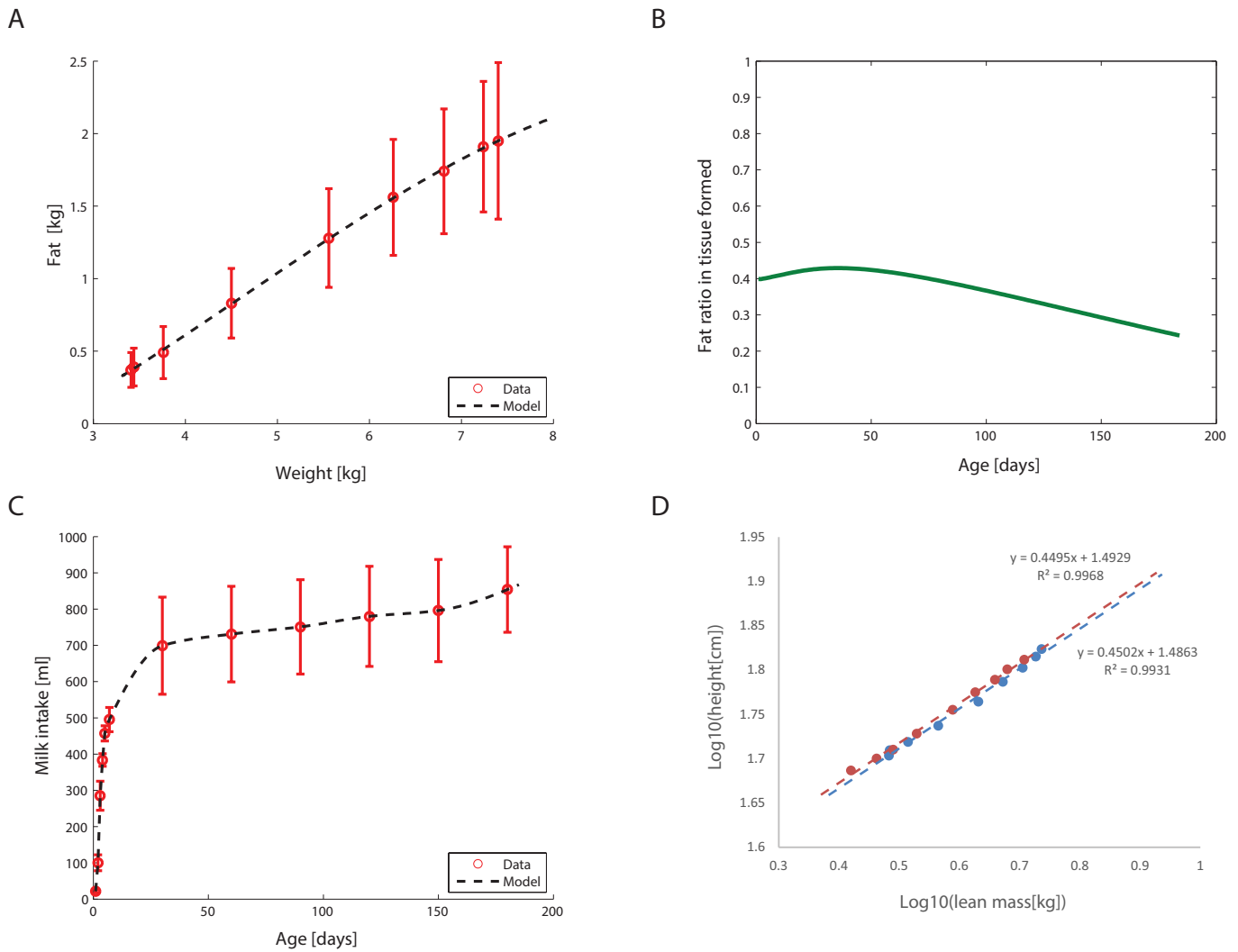


Supplementary Information

Predicting Growth of the Healthy Infant using a Genome Scale Metabolic Model

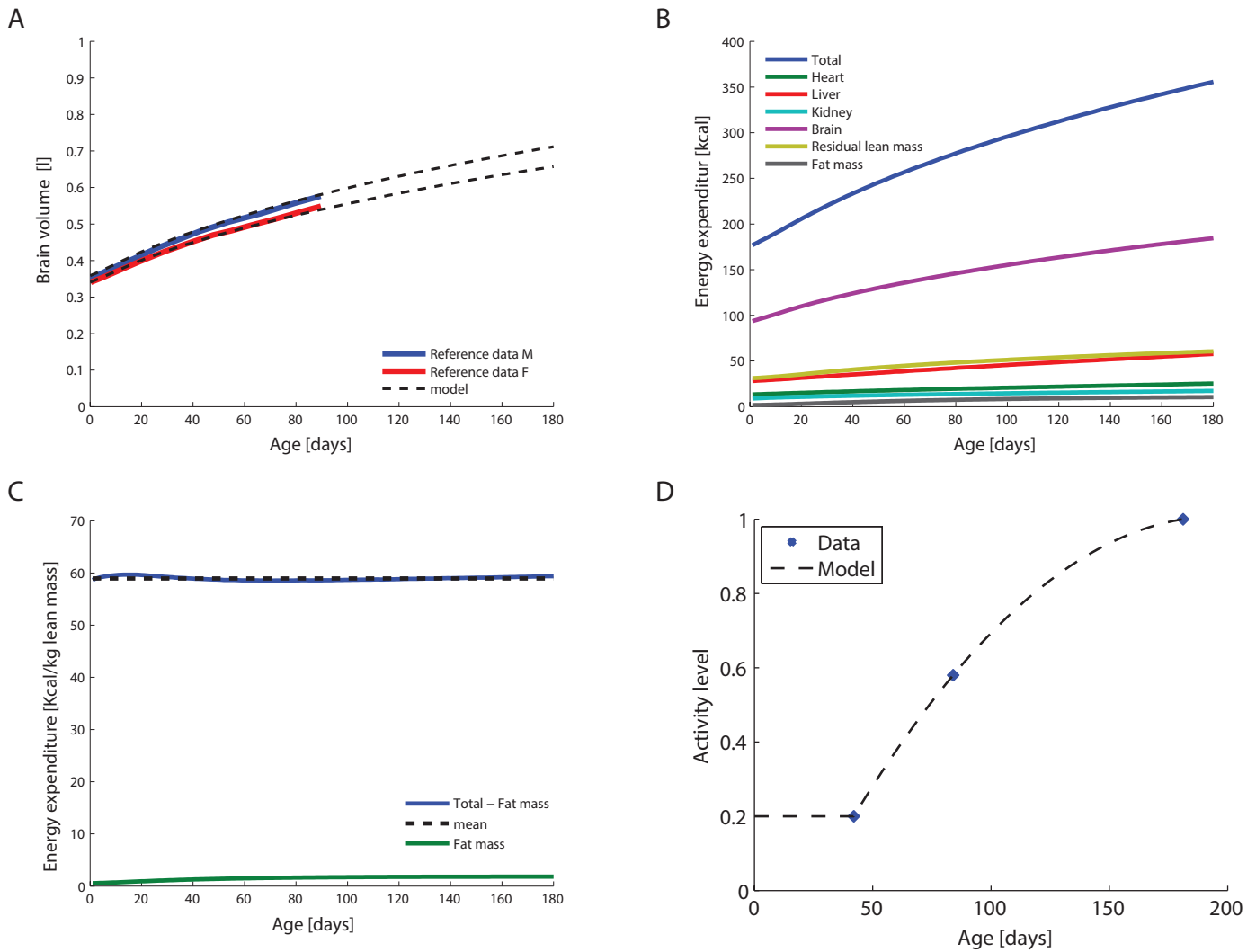
Avlant Nilsson, Adil Mardinoglu and Jens Nielsen

Figure S1



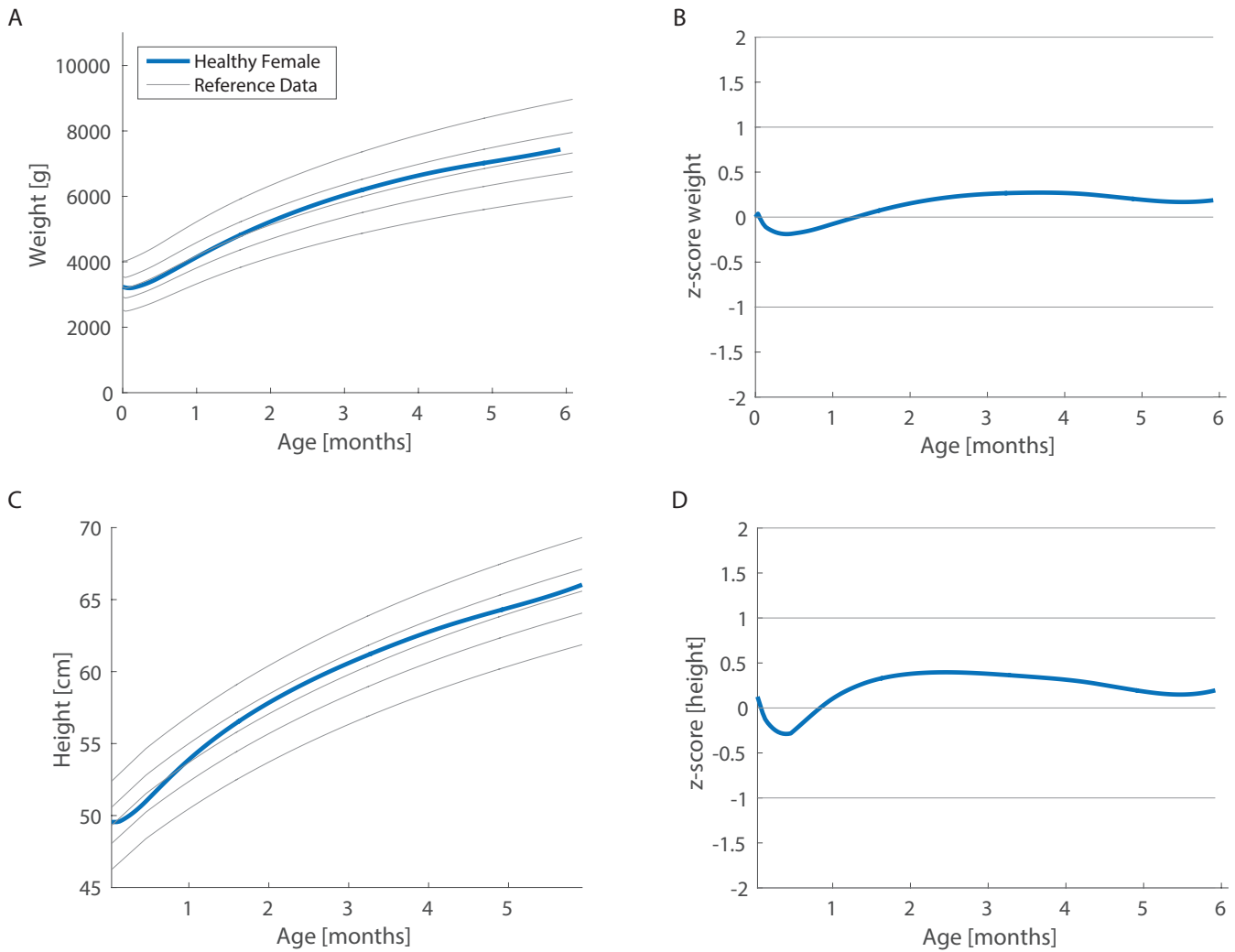
The estimation of intermediate values for parameters used in the model. (A) The fat content of infants. (B) The ratio of fat mass to total mass in newly formed tissue. (C) The intake of breast milk. (D) Linear regression of logarithmic transformed experimental measurements of lean mass and height¹ resulting in the following empirical equations: $[height] = 30.6 \times [lean\ mass]^{0.45}$ for males and $[height] = 31.1 \times [lean\ mass]^{0.45}$ for females.

Figure S2



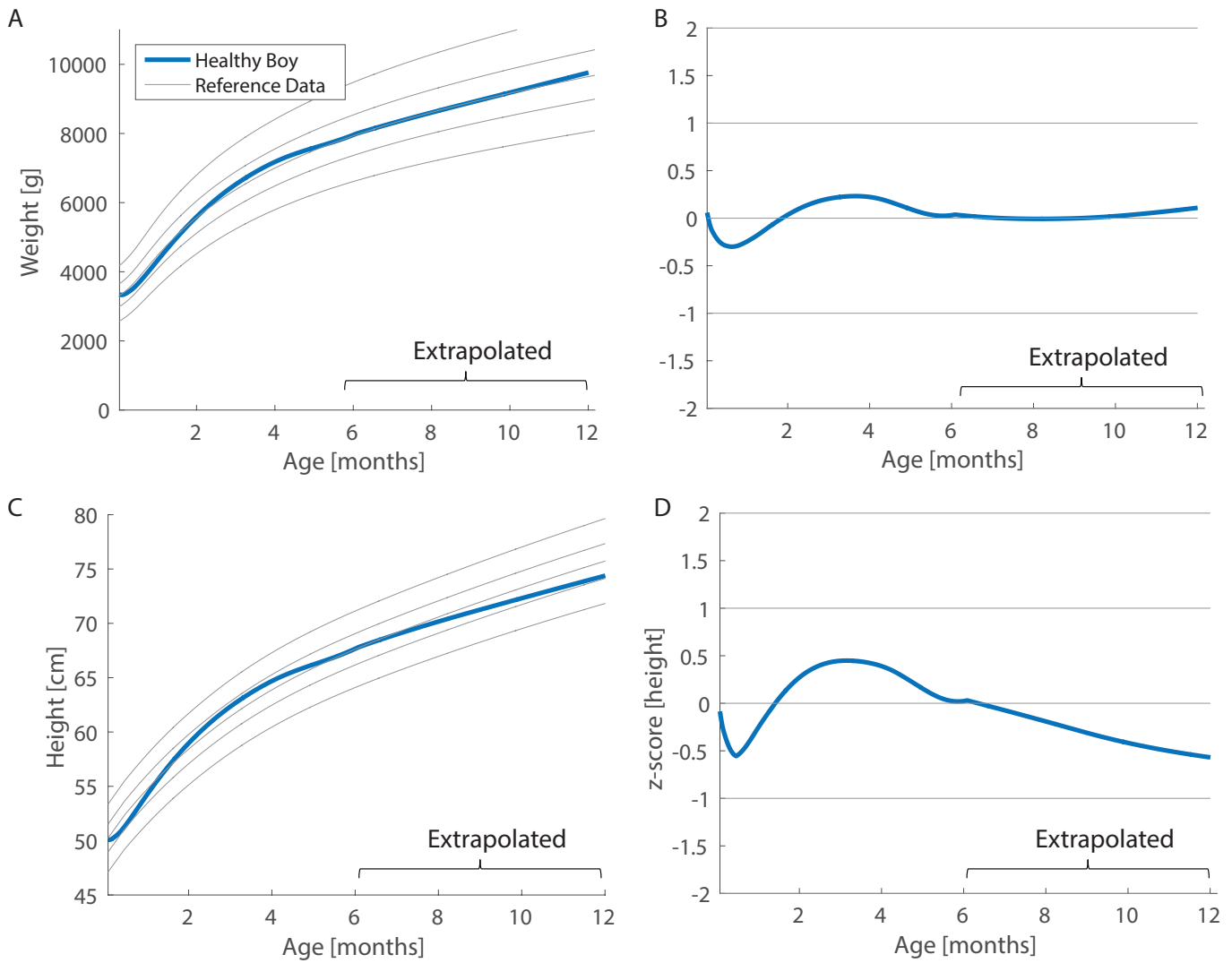
Estimation of energy expenditure in the model. (A) The brain volume calculated from World Health Organization head circumference data compared with experimental data for males (M) and females (F)². The modeled brain mass was transformed to liter using a density of 1.08 g/ml³. (B) Calculated energy expenditure for different tissues. (C) Sum of energy expenditure of all tissues except fat mass, expressed per kg lean mass, the mean is 59 kcal and the average amplitude of the difference between the model and the mean is 0.5%. (D) Specific activity level, data normalized to the value at 180 days⁴.

Figure S3



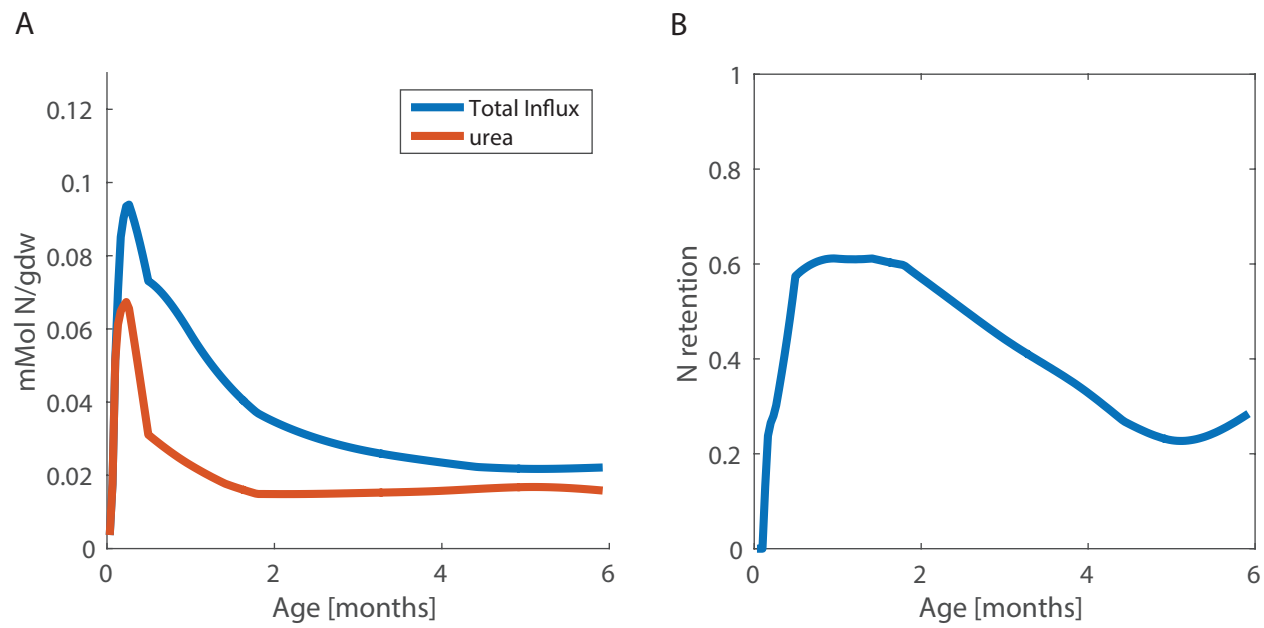
Predicted growth of female infants. Initial values are set to female averages, food intake is reduced by 7% and the fat model is fitted to female composition data. A) weight. B) Weight z-score. C) Height. D) Height z-score.

Figure S4



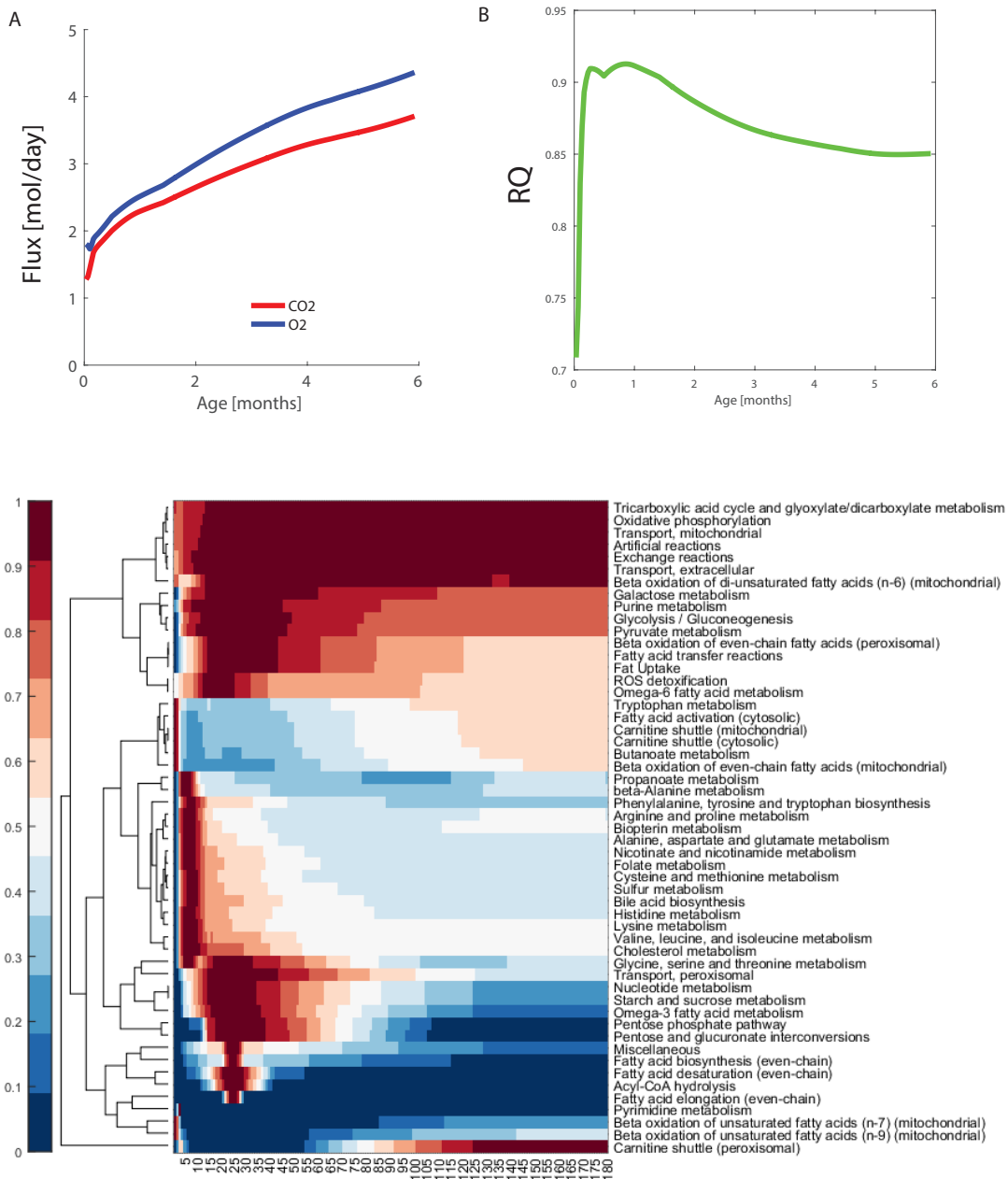
Projection of growth up to 12 months using extrapolated milk intake from time period 1 to 6 months and composition corresponding to the levels at 6 months, assuming that physical activity per kg and fat ratio remains constant beyond 6 months. A) weight, B) Weight z-score. C) Height. D) Height z-score.

Figure S5



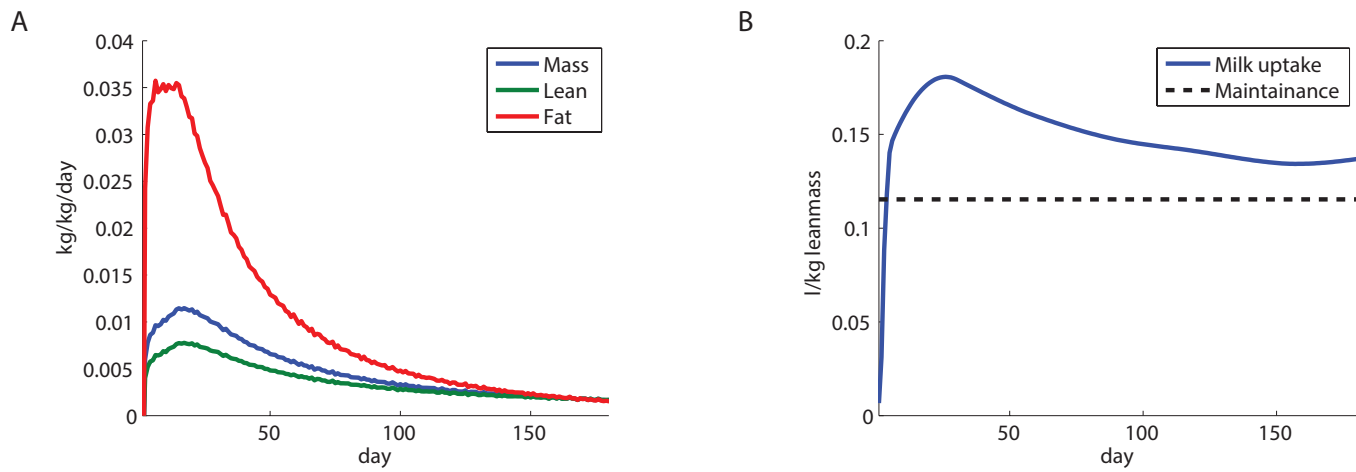
Exchange of nitrogen per gram dry weight (gdw). (A) Influx of nitrogen and out flux through urea. (B) Nitrogen retention, $(N_{in} - N_{out})/N_{in}$.

Figure S6



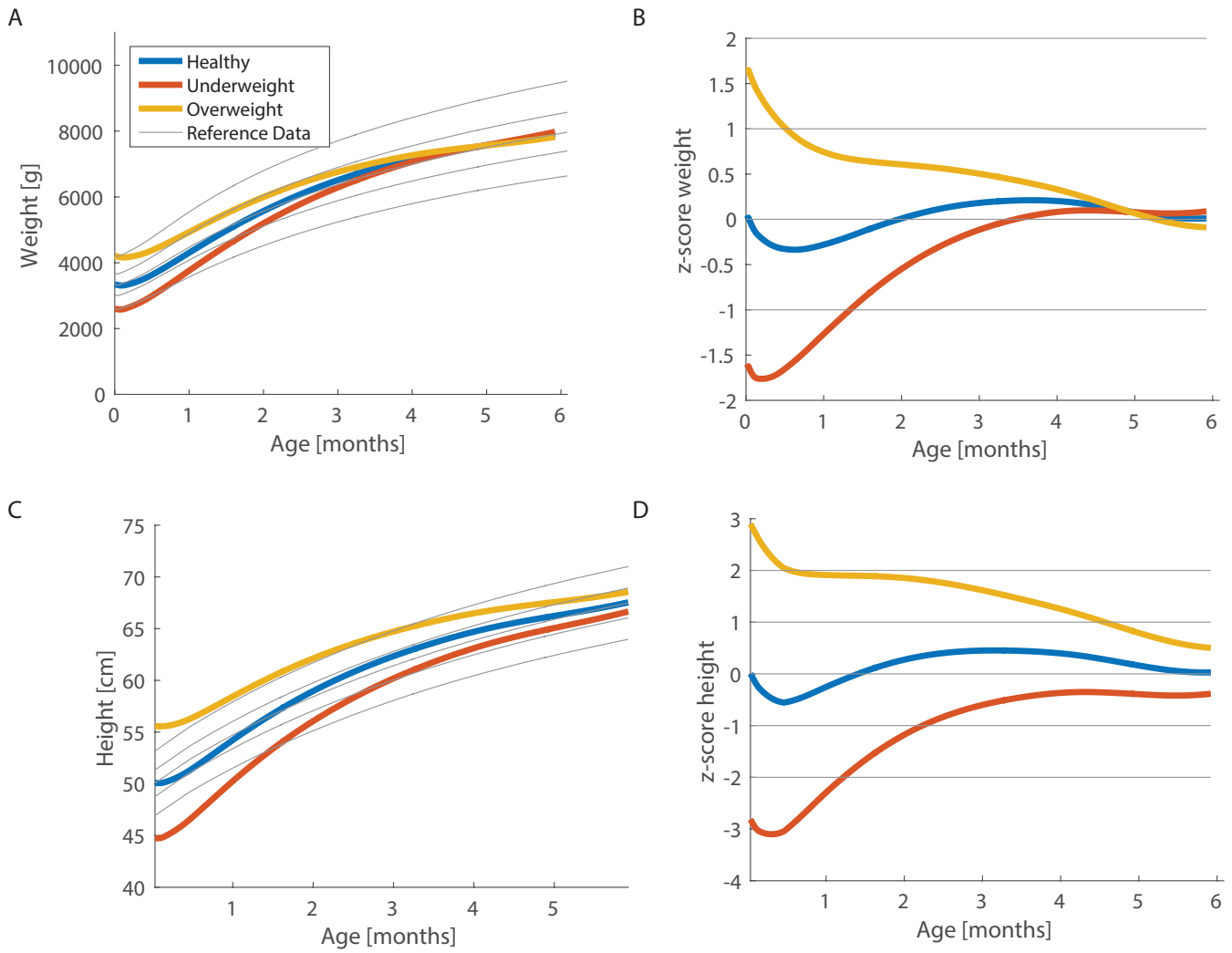
Changes in metabolism during infancy. (A) Exchange fluxes of O_2 and CO_2 . (B) Respiration quotient $RQ = CO_2/O_2$. (C) Heat map showing the clustering of the time-dependent changes in flux profiles of the metabolic subsystems of the model. The values represent the normalized sum of the absolute values of the fluxes within each subsystem.

Figure S7



Specific growth and milk uptake rates. A) Specific growth rate of fat mass (kg fat/ kg fat), lean mass (kg lean/ kg lean) and weight (kg/kg). (B) The specific uptake of milk (l/kg lean mass); the dotted line is approximate consumption for maintenance, for reference.

Figure S8



Predicted growth of infants with different starting weights at the 5th, 50th and 95th percentile. The initial fat ratio was assumed to be 10.84% at birth. A) weight. B) Weight z-score. C) Height. D) Height z-score.

Table S1

Sensitivity of nutrients and change in growth in percentage by decreasing or increasing the nutrients.

Month	Sensitivity						Decreased -50% (a factor $\frac{1}{2}$)						Increased +100% (a factor 2)					
	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
lactose	0.517	0.751	1.101	1.646	2.606	2.821	-28	-38	-55	-82	*	*	45	43	70	103	165	145
oleate	0.297	0.323	0.420	0.583	0.891	0.968	-15	-16	-21	-29	-45	-48	27	31	42	58	89	97
linoleate	0.194	0.262	0.358	0.497	0.759	0.825	-10	-13	-18	-25	-38	-41	19	24	36	50	76	82
palmitate	0.198	0.206	0.282	0.392	0.599	0.651	-10	-11	-14	-20	-30	-33	19	21	28	39	60	65
glucose	0.114	0.130	0.176	0.244	0.375	0.415	-6	-7	-9	-12	-19	-21	11	13	18	24	37	41
stearate	0.047	0.053	0.072	0.100	0.152	0.165	-2	-3	-4	-5	-8	-8	5	5	7	10	15	17
lauric acid	0.032	0.050	0.068	0.095	0.145	0.158	-2	-3	-3	-5	-7	-8	3	5	7	10	15	16
myristic acid	0.032	0.041	0.056	0.078	0.120	0.130	-2	-2	-3	-4	-6	-6	3	4	6	8	12	13
palmitolate	0.017	0.019	0.026	0.035	0.054	0.059	-1	-1	-1	-2	-3	-3	2	2	3	4	5	6
glutamate	0.014	0.018	0.024	0.034	0.052	0.057	-1	-1	-1	-2	-3	-3	1	2	2	3	5	6
leucine	0.016	0.017	0.023	0.032	0.049	0.053	-1	-1	-1	-2	-2	-3	2	2	2	3	5	5
linolenate	0.012	0.017	0.023	0.032	0.049	0.053	-1	-1	-1	-2	-2	-3	1	2	2	3	5	5
proline	0.011	0.013	0.019	0.027	0.042	0.046	-1	-1	-1	-1	-2	-2	1	1	2	3	4	5
tyrosine	0.010	0.010	0.013	0.017	0.024	0.026	0	-1	-1	-1	-1	-1	1	1	1	2	2	3
lysine	0.008	0.010	0.013	0.018	0.028	0.030	-6	-8	-1	-1	-1	-1	1	1	1	2	3	3
isoleucine	0.007	0.009	0.012	0.017	0.026	0.028	0	0	-1	-1	-1	-1	1	1	1	2	3	3
valine	0.007	0.009	0.012	0.016	0.025	0.027	0	0	-1	-1	-1	-1	1	1	1	2	3	3
aspartate	0.005	0.006	0.008	0.011	0.017	0.018	0	0	0	-1	-1	-1	1	1	1	1	2	2
phenylalanine	0.005	0.006	0.008	0.010	0.016	0.017	-2	-4	0	-1	-1	-1	1	1	1	1	2	2
arachidonate	0.004	0.005	0.007	0.009	0.014	0.015	0	0	0	0	-1	-1	0	0	1	1	1	2
threonine	0.004	0.005	0.006	0.008	0.013	0.014	0	0	0	0	-1	-1	0	0	1	1	1	1
alanine	0.003	0.004	0.005	0.007	0.011	0.012	0	0	0	0	-1	-1	0	0	0	1	1	1
(11Z,14Z)-eicosadienoic acid	0.004	0.004	0.005	0.007	0.011	0.012	0	0	0	0	-1	-1	0	0	0	1	1	1
dihomo-gamma-linolenate	0.004	0.004	0.005	0.007	0.010	0.011	0	0	0	0	-1	-1	0	0	0	1	1	1
serine	0.003	0.004	0.005	0.007	0.009	0.010	0	0	0	0	0	-1	0	0	0	1	1	1
cystine	0.003	0.003	0.005	0.006	0.010	0.010	0	0	0	0	-1	-1	0	0	0	1	1	1
arginine	0.003	0.003	0.004	0.006	0.009	0.009	0	0	0	0	0	0	0	0	0	1	1	1
DHA	0.002	0.003	0.004	0.005	0.008	0.008	0	0	0	0	0	0	0	0	0	0	1	1
histidine	0.002	0.003	0.003	0.005	0.007	0.007	0	0	0	0	0	0	0	0	0	0	1	1
tryptophan	0.002	0.002	0.003	0.004	0.006	0.007	0	0	0	0	0	0	0	0	0	0	1	1
methionine	0.001	0.002	0.002	0.003	0.005	0.005	-25	-26	-12	0	0	0	0	0	0	0	0	0
glycine	0.001	0.001	0.002	0.003	0.004	0.004	0	0	0	0	0	0	0	0	0	0	0	0
gamma-linolenate	0.001	0.001	0.002	0.003	0.004	0.004	0	0	0	0	0	0	0	0	0	0	0	0
eicosanoate	0.001	0.001	0.002	0.002	0.004	0.004	0	0	0	0	0	0	0	0	0	0	0	0
lignocerate	0.001	0.001	0.001	0.001	0.002	0.002	0	0	0	0	0	0	0	0	0	0	0	0
behenic acid	0.001	0.001	0.001	0.001	0.001	0.002	0	0	0	0	0	0	0	0	0	0	0	0
physeteric acid	0.000	0.000	0.001	0.001	0.001	0.001	0	0	0	0	0	0	0	0	0	0	0	0

* Simulated growth was negative.

Table S2

Sensitivity of important model parameters.

Month	1	2	3	4	5	6
%Fat in new formed tissues	-0.727	-0.687	-0.661	-0.634	-0.601	-0.561
Food intake	1.584	1.995	2.775	3.970	6.157	6.684
Physical Activity level	-0.030	-0.097	-0.284	-0.603	-1.186	-1.381
Energy for Lean Mass synthesis	-0.101	-0.118	-0.136	-0.157	-0.183	-0.213
Energy for Fat Mass synthesis	-0.110	-0.123	-0.121	-0.116	-0.110	-0.103
Lean maintenance energy	-0.549	-0.882	-1.454	-2.302	-3.857	-4.176
Fat maintenance energy	-0.005	-0.016	-0.037	-0.065	-0.115	-0.127
Kcal to ATP conversion constant	0.796	1.237	2.033	3.246	5.454	6.004
Water Content of lean mass	0.157	0.184	0.210	0.243	0.283	0.330

References

- [1] Fields D. A *et al.* Longitudinal body composition data in exclusively breast-fed infants: a multicenter study. *Obesity (Silver Spring)*, **19**:1887–1891, 2011.
- [2] Holland D, Chang L, TM E, et Al. SStructural growth trajectories and rates of change in the first 3 months of infant brain development. *JAMA Neurol.*, **71**(10):1266–1274, oct 2014.
- [3] Barber T. E. D. W, Brockway J. A, Higgins L. S. THE DENSITY OF TISSUES IN AND ABOUT THE HEAD. *Acta Neurol. Scand.*, **46**(1):85–92, mar 1970.
- [4] Wells J. C, Davies P. S. Estimation of the energy cost of physical activity in infancy. *Arch. Dis. Child.*, **78**(2):131–6, 1998.