453	1	174	221	65	460	2	0.0152	3.14E-07	0.0164	1.63E-07
MAP2K5	15	rs2241423	A	G	193	204	57	454	0	216	194	50	460	2	-0.0304	2.25E-18	-0.031	2.37E-17
MAP2K5	15	rs4776970	T	A	135	220	98	453	1	126	237	99	462	0	-0.0248	3.23E-16	-0.0244	8.87E-15
MAP2K5	15	rs997295	T	G	112	232	107	451	3	115	227	114	456	6	0.021	3.66E-12	0.0209	5.76E-11
MAPK3/KCTD13/INO80E/TAOK2/Y	16	rs4787491	A	G	131	225	98	454	0	113	240	106	459	3	-0.0151	2.34E-06	-0.0159	2.24E-06
MC4R	18	rs12970134	A	G	188	211	55	454	0	256	175	27	458	4	0.0504	3.77E-51	0.0498	4.69E-47
MC4R	18	rs17782313	C	T	182	218	54	454	0	268	167	23	458	4	0.057	8.14E-55	0.0566	7.95E-48
MC4R	18	rs2331841	A	G	102	215	136	453	1	180	199	79	458	4	0.0286	1.42E-22	0.0274	2.99E-19
MC4R	18	rs7234864	C	T	56	204	193	453	1	31	182	244	457	5	-0.0442	3.08E-40	-0.0457	8.95E-40
NEGR1	1	rs2815752	G	A	160	231	63	454	0	199	214	46	459	3	-0.0312	9.32E-25	-0.0326	2.97E-25
OLFM4	13	rs12429545	G	A	16	120	317	453	1	11	116	329	456	6	-0.0324	3.15E-13	-0.0334	1.09E-12
OLFM4	13	rs9568856	G	A	20	152	282	454	0	12	138	310	460	2	-0.0277	1.18E-06	-0.0291	5.24E-07
PCSK1	5	rs261967	A	C	71	223	159	453	1	94	207	158	459	3	-0.0175	2.25E-06	-0.0175	4.12E-06
RALYL	8	rs2033732	C	T	21	183	250	454	0	26	172	259	457	5	0.0176	2.26E-07	0.0192	4.89E-08
RARB	3	rs6804842	A	G	123	203	127	453	1	161	208	89	458	4	-0.0183	8.02E-10	-0.0185	2.48E-09
SEC16B	1	rs543874	G	A	319	125	10	454	0	315	133	12	460	2	0.0497	2.29E-40	0.0482	2.62E-35
TDRG1/LRFN2	6	rs2033529	G	A	305	131	16	452	2	271	158	27	456	6	0.0183	1.45E-08	0.019	1.39E-08
TFAP2B	6	rs734597	A	G	270	157	26	453	1	302	138	18	458	4	0.0446	1.68E-30	0.0445	2.25E-27
TLR4	9	rs1928295	C	T	165	223	66	454	0	151	228	83	462	0	-0.0182	4.32E-10	-0.0188	7.91E-10
TMEM18	2	rs4854344	G	T	324	116	12	452	2	311	127	20	458	4	-0.0592	5.16E-53	-0.0591	5.13E-49
TNNI3K	1	rs1514175	A	G	109	214	130	453	1	141	221	98	460	2	0.0218	2.51E-13	0.023	1.46E-13

Statistical analyses

- <u>At birth : Association between obesity GRS (including 42 SNPs) and anthropometric variables :</u>

- birth weight, Z-score birth weight, Z-score weight for length (WfL), Z-score BMI

- Linear regression model

- Adjusted on covariates: gestational age (continuous), pre-gestational maternal BMI (continuous), maternal gestational diabetes (binary), smoking exposure (ordinary),
  - Gender : added in the model for the birth weight analysis
  - Ethnicity: added in the model for CHILD
  - Geographical center : not added at this step, as all genotyped infants are from Canada

Statistical analyses

- <u>During follow-up : Associations between obesity GRS and anthropometric phenotypes evolution during the follow-up :</u>

- BMI, Z-score weight for length (WfL), Z-score BMI

- Linear mixed-effect regression model with repeated measures

- Random effects : age at measurement
- Fixed effects: visit, breastfeeding, maternal educational level
  - Ethnicity: added in the model for CHILD
  - Gender : added in the model for BMI analysis

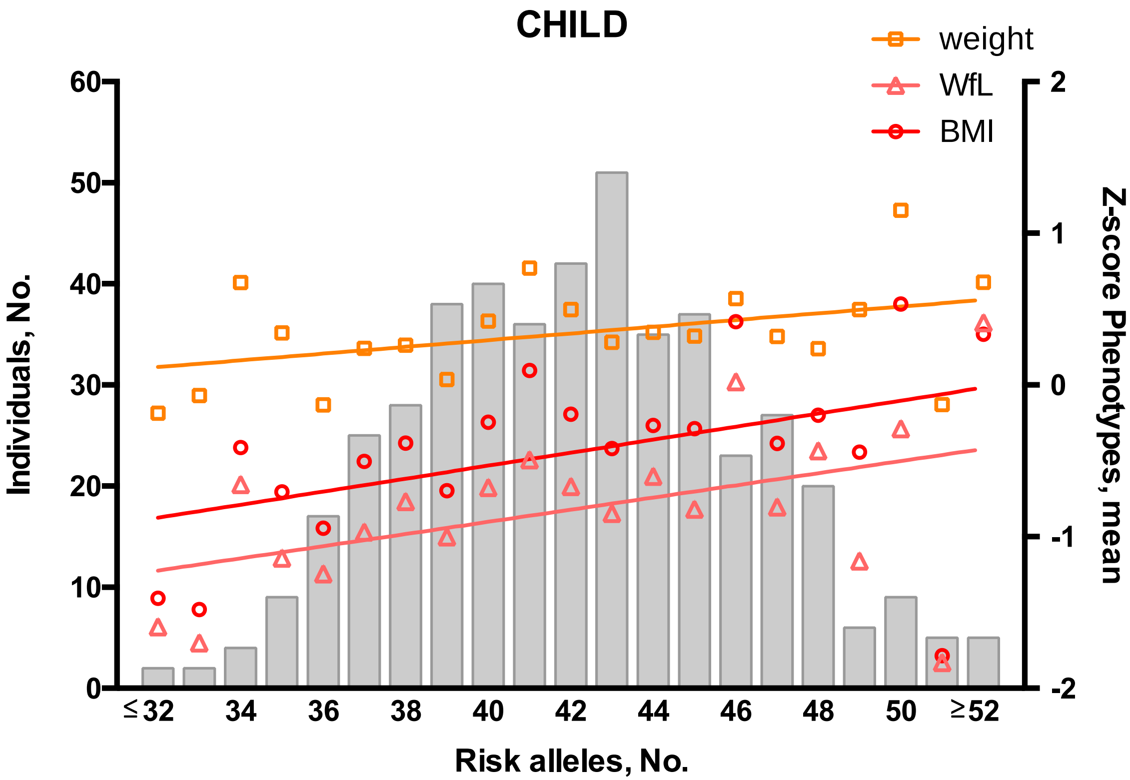
RESULTS

Descriptive of study variables at birth

	CHILD n=462		START n = 454	
Gender, No.	Male	228	Male	216
	Female	218	Female	238
Ethnicity, No	Hispanic	8	South Asian	454
	European	308		
	South-Asian	20		
	Arab	6		
	East-Asian	59		
	African	6		
	First nation	8		
	Mixed	40		
	Other	4		
Mother's Pre-pregnancy BMI	24.36 (4.95)		23.81 (4.42)	
Gestational diabetes (Y/N), No	20/431		54/398	
Mother smoking during pregnancy (Y/N), No	31/425		0/454	
Gestational age at birth (weeks)	39.51 (1.29)		39.21 (1.35)	
Weight at birth (kg)	3.46 (0.49)		3.28 (0.46)	
Length at birth (cm)	49.73 (9.26)		51.63 (2.75)	
BMI (kg/m2)	13.06 (1.5)		12.28 (1.34)	
z-score BMI	-0.31 (1.2)		-0.97 (1.16)	
-2DS<Z-score-BMI< +2DS, No	27/304/8		82/362/2	
z-score Weight-for-length	-0.73 (1.43)		-1.52 (1.51)	

Values are means (SD)

Associations with obesity GRS and adiposity phenotypes at birth



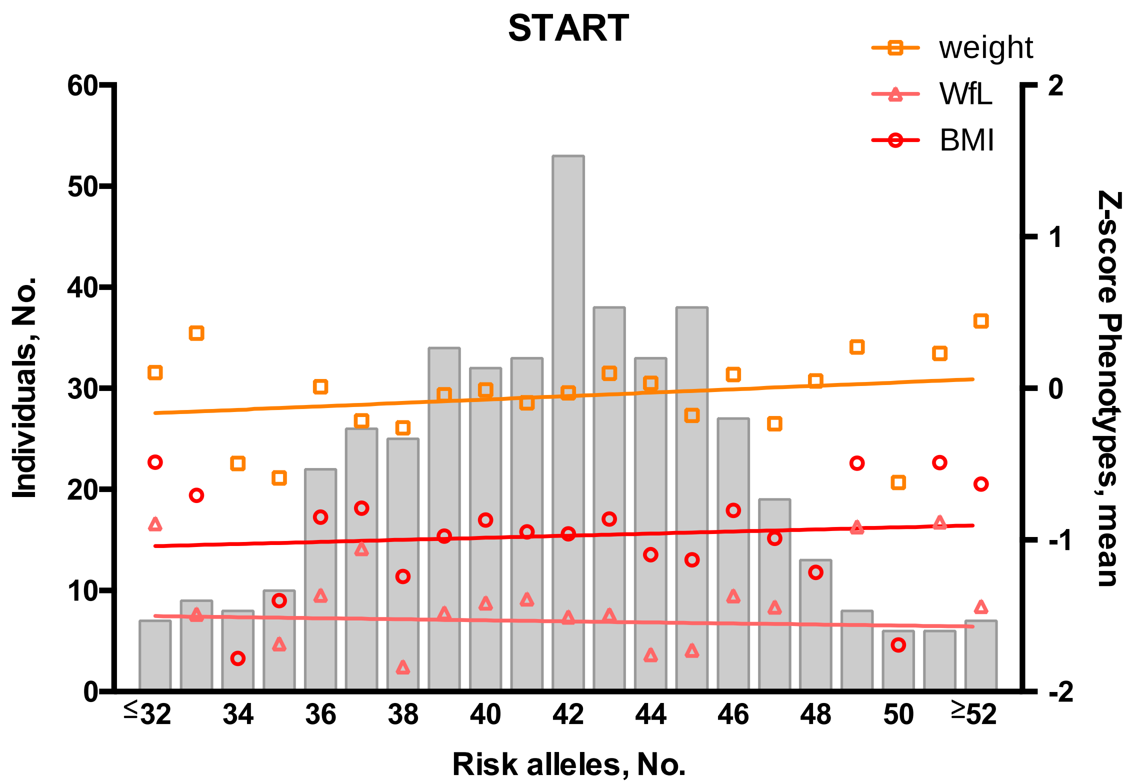
Range of GRS : 31 to 55
Mean : 42.20
SD: 4.05

Correlations between the obesity GRS and adiposity phenotypes at birth in CHILD

	beta	se	95% IC	*p-value*	*p-value (adjusted)*
Gender adjusted-weight	0.010	0.006	-0.001 - 0.022	0.0741	**0.0431**
z-score weight	0.022	0.012	-0.002 - 0.045	0.0690	**0.0362**
z-score WfL	0.038	0.020	-0.001 - 0.077	0.0541	0.0972
z-score BMI	0.043	0.016	0.011 - 0.075	**0.0090**	**0.0330**

Adjustment : gestational duration, gestational diabetes, ethnicity, smoking status, maternal pre-pregnancy BMI

Associations with obesity GRS and adiposity phenotypes at birth



Range of GRS : 28 to 55
Mean : 41.76
SD: 4.45

Correlations between the obesity GRS and adiposity phenotypes at birth in START

	beta	se	95% CI	*p-value*	*p-value (adjusted)*
Gender adjusted-weight	0.005	0.005	-0.005 - 0.014	0.3060	0.7823
z-score weight	0.012	0.011	-0.009 - 0.032	0.2690	0.7602
z-score WfL	-0.008	0.016	-0.040 - 0.024	0.6157	0.3446
z-score BMI	0.004	0.012	-0.021 - 0.028	0.7631	0.7455

Adjustment: gestational duration, gestational diabetes, smoking status, maternal pre-pregnancy BMI

Descriptive of longitudinal variables

	CHILD n=462		START n = 454	
	Follow-up (%)		Follow-up (%)	
Weight at 3 month (kg)	93.51%	6.47 (1.01)	70.93%	5.59 (1.01)
Length at 3 month (cm)	90.48%	62.77 (3.42)	26.65%	60.61 (4.40)
BMI (kg/m2)	90.26%	16.44 (1.74)	26.43%	15.7 (2.39)
z-score BMI	87.01%	-0.27 (1.17)	26.43%	-0.85 (1.69)
-2DS<Z-score-BMI< +2DS, No		23/373/8		25/89/6
z-score Weight-for-length	87.01%	-0.24 (1.22)	26.43%	-0.59 (2.02)
Weight at 6 month (kg)			62.11%	7.8 (1.15)
Length at 6 month (cm)			22.91%	68.45 (3.73)
BMI (kg/m2)			22.03%	16.98 (2.24)
z-score BMI			22.03%	-0.18 (1.46)
-2DS<Z-score-BMI< +2DS, No				7/85/8
z-score Weight-for-length			22.03%	-0.05 (1.47)
Weight at 1 year (kg)	98.48%	9.82 (1.22)	81.50%	10.34 (1.43)
Length at 1 year (cm)	98.27%	76.28 (3.22)	73.35%	76.83 (3.45)
BMI (kg/m2)	98.05%	16.86 (1.61)	73.35%	17.54 (2.2)
z-score BMI	94.81%	0.15 (1.12)	73.35%	0.65 (1.42)
-2DS<Z-score-BMI< +2DS, No		11/406/21		9/273/51
z-score Weight-for-length	94.81%	0.23 (1.09)	73.35%	0.69 (1.35)
Weight at 2 years (kg)			54.19%	13.08 (2.13)
Height at 2 years (cm)			44.71%	88.56 (4.17)
BMI (kg/m2)			44.71%	16.7 (2.36)
z-score BMI			44.71%	0.5 (1.55)
-2DS<Z-score-BMI< +2DS, No				5/176/22
z-score Weight-for-height			44.71%	0.53 (1.5)
Weight at 3 years (kg)	86.15%	15.0 (1.85)		
Height at 3 years (cm)	85.93%	96.01 (4.69)		
BMI (kg/m2)	85.93%	16.25 (1.38)		
z-score BMI	82.68%	0.52 (1.03)		
-2DS<Z-score-BMI< +2DS, No		3/358/21		
z-score Weight-for-height	82.47%	0.54 (0.93)		
Weight at 5 years (kg)	18.40%	19.52 (3.11)		
Height at 5 years (cm)	18.40%	109.49 (5.11)		
BMI (kg/m2)	18.40%	16.2 (1.68)		
z-score BMI	18.40%	0.57 (1.03)		
-2DS<Z-score-BMI< +2DS, No		1/78/6		
z-score Weight-for-height	16.45%	0.44 (1.03)		
Infant was breastfed ever in first year (Y/N), No		438/15		364/30
Mother's years in education, No		8.59 (3.15)		7.57 (2.28)

Values are means (SD)

Associations with obesity GRS and adiposity phenotypes during follow-up

Correlations between the obesity GRS and adiposity phenotypes during follow-up in CHILD (n=1622 measures)

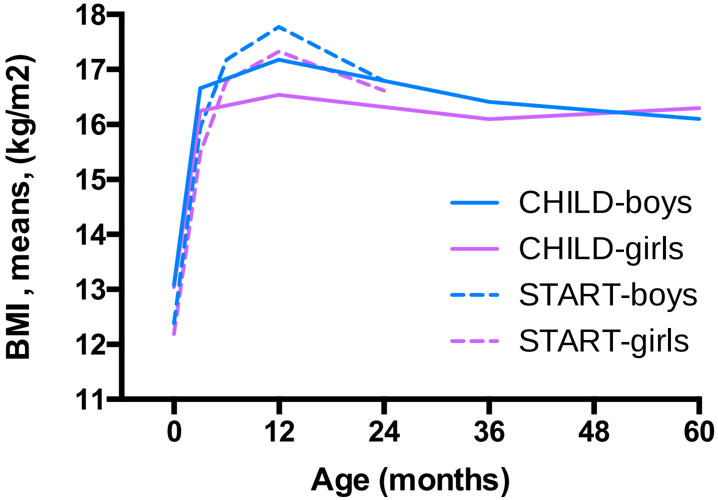
	beta	se	95% CI		*p-value*	*p-value (adjusted)*
Gender-adjusted BMI	2.61E-02	9.63E-03	0.0072	0.0449	**0.0068**	**0.0044**
z-score WfL	1.87E-02	7.20E-03	0.0046	0.0328	**0.0094**	**0.0105**
z-score BMI	1.85E-02	6.92E-03	0.0049	0.0320	**0.0076**	**0.0081**

Adjustement variables : visit, ethnicity, breastfeeding, maternal education level

Correlations between the obesity GRS and adiposity phenotypes during follow-up in START (n=1229 measures)

	beta	se	95% CI		*p-value*	*p-value (adjusted)*
Gender-adjusted BMI	0.0162	0.01282	-0.0089	0.0413	0.2064	0.1509
z-score WfL	1.04E-02	9.78E-03	-0.0088	0.0296	0.2890	0.1506
z-score BMI	1.26E-02	8.91E-03	-0.0049	0.0301	0.1581	0.0954

Adjustement variables : visit, breastfeeding, maternal education level



No association was observed at 3, 6, 12, 24, 36 or 60 months.

DISCUSSION

DISCUSSION

- Significant association between the obesity GRS (built from 42 snps-related to BMI and obesity in adults)
  - and Z-score weight, Z-score BMI at birth,
  - and Z-score WfL and Z-score BMI evolution

in CHILD cohort

- These preliminary results confirm an **early effect** of the common variants involved in the weight regulation in a multiethnic infant cohort (66% of European ancestries), but not in South Asians (living in Canada)

DISCUSSION

- Concordance of our results with the FAMILY study

Linear mixed modeling of the associations between the BMI-GRS and overall changes in weight and BMI Z-score from birth to 5 years of age.

Trait	N	β±SE	P
Weight	540 (2263*)	0.016 ± 0.006	9.51×10^{-3}
BMI	539 (2237*)	0.016 ± 0.006	5.08×10^{-3}

Aihua Li, at al; paper in revision

Original Investigation

Satiety Mechanisms in Genetic Risk of Obesity

Llewellyn, JAMA Pediatr, 2014

- Using GRS from 28 snps-related to BMI and obesity in the Twins Early Development study (but only in unrelated children, n=2250)
- Showed stronger associations with adiposity phenotypes and GRS (beta coefficient range : 0.167-0.177) , but was performed on 9 y-old children
- They also demonstrated associations with appetite traits (satiety responsiveness)

Original Investigation

Polygenic Risk, Appetite Traits, and Weight Gain in Middle Childhood

A Longitudinal Study

Steinsbekk, JAMA Pediatr, 2015

- Using GRS from 32 snps-related to BMI and obesity in the Trondheim early secure Study (n=652 children, from 4 to 8 years-old)
- Showed stronger associations with adiposity phenotypes evolution and GRS (beta coefficient range : 0.10-0.09)
- They also demonstrated associations with appetite traits (CEBQ)

DISCUSSION

- Associations observed only in CHILD cohort
  - Suggests an ethnic-dependent effect of the GRS on early adiposity
- GRS built from published data, based on predominantly European ancestries (and adults)
  - Genetic architecture (or linkage disequlibrium block patterns) of obesity may be different in South Asians
  - Interaction between genes and other « ethnic-dependent» factors (biological, cultural (food intake)…) that can also impact the relationships between the GRS and the phenotype
- Validation of Growth standard cut-offs in South-Asian children
  - Preliminary validation of standard growth curves with a referent assessment method of body composition may be required

NEXT STEPS

- To consolidate the genetic results in CHILD and START cohorts
  - By testing the GRS on a larger sample of genotyped infants
  - By including more snps in the GRS (by adding proxy snps)
    - > Should increase the genetic part of the BMI variance
  - By calculating an enrichment of risk alleles according to the expected frequency for the ethnic group
  - By taking account the genotype of mother

NEXT STEPS

- To Assess the association between energy intake evolution of children from birth to five years-old and the obesity-GRS
  - Available nutritional data in CHILD: breastfeeding practices, formula and age of introduction for certain food items-related to allergy

  - Available nutritional data in START :
    - breastfeeding practices,
    - food questionnaire frequency at 2 & 3 y-old
      - could be scored to design different food patterns : healthy / unhealthy
    - appetite trait (feeding behavior question)

CONCLUSION

- We estimated the effect of obesity and BMI susceptibility on evolution of BMI in children from birth to 5 years-old
- We highlighted ethnic differences in the obesity genetic susceptibility in the early life
- Additional analyses are required to validate this preliminary results
- Finding predictive factors to BMI evolution in children would aid the development and implementation of effective obesity prevention initiatives, appropriate to each ethnicity