The Association of Leg Length with Metabolic Abnormalities Underlying Type 2 Diabetes Mellitus: The PROMISE Cohort

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Introduction

- Early life deprivation has been associated with the development of type 2 diabetes mellitus (T2DM) [1]. Leg length is the component of stature that predominately grows during the early childhood period (0–4 years) [2]. Adverse conditions during early childhood have been associated with shorter adult leg length [3, 4], and thus leg length is used as a marker of early childhood conditions.
- Shorter leg length has been associated with T2DM [5, 6] and HOMA-IR [7]. Few studies have looked at insulin resistance and none have studied β-cell dysfunction.

Objectives & Hypothesis

- **Objective:** i) To determine the cross-sectional association of leg length with insulin resistance and β-cell dysfunction in adults at-risk for diabetes and ii) to determine the interaction between leg length and waist circumference
- **Hypothesis:** i) Shorter legs will be associated with greater insulin resistance and β-cell dysfunction and ii) short legs and a large waist in combination will be associated with poorest metabolic profile.

Methods

- Data were utilized from the 3-yr visit (2007–2009) of the longitudinal observational PROspective Metabolism and ISlet cell Evaluation (PROMISE) cohort. Subjects with $\geq$ 1 risk factors for diabetes were recruited from Toronto and London, Ontario. Only subjects without diabetes at the 3-yr visit were included in the analysis (n=462).
- Subjects underwent an 8–12hr fasting oral glucose tolerance test (OGTT) with blood samples taken at 0, 30, and 120 minutes. These samples allowed for the calculation of insulin resistance (HOMA-IR and the Matsuda Insulin Sensitivity Index (ISI) based on the OGTT) and β-cell function (Insulogenic Index over HOMA-IR (IGI/IR) and Insulin Secretion Sensitivity Index 2 (ISSI-2)).
- Height, weight, sitting height, and natural waist circumference were measured. Leg length was calculated by subtracting sitting height from height. Leg-to-height ratio was calculated by dividing leg length by height.
- Standardized questionnaires obtained sociodemographic and lifestyle information.
- Statistical analysis involved multiple linear regression analysis adjusted for covariates.

Results: Basic characteristics

Basic characteristics of participants from the PROMISE cohort at the 3-yr visit (2007–2009).

(a)

	N (%)
Female	336 (72.7)
Caucasian	330 (71.4)
Hispanic	60 (13)
South Asian	27 (5.8)
Other ethnicity	45 (9.7)
IFG	23 (5.0)
IGT	86 (18.6)
NGT	353 (76.4)

(b)

	Mean (SD)
Age (y)	53.57 (9.69)
BMI (kg/m^2)	31.31 (6.41)
Weight (kg)	86.3 (19.43)
WC (cm)	98.79 (15.32)
Height (cm)	165.84 (9.1)
SH (cm)	88.2 (4.53)
LL (cm)	77.66 (5.66)
LHR	0.468 (0.015)

(c)

	Median (IQR)
FG (mmol/L)	5.2 (4.8-5.6)
2-hr G (mmol/L)	6 (5-7.4)
FI (pmol/L)	69 (44-103)
2-hr I (pmol/L)	344 (203-628)
HOMA-IR	2.21 (1.39-3.57)
ISI	4.73 (2.95-7.72)
ISSI-2	639 (518-845)
IGI/IR	7.86 (4.89-14.12)

Note: IFG = impaired fasting glucose, IGT = impaired glucose tolerance, NGT = normal glucose tolerance, WC = waist circumference, SH = sitting height, LL = leg length, LHR = leg-to-height ratio, FG = fasting glucose, G = glucose, FI = fasting insulin, I = insulin.

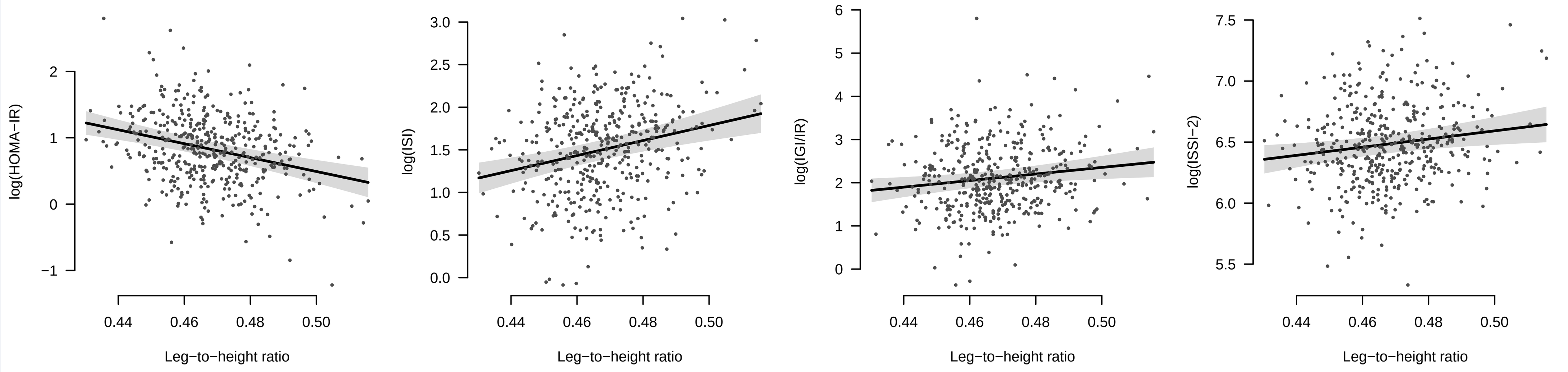
Results: Regression Analysis

Linear regression models showing associations of height, sitting height, leg length, and leg-to-height ratio with insulin sensitivity and β-cell function measures from non-diabetic PROMISE subjects at the 3-yr visit (2007–2009), adjusted for covariates.

	Height		Sitting height		Leg length		Leg-to-height ratio	
	β (SE)	*p*-value	β (SE)	*p*-value	β (SE)	*p*-value	β (SE)	*p*-value
Insulin Resistance/Sensitivity								
HOMA-IR								
Model 1	-0.005 (0.005)	0.37	0.010 (0.01)	0.33	**-0.016 (0.008)**	**0.04**	**-6.98 (2.44)**	**0.005**
Model 2	-0.005 (0.005)	0.30	0.010 (0.01)	0.33	**-0.018 (0.008)**	**0.03**	**-7.50 (2.47)**	**0.003**
Model 3	-0.002 (0.005)	0.63	0.017 (0.01)	0.10	-0.014 (0.008)	0.06	**-7.44 (2.43)**	**0.002**
Model 4	**-0.019 (0.005)**	**<0.0001**	0.001 (0.009)	0.91	**-0.037 (0.007)**	**<0.0001**	**-10.49 (1.94)**	**<0.0001**
ISI								
Model 1	0.009 (0.005)	0.07	0.002 (0.01)	0.87	**0.019 (0.007)**	**0.01**	**5.92 (2.35)**	**0.01**
Model 2	0.010 (0.005)	0.06	0.002 (0.01)	0.88	**0.020 (0.008)**	**0.01**	**6.33 (2.40)**	**0.01**
Model 3	0.007 (0.005)	0.18	-0.005 (0.01)	0.64	**0.017 (0.007)**	**0.02**	**6.18 (2.35)**	**0.01**
Model 4	**0.021 (0.005)**	**<0.0001**	0.006 (0.01)	0.50	**0.035 (0.007)**	**<0.0001**	**8.83 (1.97)**	**<0.0001**
β-Cell Function								
IGI/IR								
Model 1	-0.010 (0.007)	0.14	**-0.030 (0.013)**	**0.02**	-0.003 (0.01)	0.76	4.04 (3.17)	0.20
Model 2	-0.008 (0.007)	0.28	**-0.029 (0.013)**	**0.03**	0.001 (0.01)	0.92	5.00 (3.27)	0.13
Model 3	-0.010 (0.007)	0.15	**-0.035 (0.014)**	**0.01**	-0.001 (0.01)	0.93	5.12 (3.27)	0.12
Model 4	0.005 (0.007)	0.50	-0.017 (0.014)	0.23	**0.021 (0.01)**	**0.05**	**7.60 (3.01)**	**0.01**
ISSI-2								
Model 1	-0.005 (0.003)	0.10	**-0.013 (0.006)**	**0.02**	-0.003 (0.004)	0.56	1.26 (1.38)	0.37
Model 2	-0.004 (0.003)	0.15	**-0.013 (0.006)**	**0.02**	-0.001 (0.005)	0.82	1.82 (1.42)	0.20
Model 3	-0.005 (0.003)	0.08	**-0.016 (0.006)**	**0.01**	-0.002 (0.005)	0.68	1.84 (1.43)	0.20
Model 4	0.003 (0.003)	0.37	-0.006 (0.006)	0.30	**0.010 (0.004)**	**0.03**	**3.34 (1.27)**	**0.01**

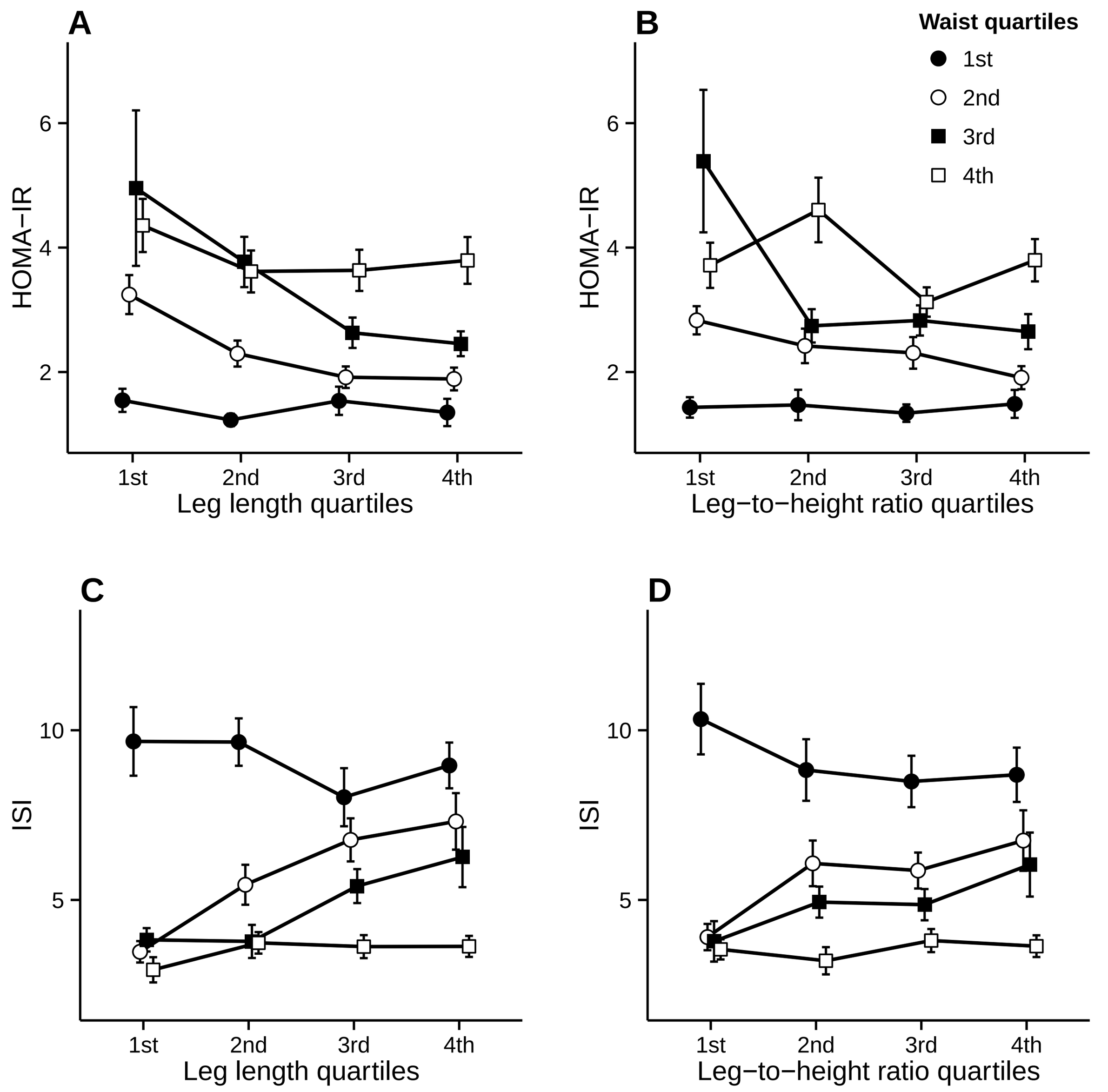
$n = 413 - 422$ in Model 4. Outcome variables were log transformed. Model 1: Age, sex, and ethnicity. Model 2: Model 1 plus socioeconomic status (occupation and education) and parental education. Model 3: Model 2 plus presence of other chronic diseases (i.e. cancer, stroke, history of myocardial infarction, PCOS, hypertension, kidney/thyroid/peripheral arterial disease, and/or known high cholesterol) and family history of diabetes. Model 4: Model 3 plus weight and waist circumference.

Results: Partial Residual Plots



Partial residual plots of the model 4 association of leg-to-height ratio with insulin resistance/sensitivity and β-cell function.

Results: Interaction Plot



There was a significant interaction of leg length on the association of waist circumference with measures of insulin sensitivity (all $p < 0.025$), adjusted for sex, ethnicity, and age. Points are means with standard error bars. Lines within the plots depict quartiles of waist circumference. Leg length and leg-to-height ratio are in quartiles (A) HOMA-IR with leg length, (B) HOMA-IR with leg-to-height ratio, (C) ISI with leg length quartiles, and (D) ISI with leg-to-height ratio. Waist size ranges are, by quartile: 60.0-88.3 cm (1st), 88.4-98.9 cm (2nd), 99.0-108.0 cm (3rd), 108.1-141.0 cm (4th). Leg length ranges are, by quartile: 63.6-73.7 cm (1st), 73.8-77.0 cm (2nd), 77.1-81.5 cm (3rd), 81.6-94.5 cm (4th). Leg-to-height ratio ranges are, by quartile: 0.430-0.457 (1st), 0.458-0.466 (2nd), 0.467-0.476 (3rd), 0.477-0.516 (4th).

Conclusions

We found that shorter leg length was associated with greater insulin resistance and β-cell dysfunction. Since leg length is a marker of early childhood conditions, this finding suggests that early childhood deprivation may result in decreased insulin sensitivity and β-cell function. In addition, the combination of shorter legs and a larger waist was associated with the poorest insulin sensitivity. The implications of these findings are that improving early childhood conditions may decrease the risk for developing diabetes.

Acknowledgements

- LWJ received a University of Toronto Banting and Best Diabetes Centre Travel Award and an Ontario Graduate Scholarship.
- This study is supported by grants from the Canadian Diabetes Association and the Connaught Fund from the University of Toronto.

Canadian Diabetes Association

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