Infant Growth as an Effect Modifier of Genetic-Lipid Associations: Evidence From a Chilean Infancy Cohort

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Introduction

- Early infancy serves as a window of time in which environmental exposures are associated with chronic disease risk factors in adulthood.
- Extensive studies support functional association between genetic regions and lipid levels.
- Infant growth may influence genetic mechanisms and subsequent metabolic programming of lipid metabolism.

Hypothesis Infant growth influences the strength of association between selected genetic variants and adverse lipid levels for children.

Aim

- Assess SNP-lipid additive association across latent early infancy growth classes for 20 candidate genetic variants underlying lipid metabolism and fasting lipid profiles assessed at average 17 years of age.

Sample

Santiago Longitudinal Study (SLS)

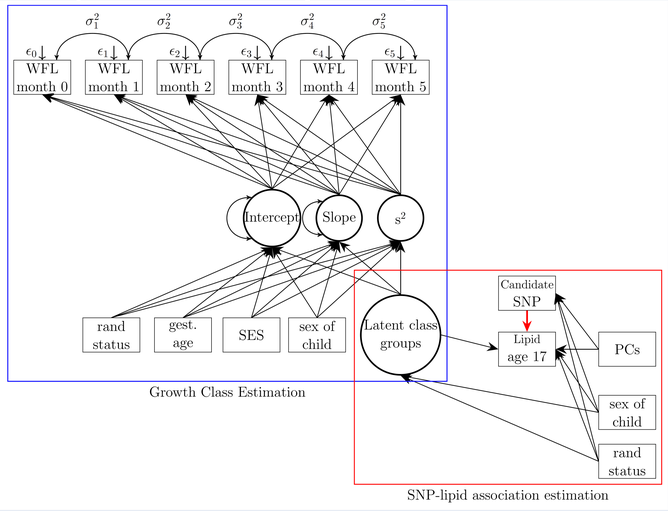
- 1,645 infants were enrolled in SLS between 1991-1996 from low- to middle-income neighborhoods in Santiago, Chile.
- Started as a randomized preventive trial for iron deficiency anemia.
- Participants are from admixed Latino families.
- Analysis includes participants (n=546) with genotyped data and measures during infancy and adolescence.
- Lipid traits measured after overnight fasting at mean age 17 years.

Methods

Statistical Methods

1. Find candidate SNPs by screening main effects.
2. Use latent growth mixture models (LGMM) to determine heterogeneous latent growth classes
3. Within each latent class estimate SNP-lipid association
4. Use Bonferroni multiple comparison correction

Figure. Structural equation model used to estimate SNP-lipid associations by latent growth class

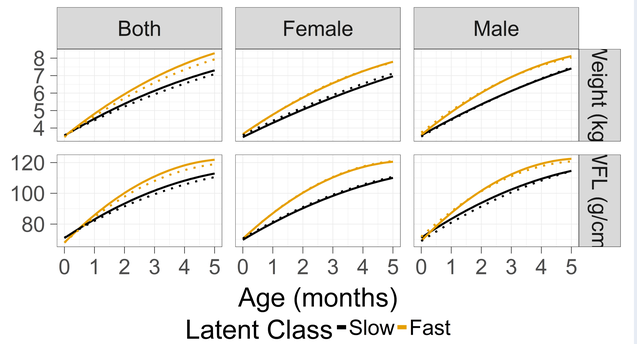


Effect modifier: Latent class growth group

Outcome: Additive association between SNP-lipid

Results

Growth trajectories by sample stratification status and type of trajectory



Note: Dotted lines represent curves in analyses adjusting for sex of child (for pooled sample), randomization status, and socioeconomic sta

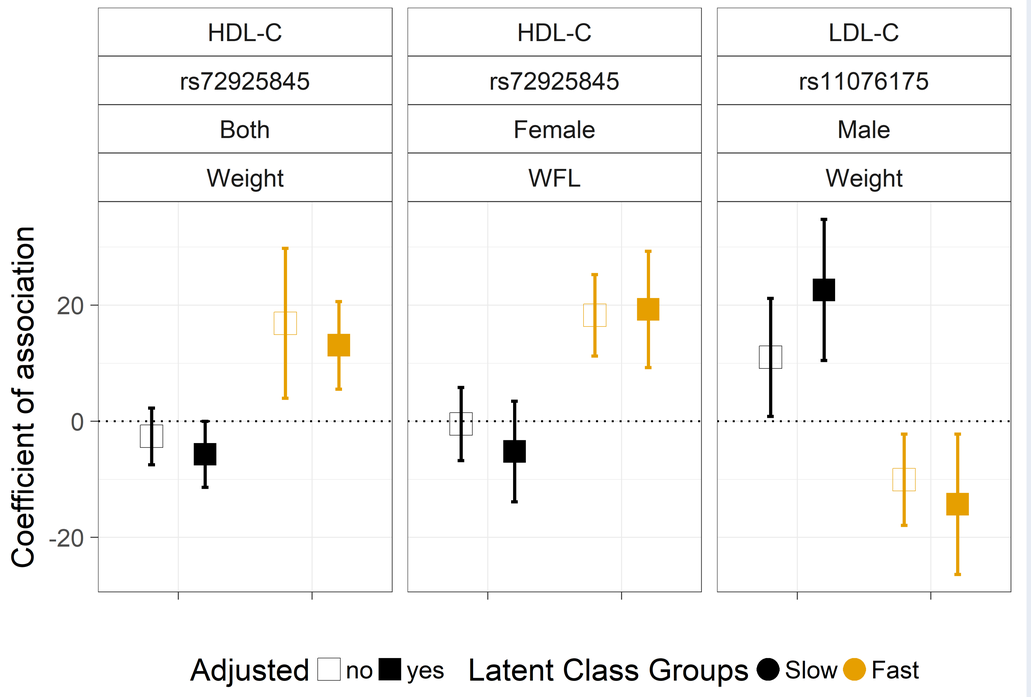
Latent growth class pairwise differences (95% CI) in coefficient of association between distal lipid outcome (mg/dL) and candidate SNP

	Categories			Low vs High		Overall test: p-value, (Chi-sq, df)	
Sex of child	Outcome	Lipid	SNP	Not adjusted	Adjusted[a]	Not adjusted	Adjusted[a]
Both	Weight	HDL	rs72925845	-19.47 (-34.47, -4.48)	**-18.78 (-28.98, -8.58)**	0.011, (6.48,1)	0.000, (13.03,1)
Female	WFL	HDL	rs72925845	**-18.73 (-28.60, -8.85)**	**-24.47 (-36.49, -12.46)**	0.000, (13.80,1)	0.000, (15.93,1)
Male	Weight	LDL	rs11076175	21.09 (6.60, 35.57)	**36.92 (18.36, 55.48)**	0.004, (8.14,1)	0.000, (15.20,1)
	Weight	LDL	rs4420638	-27.84 (-49.20, -6.49)	**-51.06 (-75.46, -26.66)**	0.011, (6.53,1)	0.000, (16.82,1)

Note:
Bold values indicate Bonferroni corrected statistical significance at alpha level = 0.05.
[a] Adjusted for sex of child in pooled sample, randomization status, and socioeconomic status.

Results, cont...

Coefficent of SNP-lipid associations by lipid, SNP, sex of child, and type of trajectory



Note: Adjusted analyses includes sex of child (for pooled sample), randomization status, and socioeconomic status.

SNP background information

SNP	Chr	Gene	Type	MAF	A1/A2	Reference study	Trait
rs72925845	17	DNAH17	Intronic	0.05	A/G	Ko et al 2014	TG (OR 1.64)
rs11076175	16	CETP	Intronic	0.17	A/G	Zubair et al 2016	HDL (OR 0.36)

Note: A1=coded allele, A2=non-coded allele

- Faster weight (pooled) and WFL (female) growth groups: positive association between rs72925845 and HDL-C.
  - ⇒ HDL-C inversely associated with cardiovascular disease risk.
  - ⇒ Expect negative association with HDL-C given established positive association with TG.
- Faster weight growth group: inverse association between rs11076175 and LDL-C.
  - ⇒ LDL-C positively associated with cardiovascular disease risk.
  - ⇒ Expect positive association with LDL-C given established inverse association with HDL-C.

Summary

- Faster growth appears to be protective against a few deleterious SNP-lipid associations.
- Heterogeneity of SNP-lipid association across growth patterns in this period suggests plasticity of response on a molecular level.

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