

# BMJ Open Cross-sectional associations between dietary intake and carotid intima media thickness in type 2 diabetes: baseline data from a randomised trial

Laura Chiavaroli,<sup>1,2</sup> Arash Mirrahimi,<sup>2,3</sup> Christopher Ireland,<sup>1,2</sup> Sandra Mitchell,<sup>1,2</sup> Sandhya Sahye-Pudaruth,<sup>1,2</sup> Judy Coveney,<sup>2</sup> Omodele Olowoyeye,<sup>4,5</sup> Darshna Patel,<sup>1,2</sup> Russell J de Souza,<sup>2,6,7</sup> Livia S A Augustin,<sup>2,8</sup> Balachandran Bashyam,<sup>1,2</sup> Sathish Chandra Pichika,<sup>2</sup> Sonia Blanco Mejia,<sup>1,2</sup> Stephanie K Nishi,<sup>1,2</sup> Lawrence A Leiter,<sup>1,2,7,9</sup> Robert G Josse,<sup>1,2,7,9</sup> Gail E McKeown-Eyssen,<sup>1,10</sup> Alan R Moody,<sup>4,5</sup> Cyril W C Kendall,<sup>1,2,11</sup> John L Sievenpiper,<sup>1,2,7,9</sup> David J A Jenkins<sup>1,2,7,9</sup>

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For numbered affiliations see end of article.

#### Correspondence to

Dr David J A Jenkins;  
[nutritionproject@smh.ca](mailto:nutritionproject@smh.ca)

#### ABSTRACT

**Objective:** To assess associations between dietary intake and carotid intima media thickness (CIMT) by carotid ultrasound (CUS), a surrogate marker of cardiovascular disease (CVD) risk, in those with type 2 diabetes.

**Design:** Cross-sectional analysis of baseline data from 325 participants from three randomised controlled trials collected in the same way.

**Setting:** Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Canada.

**Participants:** 325 participants with type 2 diabetes, taking oral antidiabetic agents, with an HbA1c between 6.5% and 8.0% at screening, without a recent cardiovascular event.

**Main outcome measures:** CIMT by CUS and associations with dietary intake from 7-day food records, as well as anthropometric measures and fasting serum samples.

**Results:** CIMT was significantly inversely associated with dietary pulse intake ( $\beta=-0.019$ ,  $p=0.009$ ), available carbohydrate ( $\beta=-0.004$ ,  $p=0.008$ ), glycaemic load ( $\beta=-0.001$ ,  $p=0.007$ ) and starch ( $\beta=-0.126$ ,  $p=0.010$ ), and directly associated with total ( $\beta=0.004$ ,  $p=0.028$ ) and saturated ( $\beta=0.012$ ,  $p=0.006$ ) fat intake in multivariate regression models adjusted for age, smoking, previous CVD event, blood pressure medication, antidiabetic medication and ultrasonographer.

**Conclusions:** Lower CIMT was significantly associated with greater consumption of dietary pulses and carbohydrates and lower total and saturated fat intake, suggesting a potential role for diet in CVD risk management in type 2 diabetes. Randomised controlled trials are anticipated to explore these associations further.

**Trial registration number:** NCT01063374.

#### Strengths and limitations of this study

- A strength of the study methods includes the use of carotid intima media thickness (CIMT) by carotid ultrasound, which is the recommended screening tool for assessing cardiovascular disease (CVD) risk by some CVD prevention clinical practice guidelines, considered a biomarker of atherosclerosis and is associated with overall CVD risk, particularly in those with type 2 diabetes.
- The CIMT scans were all performed by one of two highly trained ultrasonographers using the same scanner at the same site and using the same reading protocol.
- The dietary data are obtained from 7-day dietary food records in which participants were trained on how to complete by study dietitians and which at each visit were reviewed in detail by study dietitians in the presence of the participant.
- A limitation of the analyses includes that they are conducted using CIMT results from only one CIMT scan obtained at baseline; however, studies have demonstrated mean max CIMT measurements to have good reproducibility, particularly using the method we adopted where measurements are made of 12 segments of the carotid artery.
- Although at higher CVD risk, participants in this study had relatively well-controlled diabetes, blood pressure and low-density lipoprotein cholesterol, with the majority on blood pressure and cholesterol-lowering medication at baseline, therefore possibly limiting the ability to assess associations between risk factors for CVD and CIMT and dietary intake, as well as limiting application to those with uncontrolled risk factors.

## INTRODUCTION

People with type 2 diabetes are at high risk of cardiovascular disease (CVD), the leading cause of death in this population.<sup>1 2</sup> Risk assessment through atherosclerosis imaging includes the use of carotid intima media thickness (CIMT) by carotid ultrasound (CUS), the recommended screening tool for assessing CVD risk by some CVD prevention clinical practice guidelines.<sup>3 4</sup> CIMT is considered a biomarker of atherosclerosis and is associated with overall CVD risk, particularly in those with type 2 diabetes.<sup>5 6</sup> Observational studies have recently demonstrated that carotid atherosclerosis, assessed by CIMT, is associated with glycaemic status<sup>7–9</sup> and intervention trials with antidiabetic agents have demonstrated reductions in CIMT both in those with and without diabetes.<sup>10–12</sup> Some of these antidiabetic agents exert their effect postprandially, by reducing the postprandial blood glucose peak. Trials of insulin secretagogues (nateglinide and repaglinide) and the  $\alpha$ -glucosidase inhibitor, acarbose, have demonstrated reductions in CIMT and identified markers of glycaemia (HbA1c and glucose peak) as determinants of changes in CIMT.<sup>10 13–15</sup>

In addition to antidiabetic drugs, dietary strategies continue to be sought as means to assist in diabetes management. However, few dietary intervention trials have explored the effect on CIMT. These have demonstrated regression of CIMT with a Mediterranean diet pattern.<sup>16</sup> Dietary strategies that may be useful for diabetes management, including low-GI (low-glycaemic index) diets<sup>17 18</sup> and those rich in dietary pulses,<sup>19 20</sup> have demonstrated associations with improved CVD risk,<sup>21</sup> thus warrant exploration of their effects on CIMT as a subclinical biomarker of CVD.

The objective of the present study was to determine the associations between dietary intake variables, particularly GI, and risk of CVD assessed by CIMT in participants with type 2 diabetes.

## METHODS

### Participants

Details of the study protocol have been previously published.<sup>22</sup> Participants recruited for a 3-year dietary intervention study had a diagnosis of type 2 diabetes >6 months prior to the start of the study, an HbA1c between 6.5% and 8.0% at screening, were on oral antidiabetic agents at a stable dose for  $\geq 8$  weeks, not on insulin, without gastrointestinal disease, clinically significant liver disease or history of cancer, except non-melanoma skin cancer, and had not had a major cardiovascular event or major surgery in the past 6 months. Participants also had a CUS scan at the Medical Imaging Department at Sunnybrook Health Sciences Centre to assess CIMT as part of screening criteria, where only those participants with a maximum CIMT  $\geq 1.2$  mm were eligible for the 3-year study. Those who did not meet this CIMT cut-point had the option to participate in one of two concurrent trials of

shorter duration, the details of which have been published.<sup>23 24</sup> This cross-sectional study was conducted on 325 study participants using baseline data from these three trials, all of which had the same inclusion criteria (with the exception of the additional criteria of a maximum CIMT  $\geq 1.2$  mm for the 3-year trial) and included 7-day food records, anthropometric measures, fasting blood samples and CIMT measures which were collected in the same way.

Written consent was obtained from all participants.

### Design

In this cross-sectional analysis, data were obtained from baseline measures of study participants including CIMT data obtained from CUS scans completed at the Medical Imaging Department at the Sunnybrook Health Sciences Centre MRI research unit. One of two highly trained and certified sonographers performed CIMT measures using a Philips iU22 Ultrasound system (Philips Healthcare, Andover, Massachusetts, USA) with standardised CUS scanning and reading protocols.<sup>25 26</sup> CIMT was measured with the subject recumbent, with the neck extended and rotated away from the side of interest. As previously described,<sup>22</sup> imaging was performed on the right and left carotid arteries, with identification of the near wall (closest to the skin surface) and the far wall (farthest from the skin surface) of three arterial segments: the proximal 8 mm of the internal carotid artery, the carotid bifurcation beginning at the tip of the flow divider (site of the division of flow between the external carotid artery and internal carotid artery) and extending 8 mm proximally, and the common carotid artery 8–16 mm proximal to the flow divider, and measurements included posterior wall plaque, if present. The mean value of the 12 maximal CIMT measurements (mean maximum CIMT) was used as the outcome measure, which has demonstrated good reproducibility (interclass correlation coefficient (ICC)  $>0.8$ ).<sup>27</sup>

For participant baseline data on risk factors, all three studies included two baseline clinic visits at the Risk Factor Modification Centre, St. Michael's Hospital and occurred within 1 month of each other. At the first, baseline anthropometric and fasting blood measures were obtained. Participants were given detailed instruction on how to complete a 7-day food record which was returned at the next visit. At the second baseline clinic visit, anthropometric and fasting blood measures were again obtained and each participant was randomised. Anthropometric data included body weight, seated blood pressure measured as the mean of triplicate measures made with an automatic sphygmomanometer (Omron HEM 907 XL, OMRON Healthcare, Burlington, Ontario, Canada), and waist (at the umbilicus, 2 inches above and lying down) and hip circumference. Blood measures included HbA1c, fasting glucose and fasting lipids. Data were also obtained on demographics including age, sex, estimated duration of diabetes, smoking and medication use.

For those who participated in more than one of the three studies (n=14), their first CUS and corresponding baseline study measurements were used in the present analyses.

### Biochemical and dietary analyses

The HbA1c value was analysed within 24 hours using whole blood collected in EDTA Vacutainer tubes (Vacutainer; Becton, Dickinson and Co) in the hospital routine analytical laboratory by a turbidimetric inhibition latex immunoassay (TINIA Roche Diagnostics) with a coefficient of variation between assays of 3–4%. Blood glucose and serum lipid levels were also measured in the hospital routine analytical laboratory using a Random Access Analyzer and Beckman reagents (SYNCHRON LX Systems; Beckman Coulter), with a coefficient of variation of 1.6–2.3% for blood glucose level and 1.3–3.0% for total cholesterol (total-C), triglycerides, and high-density lipoprotein cholesterol (HDL-C) levels. The low-density lipoprotein cholesterol (LDL-C) level was calculated by the method of Friedewald *et al.*<sup>28</sup> ( $\text{LDL-C level} = \text{total-C} - [(\text{triglycerides}/5) \times (\text{HDL-C level})]$ ).

Dietary assessments using participant completed 7-day food records were analysed using a computer program (ESHA Food Processor SQL V.10.9; ESHA, Salem, Oregon, USA) based on the USDA database,<sup>29</sup> supplemented with data from the Canada Nutrient File,<sup>30</sup> and with GI values from international GI tables<sup>31</sup> using the bread scale (where bread=100; for the glucose scale, multiply by 0.71). Glycaemic load (GL) was calculated as  $\text{GI} \times \text{available carbohydrate} \div 100$ . Product data were updated with manufacturers' nutrient information and relevant foods were analysed by Covance Laboratories (3301 Kinsman Blvd, Madison Wisconsin, USA). Owing to interest in GI, in addition to general dietary variables, data on particularly low-GI foods, which we and others had previously demonstrated to have benefit in diabetes management,<sup>23 32 33</sup> were extracted from the food records, including dietary pulses, temperate climate fruit and nut intake.

### Statistical analyses

These are post hoc analyses performed on all baseline study participants who had a CUS scan (n=325). The original power calculation was based on the main intervention trial. However, we performed post hoc sample size calculations to assess our ability to detect associations of GI and CIMT. Given the slope of  $-0.210$  for GI and CIMT, the SD of our log transformed GI of 0.075, the SD of our Box-Cox transformed CIMT of 0.229, and with 80% power and  $\alpha=0.05$ , to detect an association, we would need a sample size of 1640. This may be a reflection of our lack of range of exposure levels of GI at baseline (range: 58–98 and IQR: 76–83, bread scale). We have also calculated a post hoc sample size for dietary pulses, as a particularly low-GI food which we previously demonstrated to have benefit on CVD risk factors in diabetes,<sup>23</sup> given a slope of  $-0.025$  for dietary pulses and

CIMT, and an SD of our log transformed dietary pulses of 1.592, 254 participants would have been sufficient to detect an association at  $\alpha=0.05$ ,  $1-\beta=0.80$ . Data are expressed as means $\pm$ SD unless otherwise indicated. Multivariate mixed-effects regression models were conducted using SAS software, V.9.4 (SAS Institute: SAS/STAT Proprietary Software 9.4. Cary, NC: SAS Institute; 2002–2012.) to assess the association between dietary intake and CIMT. Dietary variables were energy adjusted by expressing intake as g/1000 kcal or as a percentage of energy. To adjust for energy in GI and GL analyses, total caloric intake was added to the models as a continuous variable. All dietary variables were analysed as continuous variables. Sensitivity analyses were performed where energy was alternatively adjusted for using the residual method. Since there are multiple potential confounders with CIMT, including age, sex, smoking, prior CVD event, cholesterol medication use, blood pressure medication use, duration of diabetes, type of antidiabetic medication and waist circumference, we included only those that were significantly associated with CIMT in our data set (at  $p<0.1$ ). Therefore, the multivariate model was adjusted for age, smoking, previous CVD event, blood pressure medication and type of antidiabetic medication. Smoking was defined using three categories: current (current smoker or quit within the past year), former (quit between 1 and 15 years ago), and non-smoker (never smoked, or quit over 15 years ago) according to the WHO definitions of coronary heart disease (CHD) risk.<sup>34</sup> Previous CVD event was defined as yes or no. Use of blood pressure-lowering medication was defined as user or non-user based on the baseline visits. Type of antidiabetic medication was defined as user of a sulfonylurea or thiazolidinediones or non-user since these have been demonstrated to have potential negative associations with CVD risk.<sup>13 35 36</sup> Of the 325 participants with a CIMT measurement and who were randomised into one of the three studies, one participant did not attend their week 0 visit, thus did not have dietary data. Overall 10-year CVD risk was calculated using the Framingham risk score according to the 2008 Framingham cardiovascular risk equation.<sup>37</sup> Ultrasonographer, another potential confounder, was treated as a random effect throughout analyses. CIMT was non-normally distributed, therefore was transformed using the Box-Cox transformation.<sup>38</sup> The  $\lambda$  for CIMT was  $-1$ , thus,  $(\text{CIMT}^{-1}-1)/-1$  was used for the transformation. Dietary variables were transformed using the natural logarithm in models where the model fit improved (adjusted R-squared increased) in the adjusted model when being regressed against transformed CIMT. The transformed dietary variables include: GI, dietary pulses, temperate climate fruit, dietary fibre, viscous fibre, cereal fibre, starch, monounsaturated fatty acids, omega 3 fatty acids, dietary cholesterol and vegetable protein. Thus, these dietary variables were transformed as  $\ln[\text{g}/1000 \text{ kcal (or \% kcal)} + 1]$ . Probability values  $<0.05$  were considered statistically significant.

## RESULTS

Characteristics of the 325 study participants are presented in [table 1](#). The average mean maximum CIMT was  $1.0\pm 0.3$  mm and maximum CIMT was  $2.0\pm 0.9$  mm. The mean age for all participants was  $60.3\pm 8.7$  years, 56% were male, the mean body mass index (BMI) was  $30.3\pm 5.7$  kg/m<sup>2</sup>, and the mean waist circumference was  $105.5\pm 15.0$  cm in females and  $104.1\pm 12.3$  cm in males. Fifteen participants (4.6%) had a previous CVD event, 84.6% non-smokers, 10.2% former smokers and 5.2% were current smokers. Of the participants, 72.3% were

taking cholesterol-lowering and 66.5% blood pressure-lowering medications.

### CIMT and baseline dietary intake

The associations between CIMT and dietary variables using multivariate regression models are presented in [table 2](#). CIMT was significantly inversely associated with GL ( $\beta=-0.001$ ,  $p=0.007$ ), dietary pulses ( $\beta=-0.019$ ,  $p=0.009$ ), available carbohydrate ( $\beta=-0.004$ ,  $p=0.008$ ) and starch ( $\beta=-0.126$ ,  $p=0.010$ ), and positively associated with total fat ( $\beta=0.004$ ,  $p=0.028$ ) and saturated fat ( $\beta=0.012$ ,  $p=0.006$ ), in multivariate models. Sensitivity analyses using the residual model for energy adjustment, revealed consistent results (data not shown).

### CIMT and risk factors

CIMT was significantly positively associated with age ( $\beta=0.011$ ,  $p<0.001$ ; unadjusted), waist-to-hip ratio ( $\beta=0.529$ ,  $p=0.019$ ), systolic ( $\beta=0.004$ ,  $p<0.001$ ) and diastolic blood pressure ( $\beta=0.003$ ,  $p=0.035$ ), mean arterial pressure ( $\beta=0.005$ ,  $p=0.002$ ), pulse pressure ( $\beta=0.005$ ,  $p<0.001$ ), total:HDL-C ratio ( $\beta=0.027$ ,  $p=0.020$ ) and FRS ( $\beta=0.005$ ,  $p<0.001$ ), and inversely with pulse (as beats per minute) ( $\beta=-0.002$ ,  $p=0.047$ ) ([table 3](#)) in multivariate models. Non-smoking was associated with significantly lower CIMT when compared to current smokers ( $\beta=-0.160$ ,  $p=0.003$ ) and to former smokers ( $\beta=-0.094$ ,  $p=0.004$ ) ([table 3](#)).

### Post hoc explorations with CIMT

Further explorations were conducted using the multivariate model to predict how CIMT in a person consuming one serving of dietary pulses per day would compare to a person not consuming any. Data points were obtained by taking mean values for log dietary pulse intake in the regression equation (at 0 and 0.5 increments up to 5) and then back transforming the  $\beta$  estimates for the response variable (transformed CIMT). The predicted model of the association between CIMT and dietary pulse intake revealed a logarithmic association ([figure 1](#)) where approximately one  $\frac{3}{4}$  cup Canadian serving/day ( $\sim 132$  g/day)<sup>39</sup> was associated with a 7.5% lower CIMT compared with no intake (0 g/day) (0.078 mm CIMT difference). The same was conducted for saturated fat which demonstrated a linear association where for every 1% of total calorie increase in saturated fat, CIMT was about 0.011 mm greater (see online supplementary figure S1).

To explore the association with starch further, each major source of starch in the diet was assessed, including potato, pasta, rice, bread and pulses. Grams of starch from each carbohydrate source were calculated using the following foods: boiled white potato, cooked macaroni for pasta, long grain rice, white and whole wheat bread, and the average starch from three beans (chickpea, black bean and kidney bean) and lentils. Starch from each source was expressed as a percentage of total calories (%kcal) for each variable in the model. All other sources were pooled (other starch). All starch

**Table 1** Participants characteristics

Participant characteristics (n=325)	Mean $\pm$ SD
Mean max bilateral CIMT, mm	1.0 $\pm$ 0.3
Max CIMT, mm	2.0 $\pm$ 0.9
Age, y	60.3 $\pm$ 8.7
Sex, female/male	142/183
Estimated diabetes duration, y	8.2 $\pm$ 6.1
Body weight, kg	84.3 $\pm$ 18.2
BMI, kg/m <sup>2</sup>	30.3 $\pm$ 5.7
Waist circumference, cm*	104.7 $\pm$ 13.5
Waist:hip ratio	1.0 $\pm$ 0.1
Systolic blood pressure, mm Hg	122.2 $\pm$ 11.2
Diastolic blood pressure, mm Hg	71.6 $\pm$ 8.2
Mean arterial pressure, mm Hg	88.5 $\pm$ 8.2
Pulse, bpm	71.9 $\pm$ 9.6
Pulse pressure, mm Hg	50.8 $\pm$ 10.0
Fasting glucose, mmol/L	7.5 $\pm$ 1.5
HbA1c, %	7.1 $\pm$ 0.5
Total-C mmol/L	4.0 $\pm$ 1.0
HDL-C mmol/L	1.2 $\pm$ 0.3
LDL-C mmol/L	2.2 $\pm$ 0.8
Serum triglycerides, mmol/L	1.5 $\pm$ 0.9
Total:HDL-C ratio	3.6 $\pm$ 1.0
Non-HDL-C, mmol/L	2.9 $\pm$ 0.9
CVD risk, FRS	19.5 $\pm$ 11.3
Previous CVD event, %	4.6
Smoking	
Non-smoker, %	84.6
Former, %	10.2
Current, %	5.2
Diabetes meds—sulfonylurea or TZD %	37.5
Cholesterol meds, %	72.3
Blood pressure meds, %	66.5
Ethnicity, %	
African	6.8
European	32.3
Far Eastern	8.9
Hispanic	1.9
Indian/South Asian	22.8
Other Caucasian	19.7
Other	20.0

\*Measured at the umbilicus.

BMI, body mass index; bmp, beats per minute; CIMT, carotid intima media thickness; CVD, cardiovascular disease; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; meds, medication use; Total-C, total cholesterol; TZD, thiazolidinediones; y, years.

**Table 2** Dietary intake and associations with carotid intima media thickness

Dietary intake* and association with CIMT (n=324)	Mean±SD	Unadjusted†			Age adjusted†			Multivariate‡		
		β	SE	p Value	β	SE	p Value	β	SE	p Value
GI§¶**	79.0±5.9	-0.210	0.172	0.222	-0.084	0.159	0.597	-0.138	0.157	0.381
GL**††	149.9±46.8	-0.001	0.000	<b>0.010</b>	-0.001	0.000	<b>0.015</b>	-0.001	0.000	<b>0.007</b>
Dietary pulses, g/1000 kcal§	18.7±29.9	-0.025	0.008	<b>0.002</b>	-0.019	0.008	<b>0.014</b>	-0.019	0.007	<b>0.009</b>
Nuts, g/1000 kcal	7.0±9.0	-0.001	0.001	0.507	-0.001	0.001	0.334	-0.001	0.001	0.313
Temperate climate fruit, g/1000 kcal§	45.9±42.0	0.015	0.009	0.101	0.004	0.009	0.643	0.004	0.008	0.638
Available carbohydrates, %	42.7±7.1	-0.004	0.002	<b>0.041</b>	-0.004	0.002	<b>0.010</b>	-0.004	0.002	<b>0.008</b>
Fibre, g/1000 kcal§	15.0±5.2	-0.008	0.042	0.853	-0.060	0.039	0.124	-0.048	0.038	0.211
Viscous fibre, g/1000 kcal§	0.4±0.8	0.021	0.038	0.587	-0.012	0.035	0.725	-0.015	0.034	0.668
Cereal fibre, g/1000 kcal§	3.6±3.0	0.016	0.020	0.430	0.004	0.018	0.835	0.011	0.018	0.540
Starch, %§	28.1±6.6	-0.154	0.054	<b>0.004</b>	-0.114	0.050	<b>0.025</b>	-0.126	0.049	<b>0.010</b>
Sugar, %	14.6±4.8	0.002	0.003	0.389	-0.002	0.003	0.386	-0.002	0.003	0.521
Total fat, %	32.8±6.3	0.003	0.002	0.165	0.004	0.002	<b>0.046</b>	0.004	0.002	<b>0.028</b>
SFA, %	10.0±2.7	0.012	0.005	<b>0.013</b>	0.012	0.004	<b>0.007</b>	0.012	0.004	<b>0.006</b>
MUFA, %§	12.9±3.4	0.037	0.053	0.487	0.057	0.052	0.273	0.059	0.048	0.223
PUFA, %	6.8±2.0	0.002	0.006	0.761	0.005	0.006	0.427	0.006	0.006	0.297
n-3, %§	0.9±0.5	0.039	0.058	0.500	0.007	0.053	0.901	0.022	0.053	0.679
n-6, %	5.7±1.7	0.004	0.007	0.631	0.007	0.007	0.292	0.008	0.007	0.210
Diet cholesterol, mg/1000 kcal§	139.9±57.1	0.026	0.021	0.234	0.022	0.020	0.255	0.020	0.019	0.310
Protein, %	18.9±3.2	0.005	0.004	0.182	0.005	0.004	0.187	0.005	0.004	0.174
Vegetable protein, %§	7.4±1.9	-0.071	0.059	0.230	-0.089	0.055	0.103	-0.096	0.053	0.072
Animal protein, %	2.4±2.2	0.005	0.003	0.104	0.005	0.003	0.071	0.006	0.003	0.058
Energy, kcal	1781.3±451.3	0.000	0.000	0.112	0.000	0.000	0.671	0.000	0.000	0.662
Sodium, mg/1000 kcal	1385.2±336.2	0.000	0.000	0.098	0.000	0.000	0.087	0.000	0.000	0.191
Alcohol, %	1.8±3.2	0.003	0.004	0.395	0.003	0.004	0.417	0.003	0.004	0.488

Bold values are <0.05 and thus statistically significant.

\*Percentages represent the percentage of total calories.

†Regression models assessing the association with CIMT where all dietary variables are analysed as continuous variables.

‡Adjusted for age, smoking, previous CVD event, blood pressure medication, antidiabetic medication and ultrasonographer.

§Log transformed where the model fit improved when regressed against CIMT.

¶GI bread scale (to convert to glucose scale, multiply by 0.71); low GI ≤78, medium GI 78–99, high GI ≥100.

\*\*Total caloric intake added to full model as a continuous variable to adjust for energy.

††GI multiplied by the mean total available carbohydrate intake per day divided by 100.

CIMT, carotid intima media thickness (mean max bilateral, average of the 12 segment measures); CVD, cardiovascular disease; GI, glycaemic index; GL, glycaemic load; MUFA, monounsaturated fatty acids; n-3, omega 3 fatty acids; n-6, omega 6 fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

**Table 3** Participant characteristics and associations with carotid intima media thickness

Participant characteristics (n=325)	Unadjusted*			Age adjusted*			Multivariate†		
	$\beta$	SE	p Value	$\beta$	SE	p Value	$\beta$	SE	p Value
Age, y	0.011	0.001	<0.001						
Sex (male vs female)	0.029	0.026	0.254	0.035	0.024	0.146	0.029	0.023	0.207
Estimated diabetes duration, y	0.002	0.002	0.322	-0.003	0.002	0.137	-0.003	0.002	0.117
Body weight, kg	0.000	0.001	0.960	0.001	0.001	0.088	0.001	0.001	0.155
BMI, kg/m <sup>2</sup>	-0.002	0.002	0.369	0.002	0.002	0.440	0.001	0.002	0.630
Waist circumference, cm‡	0.000	0.001	0.797	0.001	0.001	0.531	0.000	0.001	0.816
Waist:hip ratio	0.604	0.244	<b>0.014</b>	0.608	0.223	<b>0.007</b>	0.529	0.225	<b>0.019</b>
Systolic blood pressure, mm Hg	0.005	0.001	<0.001	0.004	0.001	<0.001	0.004	0.001	<0.001
Diastolic blood pressure, mm Hg	-0.002	0.002	0.323	0.002	0.002	0.165	0.003	0.001	<b>0.035</b>
Mean arterial pressure, mm Hg	0.002	0.002	0.123	0.004	0.001	<b>0.006</b>	0.005	0.001	<b>0.002</b>
Pulse, bpm	-0.004	0.001	<b>0.003</b>	-0.002	0.001	<b>0.043</b>	-0.002	0.001	<b>0.047</b>
Pulse pressure, mm Hg	0.009	0.001	<0.001	0.005	0.001	<0.001	0.005	0.001	<0.001
Fasting glucose, mmol/L	0.001	0.009	0.934	0.006	0.008	0.488	0.004	0.008	0.573
HbA1c, %	-0.021	0.025	0.414	-0.001	0.023	0.954	-0.003	0.023	0.905
Total-C mmol/L	0.012	0.013	0.357	0.013	0.012	0.248	0.017	0.012	0.155
HDL-C mmol/L	0.018	0.045	0.687	-0.065	0.042	0.126	-0.057	0.041	0.165
LDL-C mmol/L	0.015	0.015	0.337	0.019	0.014	0.185	0.021	0.014	0.136
Serum triglycerides, mmol/L	0.001	0.015	0.956	0.017	0.014	0.205	0.020	0.013	0.140
Total:HDL-C ratio	0.004	0.012	0.760	0.026	0.012	<b>0.024</b>	0.027	0.011	<b>0.020</b>
Non-HDL-C, mmol/L	0.012	0.014	0.387	0.021	0.012	0.088	0.025	0.013	0.052
CVD risk, FRS	0.008	0.001	<0.001	0.005	0.001	<0.001	0.005	0.001	<0.001
Previous CVD event	-0.161	0.060	<b>0.008</b>	-0.104	0.056	0.064			
Non-smokers vs current smokers	-0.089	0.057	0.118	-0.160	0.053	<b>0.003</b>			
Non-smokers vs ever smokers	-0.072	0.035	<b>0.042</b>	-0.094	0.032	<b>0.004</b>			
Not vs on sulfonylurea or TZD	-0.043	0.026	0.105	-0.025	0.024	0.302			
Not vs on cholesterol meds	-0.041	0.028	0.152	-0.022	0.026	0.407	-0.022	0.026	0.416
Not vs on blood pressure meds	-0.050	0.027	0.065	-0.013	0.025	0.592			

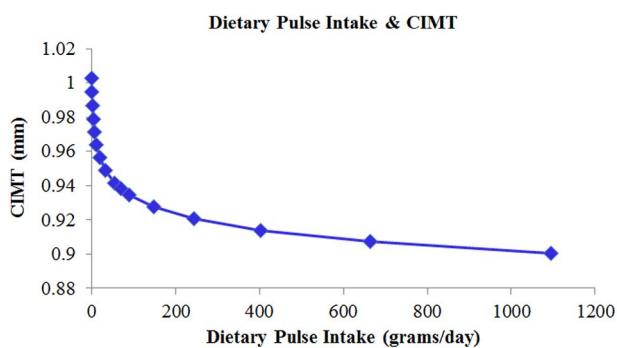
Bold values are <0.05 and thus statistically significant.

\*Regression models assessing the association with CIMT, where p<0.05 is considered statistically significant.

†Adjusted for age, smoking, previous CVD event, blood pressure medication, antidiabetic medication and ultrasonographer.

‡Measured at the umbilicus.

BMI, body mass index; bpm, beats per minute; CIMT, carotid intima media thickness (mean max bilateral, average of the 12 segment measures); CVD, cardiovascular disease; FRS, Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; meds, medication; Total-C, total cholesterol; TZD, thiazolidinediones; y, years.



**Figure 1** Model of association between dietary pulse intake and carotid intima media thickness (CIMT). The multivariate regression model is adjusted for age, smoking, previous cardiovascular disease (CVD) event, blood pressure medication, antidiabetic medication and ultrasonographer.

sources were added to the adjusted model and then removed as necessary using a backwards stepwise regression. Dietary pulse starch and rice starch were the only significant contributors to the negative association of

starch with CIMT ( $p=0.048$  and  $p=0.023$ , respectively) (table 4). Dietary pulse and rice intake were also highly positively correlated with each other ( $r=0.272$ ,  $p<0.001$ ).

Post hoc explorations were also conducted to assess associations between the metabolic profile of participants and all dietary variables (see online supplementary table S1). Of the dietary variables significantly associated with CIMT, greater intake of dietary pulses, carbohydrates, starch and GL and lower intake of fat and saturated fat were generally associated with lower body weight ( $r=-0.129$ ,  $p=0.021$ ;  $r=-0.210$ ,  $p<0.001$ ;  $r=-0.175$ ,  $p=0.002$ ;  $r=-0.157$ ,  $p=0.005$ ;  $r=0.202$ ,  $p<0.001$ ;  $r=0.321$ ,  $p<0.001$ , respectively), systolic blood pressure ( $r=-0.145$ ,  $p=0.009$ ;  $r=-0.141$ ,  $p=0.012$ ;  $r=-0.130$ ,  $p=0.020$ ;  $r=-0.143$ ,  $p=0.011$ ;  $r=0.063$ ,  $p=0.260$ ;  $r=0.030$ ,  $p=0.592$ , respectively), diastolic blood pressure ( $r=-0.172$ ,  $p=0.002$ ;  $r=-0.123$ ,  $p=0.028$ ;  $r=-0.135$ ,  $p=0.016$ ;  $r=-0.109$ ,  $p=0.053$ ;  $r=0.094$ ,  $p=0.095$ ;  $r=0.114$ ,  $p=0.042$ ), total-C ( $r=-0.118$ ,  $p=0.036$ ;  $r=-0.129$ ,  $p=0.021$ ;  $r=-0.160$ ,  $p=0.004$ ;  $r=-0.132$ ,  $p=0.019$ ;  $r=0.119$ ,  $p=0.034$ ;  $r=0.092$ ,  $p=0.101$ ) and LDL-C ( $r=-0.109$ ,  $p=0.052$ ;  $r=-0.128$ ,  $p=0.022$ ;  $r=-0.151$ ,  $p=0.007$ ;  $r=-0.116$ ,  $p=0.039$ ;

**Table 4** Starch sources and association with carotid intima media thickness

Effect on CIMT, n=324	$\beta$	SE	p Value*
<b>Full Model</b>			
Potato starch†	0.026	0.019	0.168
Whole wheat bread starch	0.001	0.004	0.709
White bread starch	-0.006	0.004	0.143
Rice starch	-0.006	0.003	0.036
Pasta starch	0.006	0.005	0.253
Pulse starch†	-0.039	0.022	0.077
Other starch†	-0.045	0.035	0.194
<b>Stepwise model‡</b>			
Rice starch	-0.006	0.003	0.023
Pulse starch†	-0.043	0.021	0.048

\*Multivariate regression model adjusted for age, smoking, previous CVD event, blood pressure medication, antidiabetic medication and ultrasonographer; starch variables are expressed as percentages of total calories.

†Log transformed.

‡Adjusted multivariate regression model where each starch variable was removed from the model one at a time based on least significance as per backward stepwise regression.

CIMT, carotid intima media thickness (mean max bilateral, average of the 12 segment measures); CVD, cardiovascular disease.

$r=0.131$ ,  $p=0.019$ ;  $r=0.059$ ,  $p=0.296$ ) in adjusted Pearson correlations.

## DISCUSSION

Using CIMT as a predictive marker of CVD risk, we evaluated the associations with dietary intake in participants with type 2 diabetes. The objective of the main study from which these baseline data are taken is to assess the effect of a low-GI diet on markers of macrovascular disease, however, in the present cross-sectional analysis, there was no significant association between GI and CIMT. This may be because we were underpowered due to the small variance of measured GI in our population, no participant had a high-GI diet and the average GI was at the low end of the medium GI range, thus limiting our ability to assess any association. Although we found no association, low-GI diets have been demonstrated in systematic reviews and meta-analyses of randomised controlled trials to significantly reduce both total-C and LDL-C compared to high-GI diets,<sup>40</sup> as well as to reduce oxidative stress and inflammation.<sup>41</sup> Interestingly, in a recent randomised controlled trial of those with the metabolic syndrome randomised to receive either metformin or a low-GI diet for 8 weeks, both groups demonstrated significant improvements in metabolic syndrome components including body weight, blood pressure, cholesterol and glycaemia.<sup>42</sup> Furthermore, the antidiabetic drug acarbose, which effectively converts the diet into a low-GI diet by delaying dietary carbohydrate absorption, has been associated with a reduced incidence of hypertension and CHD events in a small number of prediabetic participants in the Study to Prevent Non-Insulin-Dependent Diabetes

Mellitus (STOP NIDDM) trial.<sup>43</sup> Therefore, low-GI diets may have the potential to reduce CVD risk, particularly in those at high risk. Thus, further exploration into the potential benefit of low-GI diets on CVD risk is needed, particularly to assess change due to low-GI interventions.

GL was significantly associated negatively with CIMT which differs from what was expected. Systematic reviews and meta-analyses of previous studies have demonstrated a positive association between GL and CVD risk.<sup>17 18</sup> However, GL is the product of GI and available carbohydrate. We found a strong significant negative association between available carbohydrates and CIMT, but no effect of GI. We found a strong positive association between total and saturated fat intake and CIMT, therefore the surprising negative association between GL and CIMT may just mean that a higher carbohydrate and GL diet is simply an indicator of a lower total and saturated fat diet that predictably was associated with lower CIMT.

Of the specific low-GI foods of interest assessed, dietary pulse intake was significantly inversely associated with CIMT. In the predicted model (figure 1) approximately one  $\frac{3}{4}$  cup serving/day<sup>39</sup> was associated with a 7.5% lower CIMT compared to no intake (0 g/day). Although associations with CIMT have not been assessed previously, dietary pulse intake has been associated with reduced risk of CHD and CVD,<sup>19 20</sup> which supports the association found in the current study between dietary pulse intake and CIMT as a subclinical marker of CVD risk. Additionally, dietary pulses are part of a Mediterranean diet and this diet has been associated with improved CIMT in a number of studies,<sup>16 44–46</sup> as was highlighted in a recent systematic review of dietary factors and CIMT by Petersen *et al.*<sup>47</sup> We also found dietary pulse intake to be significantly associated with lower body weight, systolic and diastolic blood pressure, mean arterial pressure and cholesterol (see online supplementary table S1). A series of systematic reviews and meta-analyses have found dietary pulse intake to significantly improve body weight, blood pressure and cholesterol,<sup>48–50</sup> therefore supporting the associations observed in this study. Each of these potential pathways has been associated with lower CVD risk. Additionally, dietary pulses are high in fibre, potassium and vegetable protein, and low in saturated fat, each of which has been demonstrated to lower blood pressure<sup>23 51 52</sup> and improve cholesterol.<sup>48</sup> Furthermore, although not explored in the current study, dietary pulses may also act through reduced inflammation, as supported by another recent systematic review and meta-analysis,<sup>53</sup> which may also affect carotid plaque burden, since inflammation within atherosclerotic lesions increases the risk of plaque rupture and subsequent thromboembolism.<sup>54</sup> The Mediterranean diets in the Prevención con Dieta Mediterránea (PREDIMED) study, which have been shown to be lower GI diets,<sup>55</sup> were also found to downregulate cellular and circulating adhesion molecules and other inflammatory biomarkers.<sup>56</sup> Since, dietary pulses are particularly low-GI foods, consuming a lower GI diet

may also be beneficial for CVD risk. Our recent randomised controlled clinical trial in those with type 2 diabetes demonstrated that a low-GI diet with a particular emphasis on dietary pulses significantly lowered systolic blood pressure and heart rate, relative to a wheat fibre diet, both of which are negatively associated with CVD risk.<sup>23</sup>

Although the recent systematic review of dietary factors and CIMT by Petersen *et al*<sup>47</sup> did not reveal any studies with results on dietary pulses, they did conclude from the observational studies retrieved, that greater intake of fruit, whole grains and fibre and a lower intake of saturated fat was associated with lower CIMT. From our analyses, we find support for the association between lower saturated fat intake and lower CIMT. A previous study demonstrated that for every 10 g/day (about 5% of calories) increase in saturated fat, CIMT is 0.03 mm greater.<sup>57</sup> This is comparable to our analysis in which we found that for every 1% of total calorie increase in saturated fat, CIMT is about 0.011 mm greater (see online supplementary figure S1). The greater difference in CIMT for every 1% increase in saturated fat intake in our population compared to the previous study may be because of the higher risk of our population since they all had type 2 diabetes, were of greater age (60 vs 48 years) and greater BMI (30 vs 25 kg/m<sup>2</sup>). In recent years, new evidence from prospective studies has suggested that not all types of saturated fats play the same role in CVD development, including evidence that saturated fats from dairy products may play a protective role whereas those from other food sources may increase risk.<sup>58 59</sup> Unfortunately, we were unable to explore different sources of saturated fat from our data. We did have data on protein from dairy sources which we explored post hoc and found had a significant positive association with CIMT ( $\beta=0.075$ ,  $p=0.006$ ; multivariate model). Further exploration into effects of different sources of saturated fat is warranted.

Although we did not analyse whole grains, we did find a significant negative association between dietary starch intake and CIMT. Furthermore, in the starch post hoc analyses exploring major sources of starch, dietary pulse starch and rice starch were the only significant contributors to the negative association of starch with CIMT (table 4) and since they were also highly positively correlated with each other, this may mean they are consumed together, for example, as lentils and rice, a common dish. This result further strengthens the findings for dietary pulses.

We did not find a significant association with CIMT and dietary fibre in the present analysis ( $\beta=-0.048$ ,  $p=0.211$ ). However, the recent systematic review highlighted that the PREDIMED study found a significantly lower CIMT with low (<25 g/day) versus high (>35 g/day) fibre intakes ( $-0.051$  mm, 95% CI  $-0.094$  to  $-0.009$ ).<sup>60</sup> When we explored dietary fibre based on intakes <25, 25–35 and >35 g/day, there was a trend for lower CIMT with increasing fibre intake, but this trend

was not significant ( $p=0.119$ ). Furthermore, when we adjusted for energy using the residual method, similar to the approach used in the PREDIMED study, there was again an inverse trend, although the difference between the highest and lowest fibre groups did not reach statistical significance ( $p=0.088$ ) (see online supplementary table S2). Further exploration into any possible association between dietary fibre and CIMT is warranted, particularly since many studies have demonstrated an inverse association between dietary fibre intake and cardiovascular risk.<sup>61</sup>

Taken together, the results demonstrate that a higher carbohydrate diet may benefit CIMT, a marker of CVD risk. This is especially true for a diet with high-quality carbohydrate where the starch comes largely from dietary pulses, a particularly low-GI food, and which is also low in total fat, particularly saturated fat. The associations between these specific dietary variables and the metabolic profile of the participants reveal that they may act through better control of body weight, blood pressure and cholesterol.

### Strengths and limitations of this study

A strength of the analyses is that the CIMT scans were all performed using the same scanner at the same site and using the same reading protocol. A further strength is the method of collection of dietary data. Although the majority of participants were overweight and may have underreported their intake,<sup>62</sup> we took three important steps to minimise the impact of misreporting. First, we used prospectively collected 7-day food records: widely cited as the ‘gold standard’ of dietary measurement.<sup>63</sup> Second, these records were reviewed by the study dietitian at the time of collection and in the presence of the participant and details clarified (eg, nature of the margarine). Third, for this analysis, a priori, we aimed to exclude participants reporting intakes below 500 and 800 calories or above 3500 or 4000 calories, respectively for women and men.<sup>63</sup> No participant reported levels outside these cut-points, therefore we included all dietary records in our analyses. Finally, we have adjusted for energy in the regression models to dampen the effect of misestimation. We also found a correlation between calories and body weight ( $r=0.31$ ,  $p<0.001$ ; unadjusted). Therefore, we believe the dietary data are of reasonable quality. Limitations of these analyses include that they are conducted using CIMT results from only one CIMT scan obtained at baseline. However, studies have demonstrated mean max CIMT measurements to have good reproducibility, particularly using the method we adopted where measurements are made of 12 segments of the carotid artery.<sup>27</sup> Furthermore, although CIMT has been associated with CVD<sup>5 6</sup> a major limitation is that carotid plaque is a stronger predictor of CVD,<sup>64–66</sup> although we did include posterior wall plaques in the CIMT measures, if present. Another limitation is possible residual confounding due to unmeasured or uncontrolled variables, although CIMT



confounders were adjusted for in the analyses. The participants were also at high cardiovascular risk, thus application to a healthier cohort is limited. Furthermore, although at higher CVD risk, participants had relatively well-controlled diabetes (HbA1c, mean  $7.1\pm 0.5\%$ ), blood pressure (mean  $122\pm 11/72\pm 8$  mm Hg) and LDL-C (mean  $2.2\pm 0.8$  mmol/L), with 67% on blood pressure medication and 72% on cholesterol-lowering medication at baseline, therefore possibly limiting the ability to assess associations between risk factors for CVD and CIMT and dietary intake, as well as limiting application to those with uncontrolled risk factors. Also, due to the good glycaemic control of the participants, this may explain why there were no associations found with either HbA1c or glucose and CIMT. Importantly, the cross-sectional design of the study is a limitation to establish causality due to the possibility of reverse causation bias. Longitudinal studies and randomised controlled trials are needed to confirm the observed associations.

## CONCLUSION

Overall, greater consumption of dietary pulses, which are particularly low-GI foods, and available carbohydrates and lower saturated fat were significantly associated with lower baseline CIMT, as well as body weight, blood pressure and cholesterol, suggesting a potential role for diet in CVD risk reduction in type 2 diabetes. Properly designed randomised controlled trials are necessary to confirm if these dietary factors, including increased intake of dietary pulses and a reduction in saturated fat intake, are potential strategies to reduce CVD risk in those with type 2 diabetes. Furthermore, these types of trials will also be necessary to better assess if there is any effect of GI, where a low-GI diet is the result of healthy low-GI dietary advice. Thus the results of the main trial underway, which will allow for the assessment of changes resulting from a low-GI intervention, are greatly anticipated.

### Author affiliations

<sup>1</sup>Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

<sup>2</sup>Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Ontario, Canada

<sup>3</sup>Faculty of Health Sciences, School of Medicine, Queen's University, Kingston, Ontario, Canada

<sup>4</sup>Department of Medical Imaging, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

<sup>5</sup>Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada

<sup>6</sup>Department of Health Research Methods, Evidence & Impact, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

<sup>7</sup>Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

<sup>8</sup>National Cancer Institute 'Fondazione G. Pascale', Naples, Italy

<sup>9</sup>Division of Endocrinology and Metabolism, St. Michael's Hospital, Toronto, Ontario, Canada

<sup>10</sup>Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

<sup>11</sup>College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

**Contributors** DJAJ, LAL, RGJ, GEM, ARM, CWCK and JLS conceived the study and wrote the study protocol. LC, AM, CI, SM, SS-P, JC, OO, DP, RJDs, LSAA, BB, SBM, SKN, ARM and DJAJ contributed significantly to the acquisition of the data. LC, AM, CI, RGJ, SCP, GEM, ARM and DJAJ significantly contributed to the analyses of the data. LC and DJAJ drafted the manuscript and all authors revised the manuscript critically for important intellectual content. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work. DJAJ, LC, CI, RJD and SCP are the guarantors and take responsibility for the integrity of the data and the accuracy of the data analyses. The authors assume full responsibility for the accuracy and completeness of the ideas presented.

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North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an employee of Unilever Canada. CWCK has received research grants, travel funding, consultant fees, honoraria, or has served on the scientific advisory board for Abbott Laboratories, Advanced Food Materials Network, Agriculture and Agri-Food Canada (AAFC), Almond Board of California, American Peanut Council, American Pistachio Growers, Barilla, Bayer, California Strawberry Commission, Calorie Control Council, Canadian Institutes of Health Research (CIHR), Canola Council of Canada, The Coca-Cola Company, Danone, General Mills, Hain Celestial, International Nut and Dried Fruit Council, International Tree Nut Council Nutrition Research and Education Foundation, Kellogg, Kraft, Loblaw Brands, Nutrition Foundation of Italy, Oldways Preservation Trust, Orafiti, Paramount Farms, Peanut Institute, PepsiCo, Pulse Canada, Sabra Dipping Co., Saskatchewan Pulse Growers, Solae, Sun-Maid, Tate & Lyle, Unilever and White Wave Foods. He is on the Dietary Guidelines Committee for the Diabetes Nutrition Study Group of the European Association for the Study of Diabetes. DJAJ has received research grants from Saskatchewan Pulse Growers, the Agricultural Bioproducts Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network, Loblaw Companies, Unilever, Barilla, the Almond Board of California, Agriculture and Agri-Food Canada, Pulse Canada, Kellogg's Company, Canada, Quaker Oats, Canada, Procter & Gamble Technical Centre, Bayer Consumer Care, Springfield, NJ, Pepsi/Quaker, International Nut and Dried Fruit, Soy Foods Association of North America, the Coca-Cola Company (investigator initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company, Orafiti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, the Canola and Flax Councils of Canada, the Calorie Control Council (CCC), the CIHR, the Canada Foundation for Innovation and the Ontario Research Fund. He has been on the speaker's panel, served on the scientific advisory board and/or received travel support and/or honoraria from the Almond Board of California, Canadian Agriculture Policy Institute, Loblaw Companies, the Griffin Hospital (for the development of the NuVal scoring system, the Coca-Cola Company, EPICURE, Danone, Diet Quality Photo Navigation (DQPN), Saskatchewan Pulse Growers, Sanitarium Company, Orafiti, the Almond Board of California, the American Peanut Council, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and the Netherlands, Solae, Kellogg, Quaker Oats, Procter & Gamble, the Coca-Cola Company, the Griffin Hospital, Abbott Laboratories, the Canola Council of Canada, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi-Bred International, DuPont Nutrition and Health, Spherix Consulting and WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of Canada, the Nutritional Fundamentals for Health, AgriCulture and Agri-Food Canada, the Canadian Agri-Food Policy Institute, Pulse Canada, the Saskatchewan Pulse Growers, the Soy Foods Association of North America, the Nutrition Foundation of Italy (NFI), Nutrasource Diagnostics, the McDougall Program, the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), the American Society of Nutrition (ASN), Arizona State University, Paolo Sorbini Foundation and the Institute of Nutrition, Metabolism and Diabetes. He received an honorarium from the US Department of Agriculture to present the 2013 W.O. Atwater Memorial Lecture. He received the 2013 Award for Excellence in Research from the International Nut and Dried Fruit Council. He received funding and travel support from the Canadian Society of Endocrinology and Metabolism to produce mini cases for the Canadian Diabetes Association (CDA). He is a member of the International Carbohydrate Quality Consortium (ICQC). His wife, ALJ, is a director and partner of Glycaemic Index Laboratories, and his sister received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for one of his studies. AM, SM, SSP, JC, DP, OO, SBM, BB, SCP, LAL, RGJ and GM have no relevant conflicts of interest to declare.

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