Lipid-related Genetic Variants and Lipid Outcomes in a Cohort of Chilean Children

Ann Von Holle, Anne Justice, Misa Graff, Kari E. North, UNC, Chapel Hill, NC; Estela Blanco, Sheila Gahagan, UCSD, San Diego, CA; Bárbara Angel, Unidad de Nutrición Pública INTA, Univ de Chile, Santiago, Chile; José Luis Santos, Pontificia Univ Católica de Chile, Santiago, Chile

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Lipid concentrations

- Are a recognized heritable risk factor for cardiovascular disease (CVD)
- Associate with >150 loci in adults
- Vary across ancestral groups
- Include high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG).

Genetic architecture across racial/ethnic groups

Genetic Architecture

'...Loci influencing the trait, direction and magnitude of genetic effects, and proportions of phenotypic variation explained...'.'[1]

- Genetic architecture underlying lipid traits is similar across ancestral groups for adults.[1]
- Unclear if lipid-related loci associations found in adults extend to younger age groups.
  - One European study establishes continuity of associations across the age spectrum[2], but evidence is sparse in Hispanic/Latino (HL) populations.

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[1] M. Coram et al. "Genome-wide Characterization of Shared and Distinct Genetic Components that Influence Blood Lipid Levels in Ethnically Diverse Human Populations". In: *The American Journal of Human Genetics* 92.6 (June 2013), pp. 904–916. DOI: 10.1016/j.ajhg.2013.04.025.

[2] E. Tikkanen et al. "Association of Known Loci With Lipid Levels Among Children and Prediction of Dyslipidemia in Adults". In: *Circulation: Cardiovascular Genetics* 4.6 (Dec. 1, 2011), pp. 673–680. DOI: 10.1161/CIRCGENETICS.111.960369.

Aims

Aim 1 Estimate association between lipid risk variants first identified in adults and adolescent lipid traits from Santiago Longitudinal Cohort Study (SLCS), a Chilean infancy cohort[3].

Aim 2 Compare results between SLCS and Cardiovascular Risk in Young Finns Study Cohort[4].

[3] B. Lozoff et al. "Behavioral and developmental effects of preventing iron-deficiency anemia in healthy full-term infants". In: *Pediatrics* 112.4 (Oct. 2003), pp. 846–854.

[4] E. Tikkanen et al. "Association of Known Loci With Lipid Levels Among Children and Prediction of Dyslipidemia in Adults". In: *Circulation: Cardiovascular Genetics* 4.6 (Dec. 1, 2011), pp. 673–680. DOI: 10.1161/CIRCGENETICS.111.960369.

Sample

- 1,645 infants began SLCS between 1991-1996
- Current sample recruited from n=888, which were 2 of 3 randomized control trial groups
- n=677 with infancy and adolescent data and of those n=546 with genotyped data in analyses that follow
- Low to middle income status in Chile.
- Ancestrally mixed American Indian and Spanish descent families
- Lipid traits measured after overnight fasting at mean age 17 years.

Methods

1. Test additive association between lipid traits and adequately powered single risk variants.
   - 76 common **lipid variants** selected from a European genome-wide meta-analysis with strongest independent signal[5].
   - Association tests include 6 **single variants** with *a priori* power > 0.80.
2. Assess the association of weighted genetic risk scores (wGRS) on lipid traits using linear regression model.
   - **Coefficients** for wGRS and power calculations based on European adult association studies[6].
3. Characterize proportion of variance explained by lipid variants.

[5] M.-j. Buscot et al. "The Combined Effect of Common Genetic Risk Variants on Circulating Lipoproteins Is Evident in Childhood: A Longitudinal Analysis of the Cardiovascular Risk in Young Finns Study". In: *PLOS ONE* 11.1 (Jan. 5, 2016). Ed. by D. Fardo, e0146081. DOI: 10.1371/journal.pone.0146081.

[6] T. M. Teslovich et al. "Biological, clinical and population relevance of 95 loci for blood lipids". In: *Nature* 466.7307 (Aug. 5, 2010), pp. 707–713. DOI: 10.1038/nature09270.

1. Association tests

- We assessed single variant associations using linear regression for HDL-C, LDL-C, TG, assuming an additive genetic model, adjusted for sex and ancestry (via principal components).

Sample Model for HDL

$$HDL_i = \beta_0 + SNP_i\beta_1 + sex_i\beta_2 + ANCESTRY_i\beta + \epsilon_i$$

- SNP_i represents one single nucleotide polymorphism (SNP) with 'genotypes were coded as 0, 1, or 2 when directly genotyped or as a predicted allele dosage (range, 0-2) when imputed.'[7]
- Only six variants from the Chilean sample met the *a priori* threshold of power > 0.8 to detect an association based on effect sizes from GWAS[8].

[7] E. Tikkanen et al. "Association of Known Loci With Lipid Levels Among Children and Prediction of Dyslipidemia in Adults". In: *Circulation: Cardiovascular Genetics* 4.6 (Dec. 1, 2011), pp. 673–680. DOI: 10.1161/CIRCGENETICS.111.960369.

[8] T. M. Teslovich et al. "Biological, clinical and population relevance of 95 loci for blood lipids". In: *Nature* 466.7307 (Aug. 5, 2010), pp. 707–713. DOI: 10.1038/nature09270.

2. Polygenic risk scores

- Regress phenotypes onto weighted trait-specific genetic risk scores (GRS).

Sample model for HDL: $HDL_i = \beta_0 + \beta_1 GRS1_i + \epsilon_i$

GRS for HDL-C:

$$(0.48 * rs4660293 + 0.49 * rs2814944 + 0.59 * rs4731702 + 0.41 * rs2923084 + 0.4 * rs7134375 + 0.44 * rs7134594 + 1.45 * rs1532085 + 3.39 * rs3764261 + 0.45 * rs2925979 + 0.42 * rs4148008 + 0.39 * rs4129767 + 0.64 * rs737337 + 1.88 * rs1800961 + 0.93 * rs6065906 + 0.47 * rs1689800 + 0.61 * rs4846914 + 0.68 * rs12328675 + 0.46 * rs2972146 + 0.49 * rs6450176 + 0.39 * rs605066 + 1.95 * rs1084651 + 1.21 * rs9987289 + 0.44 * rs2293889 + 0.65 * rs581080 + 0.94 * rs1883025 + 0.78 * rs3136441 + 0.86 * rs4759375 + 0.44 * rs4765127 + 0.61 * rs838880 + 0.39 * rs2652834 + 1.27 * rs16942887 + 0.48 * rs11869286 + 1.31 * rs7241918 + 0.42 * rs12967135 + 0.45 * rs7255436 + 0.83 * rs386000 + 0.46 * rs181362 + 0.84 * rs13107325)/29.79$$

- All GRS are standardized in the regression models: regression coefficient for GRS indicates a one unit change in SD of GRS.

3. Proportion of variance explained by SNPs

- Linear models containing all lipid-related SNPs related to a specific phenotype, such as HDL-C, will be covariates.
- The continuous lipid phenotype is the outcome.
- Differences in R^2 will be calculated between models with and without the SNPs to estimate h^2.

Model for HDL: HDL_i = b0 + b1 * rs4660293 + b2 * rs2814944 + b3 * rs4731702 + b4 * rs2923084 + b5 * rs7134375 + b6 * rs7134594 + b7 * rs1532085 + b8 * rs3764261 + b9 * rs2925979 + b10 * rs4148008 + b11 * rs4129767 + b12 * rs737337 + b13 * rs1800961 + b14 * rs6065906 + b15 * rs1689800 + b16 * rs4846914 + b17 * rs12328675 + b18 * rs2972146 + b19 * rs6450176 + b20 * rs605066 + b21 * rs1084651 + b22 * rs9987289 + b23 * rs2293889 + b24 * rs581080 + b25 * rs1883025 + b26 * rs3136441 + b27 * rs4759375 + b28 * rs4765127 + b29 * rs838880 + b30 * rs2652834 + b31 * rs16942887 + b32 * rs11869286 + b33 * rs7241918 + b34 * rs12967135 + b35 * rs7255436 + b36 * rs386000 + b37 * rs181362 + b38 * rs13107325 + ϵ_i

Platform

- Multi-Ethnic Global Array (MEGA)
- Imputation with 1000 Genomes Phase III Ad Mixed American (AMR) reference sample.

Sample descriptive statistics

	Chile		Finland	
Measure	**n=263**	**n=283**	**n=661**	**n=555**
log(TG (mmol/l))	1.44 (0.53)	1.38 (0.6)	0.900 (0.37)	0.911 (0.39)
LDL-C (mmol/l)	5.26 (1.55)	5.02 (1.53)	3.07 (0.79)	2.91 (0.79)
HDL-C (mmol/l)	2.3 (0.77)	2.05 (0.66)	1.55 (0.29)	1.34 (0.24)
TC (mmol/l)	8.55 (1.79)	7.96 (1.65)	5.02 (0.89)	4.67 (0.84)
Age (years)	16.77 (0.3)	16.76 (0.31)	18	18
BMI (kg/m2)	23.25 (5.33)	22.31 (5.12)	–	–
HDL wGRS	33.13 (3.47)	33.20 (3.42)	32.46 (3.36)	32.62 (3.41)
LDL wGRS	39.96 (6.38)	39.81 (6.40)	42.1 (6.60)	41.9 (6.90)
TG wGRS	138.84 (17.33)	138.32 (17.40)	132.71 (16.81)	131.91 (15.72)

Note: Triglycerides (TG) are log transformed in all analyses.

Four of the seven association tests were nominally statistically significant.

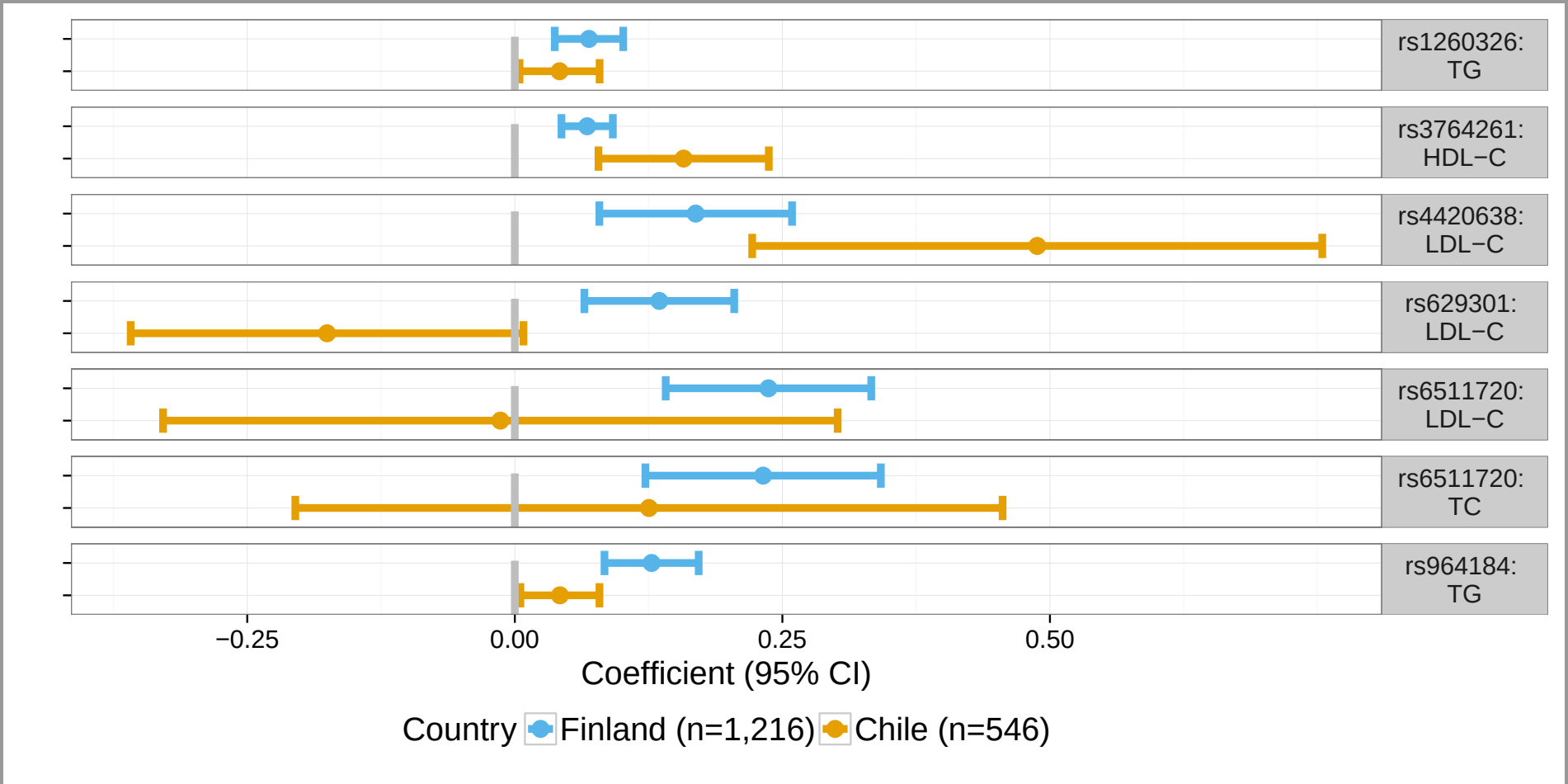
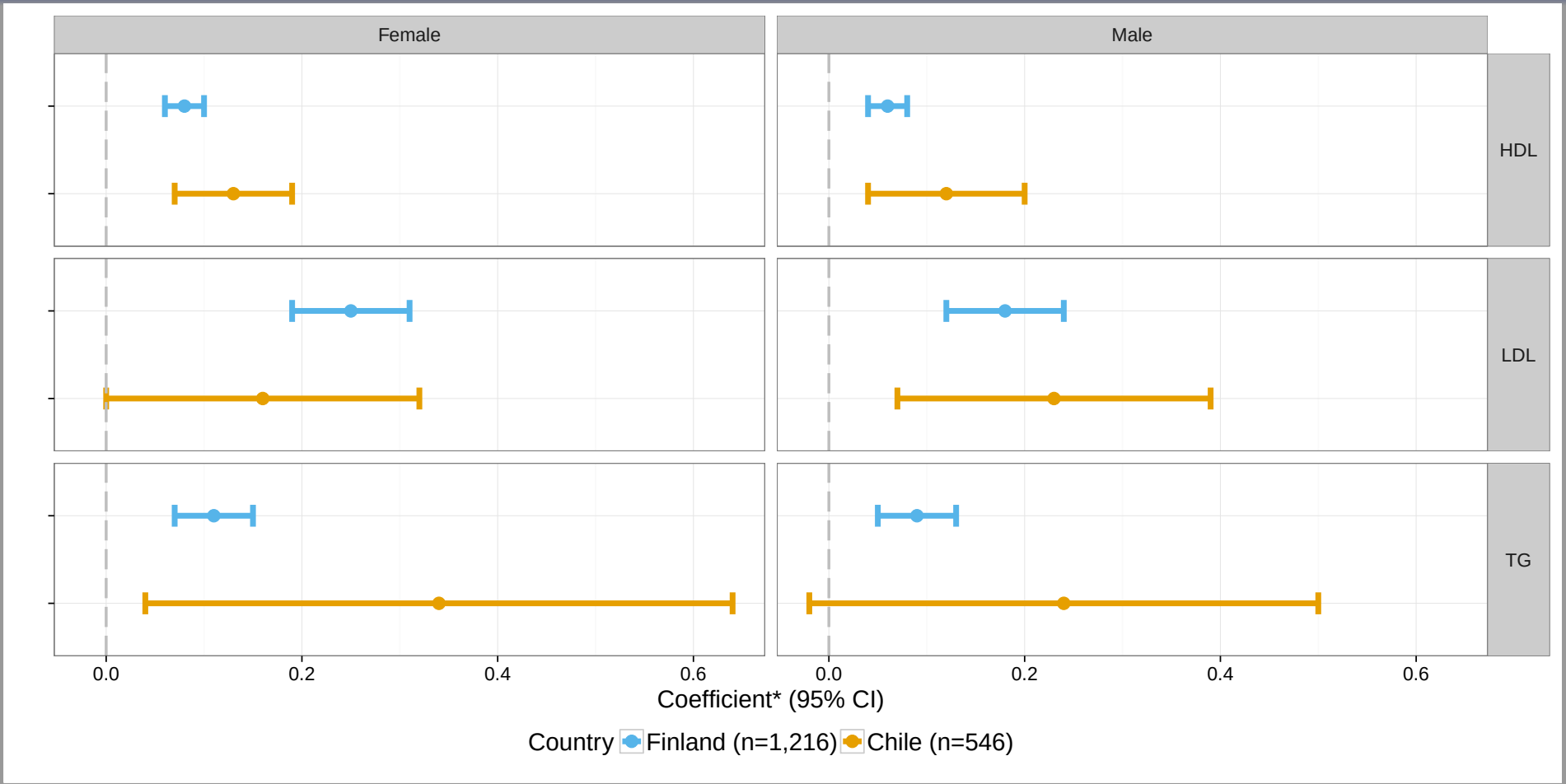


Figure 1. Candidate single variant tests of association by variant and sample

wGRS has stronger association for each lipid outcome in Chilean versus Finnish sample except LDL-C.



*Coefficients represent change in outcome per 1 SD change in wGRS, adjusted for first five principal components representing ancestry.

Figure 2. wGRS regression coefficients by sample and sex

LDL-C-related variants explain much less variance in Chilean sample.

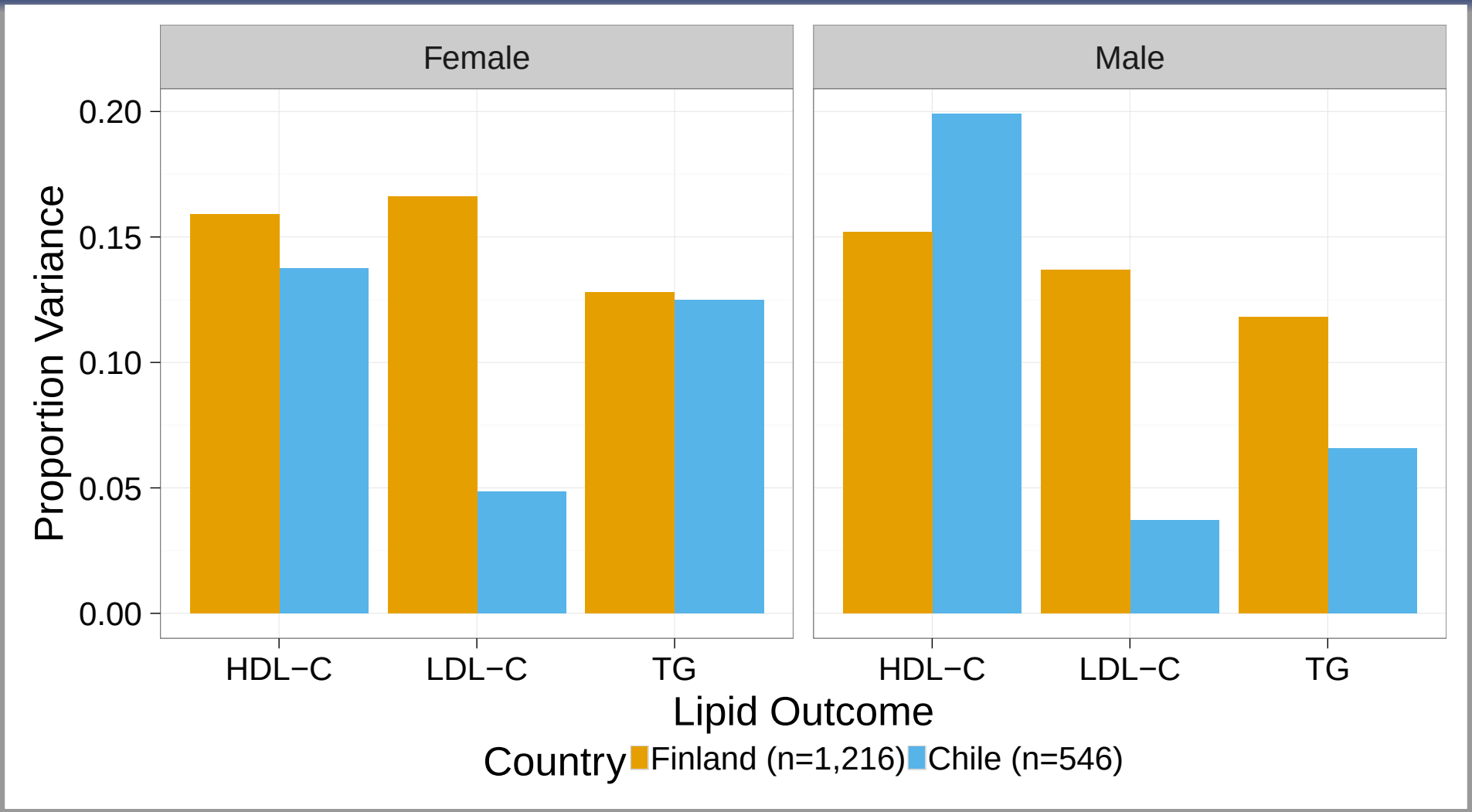


Figure 3. Proportion of lipid traits variance explained by lipid-related variants, by sex

Summary

- We found meaningful and statistically significant associations relating lipid loci in a HL cohort of Chilean adolescents despite the potential for bias given different haplotype structures across populations.
- Significant associations support concordance of effects across European and HL populations found in adults for these loci[9].
- LDL-C associations are not statistically significant although selections based on power under assumptions of European effect size.
  - Possibility that either linkage disequilibrium or different causal variant is responsible for the failure to detect a difference[10].
- Genetic risk evident in childhood presents across different populations, emphasizing younger ages as a point for intervention.

[9] D. Weissglas-Volkov et al. "Genomic study in Mexicans identifies a new locus for triglycerides and refines European lipid loci". In: *Journal of Medical Genetics* 50.5 (May 2013), pp. 298–308. DOI: 10.1136/jmedgenet-2012-101461.

[10] J. E. Below and E. J. Parra. "Genome-Wide Studies of Type 2 Diabetes and Lipid Traits in Hispanics". In: *Current Diabetes Reports* 16.5 (May 2016). DOI: 10.1007/s11892-016-0737-3.