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# Low-glycaemic index diet to improve glycaemic control and cardiovascular disease in type 2 diabetes: design and methods for a randomised, controlled, clinical trial

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## ABSTRACT

**Introduction:** Type 2 diabetes (T2DM) produces macrovascular and microvascular damage, significantly increasing the risk of cardiovascular disease (CVD), renal failure and blindness. As rates of T2DM rise, the need for effective dietary and other lifestyle changes to improve diabetes management become more urgent. Low-glycaemic index (GI) diets may improve glycaemic control in diabetes in the short term; however, there is a lack of evidence on the long-term adherence to low-GI diets, as well as on the association with surrogate markers of CVD beyond traditional risk factors. Recently, advances have been made in measures of subclinical arterial disease through the use of MRI, which, along with standard measures from carotid ultrasound (CUS) scanning, have been associated with CVD events. We therefore designed a randomised, controlled, clinical trial to assess whether low-GI dietary advice can significantly improve surrogate markers of CVD and long-term glycaemic control in T2DM.

**Methods and analysis:** 169 otherwise healthy individuals with T2DM were recruited to receive intensive counselling on a low-GI or high-cereal fibre diet for 3 years. To assess macrovascular disease, MRI and CUS are used, and to assess microvascular disease, retinal photography and 24-hour urinary collections are taken at baseline and years 1 and 3. Risk factors for CVD are assessed every 3 months.

**Ethics and dissemination:** The study protocol and consent form have been approved by the research ethics board of St. Michael's Hospital. If the study shows a benefit, these data will support the use of low-GI and/or high-fibre foods in the management of T2DM and its complications.

**Trial Registration number:** NCT01063374; Pre-results.

## Strengths and limitations of this study

- This study will be the first to document the effects of a dietary intervention on measures of macrovascular disease through the detection of changes in carotid vessel wall volume assessed by MRI as a surrogate measure of cardiovascular disease, in high-risk participants.
- This study is also the longest to assess the effect of altering the dietary GI, allowing for the exploration of sustainability of a low-GI diet.
- The MRI images obtained from this study will provide invaluable data on the natural history of vascular disease progression in type 2 diabetes.
- A potential limitation of this study is that participants may be more health conscious than average since they are volunteering to participate in a long-term dietary trial.
- Another potential limitation is that those randomised to the control high-cereal fibre diet may have difficulty avoiding many of the healthy foods which they are told to as they are on the low-GI diet (eg, beans and berries).

## INTRODUCTION

Type 2 diabetes (T2DM) is the fastest growing chronic disease worldwide and its prevalence is projected to double over the next 20 years. Given its prevalence and heavy healthcare and quality-of-life burden,[1] there is a great need for better treatment options. In uncontrolled T2DM, the macrovascular (cardiovascular disease, CVD) and microvascular (eye and kidney) risks are increased. T2DM reduces the lifespan by 10 years,[2] chiefly due to CVD deaths, which are twofold

higher in men and fourfold higher in women than in those without diabetes.[3] Further, 40% of new end-stage renal disease is accounted for by diabetic nephropathy and diabetes is a major cause of renal transplants.[4] Damage to retinal vessels can result in diabetic retinopathy (retinopathy), and macular oedema, which are major causes of vision loss in Western Nations.[5 6] The cost of medical care for those with diabetes in Western Nations is two to three times higher than those without diabetes, and has doubled over the past decade,[7 8] largely related to CVD. To reduce the risk of these complications, there is a continued focus on controlling elevated blood glucose levels through lifestyle and pharmaceutical means. Prospective cohort studies and large clinical trials have demonstrated that good glycaemic control in diabetes is associated with a reduced risk of microvascular complications.[9–14] However, the results of three large randomised trials published in 2008 (ACCORD, ADVANCE and VADT)[15–17] failed to show significant CVD benefit for improved glycaemic control over a 3-year to 5-year period. At the same time, concern about the cardiovascular safety of rosiglitazone and other antidiabetic medications led the US Food and Drug Administration to require demonstration of the cardiovascular safety of all new antidiabetic agents.[18] Longer term follow-up of some of these trials (UKPDS and VADT),[19 20] as well as the recently published EMPA REG OUTCOME study[21] with the SGLT2 inhibitor, empagliflozin, have demonstrated CVD benefit. Acarbose has shown promise in reducing CVD and incident hypertension[22] when assessed as a secondary outcome in a large randomized controlled trial in participants with prediabetes, and a larger CVD study with acarbose in patients with diabetes is underway. Acarbose converts dietary carbohydrate into a slow release or low-glycaemic index (GI) food by inhibiting pancreatic amylase and small intestinal brush border sucrase-isomaltase. Low-GI foods, although recommended for diabetes control by many diabetes agencies,[12–14 23] have not been tested specifically on vascular outcomes despite cohort studies suggesting that low-GI diets, especially in women, are associated with reduced CVD.[24] Additionally, a randomised trial, the PREDIMED study, that reduced the GI and GL of the diet[25] and included the use of nuts and olive oil to achieve this effect also reduced CVD, especially stroke.[26] We have demonstrated the greater effectiveness of low-GI diets in reducing HbA1c and blood pressure in T2DM.[27 28] We therefore designed a randomised, controlled, clinical trial to assess whether dietary advice on either a low-GI or a high-cereal fibre diet will make a significant difference on carotid plaque burden and other surrogate markers of CVD, microvascular disease and long-term glycaemic control in high-risk participants with T2DM.

## METHODS AND ANALYSIS

### Study design

#### Recruitment

In 2010, potential T2DM participants were recruited through newspapers and subway advertisements, and by phoning previous study participants from our research centre who had expressed interest in further studies. After initial telephone screening, information sessions were arranged at St. Michael's Hospital. Those interested, attended a screening visit at the clinic for a blood test to determine eligibility (box 1). All participants gave informed consent prior to participating in any screening procedures. Physicians were contacted to ensure that those responsible for diabetes care approved participation. Those satisfying initial eligibility criteria were scheduled for a screening 2D carotid ultrasound (CUS) to assess carotid artery thickening by intima media thickness (IMT). Our original screening cut point was a maximum IMT ≥2.0 mm; however, a larger than anticipated number of participants were ineligible (~66%

**Box 1** Inclusion and exclusion criteria

*Inclusion criteria*: individuals with type 2 diabetes (T2DM)

- Taking oral hypoglycaemic agents at a stable dose for ≥8 weeks;
- HbA1c ≥6.5 to ≤8.0% at initial screening visit;
- HbA1c ≥6.5% at prestudy visit (visit just prior to randomisation);
- Diabetes diagnosed >6 months;
- Stable weight for 2 months (within 3%);
- Valid Ontario Health Insurance Plan (OHIP) card and a family physician;
- If prescribed lipid medication, stable dose for ≥2 weeks;
- If prescribed blood pressure medication, stable dose for ≥1 week;
- Can keep written food records, with the use of a digital scale;
- Carotid maximum IMT ≥1.2 mm (originally ≥2.0 mm, ≥1.5 mm in early 2012, ≥1.2 mm in late 2012).

*Exclusion criteria*

- Take insulin, steroids, warfarin (Coumadin);
- Gastrointestinal disease (gastroparesis, celiac disease, ulcerative colitis, Crohn's disease, irritable bowel syndrome);
- Major cardiovascular event (stroke or myocardial infarction) or major surgery in the past 6 months;
- Major debilitating disorder;
- Clinically significant liver disease (aspartate transaminase (AST) or alanine transaminase (ALT) >130 U/L), excluding non-alcoholic fatty liver disease or non-alcoholic steatohepatitis;
- Hepatitis B or C;
- Renal failure (high serum creatinine >150 mmol/L);
- Serum triglycerides ≥6.0 mmol/L;
- History of cancer, except non-melanoma skin cancer (basal cell, squamous cell);
- Food allergies to study food components;
- Elevated blood pressure (>145/90 mm Hg) unless approved by family physician;
- Acute or chronic infections (bacterial or viral);
- Chronic inflammatory diseases (eg, rheumatoid arthritis, lupus and ulcerative colitis);
- Other conditions which in the opinion of any of the investigators would make them unsuitable for the study;
- Any condition or circumstance preventing an MRI (eg, metal workers, prostheses, metal implants or those excessively claustrophobic).

ineligible). Therefore, in early 2012, the cut point was reduced to ≥1.5 mm (~44% ineligible) in accordance with the Mannheim carotid IMT consensus[29] where ≥1.5 mm defined the beginning of atheromatous changes. It was later further reduced in late 2012 to ≥1.2 mm (~23% ineligible), the median between the Mannheim consensus (1.5 mm) and the European Society of Hypertension and the European Society of Cardiology Practice Guidelines for the management of arterial hypertension (0.9 mm).[30] These changes allowed completion of recruitment by June 2013, while including participants with some carotid thickening. At the screening CUS scan, if the maximum IMT measure was greater than or equal to the inclusion cut point of 1.2 mm (or the cut point at the time of CUS scan), the sonographer also completed a 3D CUS scan.

If individuals had a recent medication change that made them ineligible at screening or prior to randomisation, they were able to return for a rescreen after the required time had elapsed.

## Baseline measures and randomisation

Eligible consenting participants had a baseline carotid MRI scan at the Medical Imaging Department at Sunnybrook Health Sciences Centre. A gadolinium contrast agent, Gadovist (gadobutrol, Bayer, Mississauga, Canada), approved by Health Canada and one of several products commonly used for contrast during MRIs, was used after three safety procedures were passed. First, participants had to consent after being informed of the risks. Second, MRI safety forms were completed with the participant and reviewed by the study physician and staff at Sunnybrook. Third, forms were reviewed again by study staff at Sunnybrook immediately before the MRI. If it was deemed safe to proceed, MRI was undertaken with Gadovist. The same safety procedure was repeated for each of the two additional MRI scans at years 1 and 3 of the study. If Gadovist is deemed unsafe or the participant declines consent, the MRI scan is done without the use of Gadovist.

A baseline retinal examination was conducted by a vitreoretinal subspecialist ophthalmologist at the Department of Ophthalmology at St. Michael's Hospital and each participant had standardised seven-field diabetic retinal photographs taken.

Two baseline clinical visits occurred at St. Michael's Hospital, on average 2 weeks apart, but no more than 5. At the first baseline clinic visit, anthropometric and fasting blood measures were obtained and if HbA1c was ≥6.5%, participants could proceed. If HbA1c was <6.5%, participants could return for a retest after 2 weeks. Participants were given detailed instruction on how to complete a 7-day food record and 24-hour urine collection using the kit provided; both were returned at the second visit.

At the second baseline clinic visit, anthropometric and fasting blood measures were again obtained and each participant was randomised to receive dietary advice on either a low-GI or high-cereal fibre diet. Randomisation was stratified by sex, HbA1c (≤7.1%, >7.1%), smoking (yes or no) and statin use (yes or no) as documented during the first baseline visit. Participants were provided with a dietary instruction sheet based on the diet to which they were randomised (see online supplementary appendix figures S1 and S2). These diets were reviewed in detail with a study dietitian in a 30 min discussion.

Blinding the participants or the dietitians delivering the dietary advice is not possible due to the very different nature and physical form of the foods. However, it was stressed to the participants that both treatments have been considered to confer benefits in cohort studies in order to balance participant expectation of treatment benefit. To remove the possibility of bias, physicians and technical staff who are obtaining measurements are blinded to the treatments, as was the statistician who randomised the coded participants and who will analyse the data. Participants were randomised after the baseline (zero week) blood sample to avoid randomising participants who for any reason did not intend to start the study. Dropout is therefore defined as quitting post randomisation.

## Outcomes and study measures

Figure 1 depicts the timing and frequency of all study measures described in detail. MRI, CUS, 24-hour urinary collections and retinal assessments are taken at baseline and years 1 and 3 with anthropometric, fasting blood measures and 7-day food records at 3-month intervals. At the 3-monthly clinic visits, the participants' medications, noting any changes, as well as any unusual or adverse events, including illness or stressful issues, that occurred since the last clinic visit are recorded in detail.

The primary outcome of the trial is change in carotid plaque volume assessed as vessel wall volume (VWV) by MRI at year 3.

At the time of the grant submission, IMT by CUS was designated as the primary outcome based on its association with CVD when used as a screening tool. However, meta-analyses[31–33] have since shown that IMT seems suboptimal for assessing changes from interventions, although it still relates overall to risk of CVD when used for screening.[34] The original protocol proposed MRI of the carotid arteries as a secondary outcome. Over the last 6 years, advances in MRI technology produced high accuracy and reproducibility by minimising interoperator and intraoperator variability of image acquisition and so now make this the preferred modality for assessing change and monitoring therapeutic interventions in clinical trials.[35–37] Accordingly, we adopted this as our primary outcome and adjusted our power calculations to reflect recent MRI data.[38]

### Magnetic resonance imaging

MRI scans are being performed in the Medical Imaging Department at Sunnybrook Health Sciences Centre MRI research unit at a single site using a Philips 3-Tesla whole body scanner (Philips Healthcare, Markham,

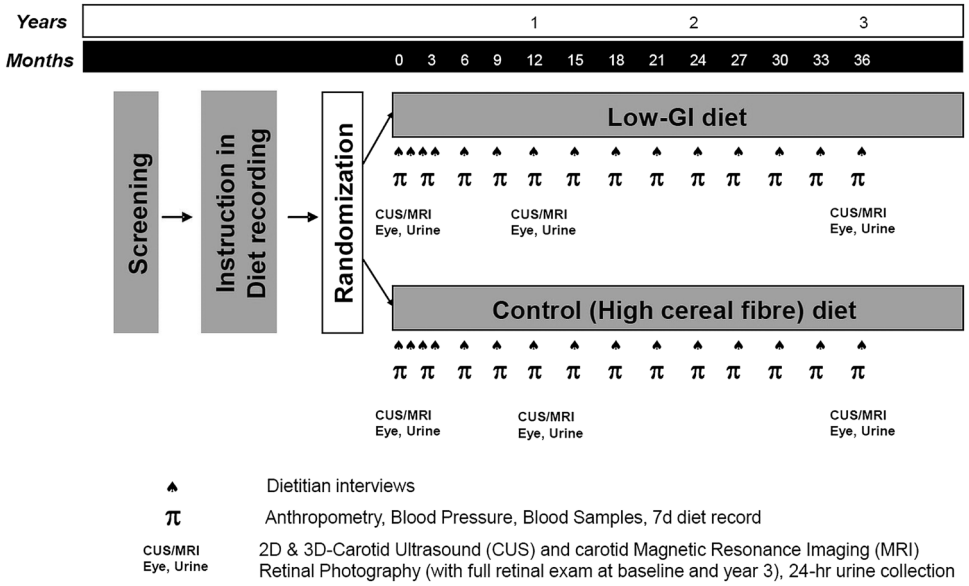


**Figure 1** Schematic representation of the study protocol. GI, glycaemic index.

Canada) with a 16-channel neurovascular coil (16-NV-SENSE). Participants are centred at the index carotid artery bifurcation as determined by carotid IMT (ie, 'index' is the side of the artery, left or right, with the highest IMT), and a shim coil covering a 10 cm region over the neck is used to improve magnetic field homogeneity. With a standardised protocol, six contrast weightings of the carotid artery are obtained: 2D precontrast and postcontrast enhanced T1-weighted (T1W), proton density weighted, and T2-weighted sequences, as well as 3D T1W gradient recalled echo and time of flight MR angiography sequences. Images are obtained of the left and right carotid arteries. Gadobutrol (Bayer) is used as the contrast agent when criteria are met at an intravenous injection of 0.1 mmol/kg (0.2 mL/kg). Sequence parameters are described in online supplementary appendix table S1. Total scan time is an average of 60 min and allows coverage of 2D imaging capturing a 32 mm segment (2 mm thickness×16 matched images among the four weightings), while 3D imaging captures the entire carotid artery from its origin to the Circle of Willis. The cardiovascular imaging software, VesselMASS (Medis, the Netherlands), is used for image analysis. Image grading is performed during the analysis (see online supplementary appendix table S2) and images with poor quality (grade <3) or with missing images will be excluded from analyses. Location matching of the available MR images is performed using the baseline index carotid artery over the different time points before lumen and outer wall contours are identified. VWV is automatically generated from the software.[39–41] Intraclass correlation values for measurements are above 0.9 (good to excellent);[42–44] however, a single, trained and blinded reader will assess all measurements.

MRI will also allow assessment of several secondary outcomes that are surrogate markers of CVD: changes in intraplaque haemorrhage, lipid-rich necrotic core and carotid artery calcium status,[37 38 45 46] each of which has an intraclass correlation value for measurements above 0.9 (good to excellent).[42 44]

### B-mode carotid ultrasound (CUS)

An additional secondary outcome assessing macrovascular disease is IMT by 2D B-mode CUS, a measure that is related to CVD risk.[34]

Standardised CUS scanning and reading protocols are used following a similar protocol to the ACAPS[47–49] and SECURE[50 51] trials, which was validated in ACAPS.[49] CUS imaging and reading is performed by two trained and certified sonographers who are unaware of the treatment assignment on a Philips iU22 Ultrasound system (Philips Healthcare, Andover, Massachusetts, USA) at Sunnybrook. Most participants are scanned with the L9-3 linear high-frequency transducer; however, when the vessel is very superficial, the 12-5 transducer is used in order to visualise the near wall. Each participant is positioned supine on the examination table, with the neck extended and rotated away from the side of interest. Transverse and longitudinal views of each carotid artery are obtained from the common carotid artery to the bifurcation and the internal carotid artery (ICA). The ICA is differentiated from the external carotid artery based on its low resistance spectral Doppler flow pattern. On the longitudinal view, each carotid artery is divided into three segments 1 cm long defined relative to the carotid flow divider (figure 2). Twelve IMT measurements of the near and far walls at each carotid segment are made using electronic calipers and the mean maximum IMT is computed as the average of the segment maximum IMTs.

Further secondary outcomes significantly related to CVD risk include anthropometric, urine and blood measures,[52] which will be analysed as previously described.[28] Briefly, anthropometric data include body weight, seated blood pressure measured as the mean of triplicate

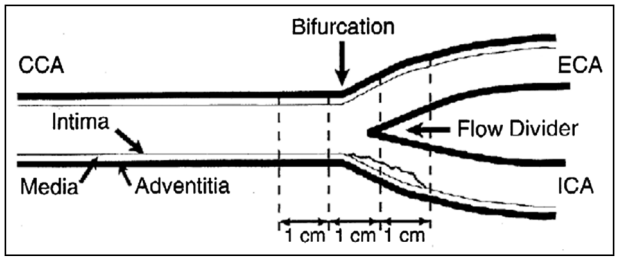


**Figure 2** Diagrammatic example of a right common carotid artery scan. The far wall of the bifurcation segment as well as part of the internal carotid artery are narrowed by a plaque. Adapted from Lonn *et al*.[51]

measures made with an automatic sphygmomanometer (Omron HEM 907XL, OMRON Healthcare, Burlington, Ontario, Canada), and waist (at the umbilicus, 2 inches above and lying down) and hip circumference. Twenty-four-hour urine is collected by discarding the first urine on waking, noting the time and then collecting each subsequent excretion up to and including the first void at the same time on waking the next morning. Urinary measures include C-peptide, urea, creatinine and electrolytes. Blood measures include HbA1c, fasting glucose, fasting lipids and liver function.

Other study outcomes include 50° stereoscopic colour fundus photographs of seven standard fields (retinal photography) to assess degree of retinopathy following a similar protocol to the ACCORD study.[53] Vitreoretinal subspecialist ophthalmologists blinded to the intervention will read the photos to assess any changes.

Dietary assessments are being made using participant completed 7-day food records that are analysed using a computer program (ESHA Food Processor SQL V.10.9; ESHA, Salem, Oregon, USA) based on a United States Department of Agriculture (USDA) database,[54] supplemented with the Canada Nutrient File,[55] with GI values from international GI tables,[56] substituted with GI testing through the University of Toronto at Glycemic Index Laboratories, Canada, using the bread scale (where bread=100; for the glucose scale, bread scale values are multiplied by 0.71). Product data are updated with manufacturers' nutrient information and with relevant foods analysed by Covance Laboratories (Madison, Wisconsin, USA).

## Interventions

Participants were randomised to receive dietary advice on either a low-GI or high-cereal fibre diet for 3 years together with advice on the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) diet. Diet histories recorded for the 7 days prior to clinic visits are being assessed for detail and consistency by the dietitian in the participant's presence, and used to guide dietary advice. Assessment is made of satiety (using a 9-point bipolar semantic scale) and on palatability and sustainability (using 10-point scales).

Both diets conform as closely as possible to NCEP ATP III guidelines with <7% saturated fat and <200 mg dietary cholesterol daily[57] and provide the same level of fibre (up to 35 g/day). Advice encouraging all participants to reach ideal body weight is standard advice for those with diabetes, 85–90% of whom are overweight, together with encouragement to exercise at a level they can sustain prior to and over the course of the study. The consistency of exercise is checked at each clinic visit and any deviations recorded.

Low-GI dietary advice encourages use of intact grains, including specific low-GI breads, pasta, parboiled rice, coarse cut oats, Red River and All Bran Buds with psyllium breakfast cereals, cooked dried or canned peas, beans or lentils, barley and low-GI temperate climate fruit, including apples, oranges and berries (see online supplementary appendix figure S1).

High-cereal fibre dietary advice encourages use of whole grains, including whole wheat breads, wheat fibre cereals, cream of wheat hot cereal, brown rice and tropical fruit, including bananas, mangos and pineapples (see online supplementary appendix figure S2). Sample nutritional profiles of each diet demonstrating a 13-unit difference in GI between test and control as demonstrated in our previous 6-month trial[27] is provided in online supplementary appendix table S3.

Dietary advice is provided through half-hour individual sessions with the dietitian every 3 months at clinic visits, as well as through monthly phone calls for the first 3 months and thereafter, at least one 10 minute phone interview for 1-day diet recalls between dietitian interviews, with additional phone interviews for those with poor (<75%) adherence to the study protocol (ie, poor diet and missed visits).

## Sample size

Our original power calculation was based on IMT by CUS which was the original primary end point. We had estimated that 160 participants would need to be randomised with 120 participants completing the study (25% attrition). A total of 169 participants were randomised.

For our primary outcome, VWV by MRI, the magnitude of difference between the groups that can be seen with 169 randomised participants was calculated using the estimate of variance of the measurement as observed (SD=252) in Saam *et al*.[38] This showed that a treatment difference of 10% can be detected with 80% power and $\alpha$=0.05, assuming a 25% attrition.

Furthermore, with a sample size of 160 participants, we will be able to detect changes in the important secondary end point, HbA1c, which could influence arterial damage. For HbA1c, if 120 of the randomised 169 participants complete the study, we will be able to detect a 0.3% treatment difference with a pooled SD of the treatment difference of 0.578 at a two-tailed significance level ($\alpha$)=0.05 and power (1−$\beta$)=0.8 using a two-treatment parallel design, with an independent-samples t-test. This calculation is based on our previous study in T2DM using similar treatments over a 6-month period.[27]

### Statistical analysis planned

All randomised participants will be included in the intention-to-treat analyses. Results will be expressed as means±SEM or 95% CIs.

#### Primary analysis

The primary analysis will assess the between-treatment difference in change from baseline in VWV, where change is assessed as years 1 and 3 adjusted for baseline using a repeated-measures mixed model (PROC MIXED in SAS 9.4) (SAS Institute: SAS/STAT Proprietary Software 9.4. Cary, NC: SAS Institute; 2002–2012) in an intention-to-treat analysis, without adjustment for covariates. Every effort will be made to obtain final vascular imaging and blood samples from those who do not provide these in clinic due to attrition or loss to follow-up.

#### Sensitivity analysis

Robustness will be assessed of our primary finding to model assumptions: (1) To address the impact of potential imbalance in prognostic factors, we will repeat the primary analysis using mixed models but controlling for age, sex, duration of diabetes, waist circumference, cholesterol medication use, baseline VWV, smoking, blood pressure and family history of CVD, together with dietary variables (baseline GI, saturated fat, dietary cholesterol, dietary pulse and nut intake). Missing data for covariates will be handled using the missing indicator method; (2) To assess the robustness of our primary analysis of missing data, we will repeat the primary analysis using completer and per-protocol analyses, and multiple imputations to generate missing data and (3) To assess the impact of participant-level factors on the primary outcome, we will examine changes in indices of vascular damage separately in (a) those who meet HbA1c target versus those with less good glycaemic control (eg, HbA1c≤7% vs HbA1c>7% at the end of the study); (b) those with good compliance, that is, by quartiles of change in GI at years 1 and 3, those in the highest quartiles of specific low-GI components (dietary pulses, temperate climate fruit, nuts, etc) and high-fibre completers by quartiles of change in fibre and (c) by IMT at study entry. Exploratory assessment of the significance of between-subgroup changes in the primary outcome will be undertaken with Wald tests of the interaction terms.

#### Exploratory analyses

We anticipate that this study will yield a rich data set. We have therefore mapped out some exploratory analyses: (1) to assess response trajectories, by comparing treatment slopes across all post-treatment measures, that is, an assessment of whether year 1 values differ from year 3 values; (2) to assess treatment differences in medication use over all post-treatment values; (3) further analyses will examine causal pathways between diet, metabolic parameters and measures of arterial function using methods of path analysis and structural equation modelling, as appropriate.

## ETHICS AND DISSEMINATION

The protocol and consent forms were approved by the research ethics board of St. Michael's Hospital. The study was registered with clinicaltrials.gov (identifier: NCT01063374).

### Participant safety

Privacy will be enhanced by data deidentification. Databases with personal health information will be password protected. Paper forms with personal health information (eg, participant charts) will be kept in locked cabinets and in locked rooms, and the department door locked after hours.

Electronic files will identify participants only through identification codes. Access to paper and electronic data files is limited to the principle investigator (PI), statisticians, dietitians, students and data entry personnel working on the project.

A separate chart with routine clinical information is maintained for contact with participants' family physicians and will be accessible only to the PI and study staff.

A Data Safety Monitoring Board will periodically review (approximately once per year or when safety issues arise) the progress of the trial to oversee participant safety and provide advice on the status and continuation of the overall study.

HbA1c is reviewed at each visit and as necessary with one of the physicians of the Safety Committee who are not involved in the day-to-day running of the trial (RGJ, LAL) with participants identified only by code. Participants will be referred to his/her family physician for treatment if HbA1c exceeds the 8.5% threshold of recommended targets for glycaemic control, according to diabetes guidelines,[11 12] on two successive occasions, or if hypoglycaemic symptoms associated with low blood glucose levels occur. If a participant's physician considers that a change in dosage or medication is required, a predetermined paradigm will be used, and the Safety Committee notified. Blood pressure is also reviewed. If levels surpassed the screening cut-off of 145/90 mm Hg, the participant's physician is notified. Adverse events will be dealt with on a case-by-case basis depending on whether the situation is likely to resolve spontaneously or whether medical intervention is required.

### Discussion and implications

This study will be the first to document the effects of a dietary intervention on measures of macrovascular disease through the detection of changes in carotid VWV as a surrogate measure of CVD, in high-risk participants. We believe this will open the way for other investigators to use vascular MRI in their research and for use in clinical practice as a diagnostic tool and especially for follow-up. It is also the longest trial to date to assess the

effect of altering the dietary GI and will also provide invaluable data on the natural history of vascular disease. In view of the global rise in the incidence of T2DM and the associated vascular complications, including increased CVD risk, therapeutic approaches that address microvascular and macrovascular risk factors are now urgently required.

At present, diabetes is an immense burden on the healthcare system of Western Nations, projected to continue to increase, and largely related to CVD and microvascular complications.[7 8] A 25% sparing of T2DM microvascular complications would result long term from a 0.9% reduction in HbA1c according to the UKPDS data.[58] We achieved a 0.5% reduction in HbA1c in our previous 6-month randomised, controlled trial of similar low-GI dietary advice in those with T2DM,[27] so we expect a similar reduction in this investigation. The economic (let alone social) impact of even one-third the reduction in HbA1c seen in the UKPDS[58] is likely to be considerable. If low-GI diets can be shown to reduce macrovascular disease risk factors in addition to reducing microvascular disease, results will not only increase understanding of the role of diet and nutrition in macrovascular disease development in T2DM but will also influence guidelines for the treatment of diabetes and the nature of the products produced by the food industry, and the savings in cost and suffering will be significant.

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**Competing interests** LC has received research support from the Canadian Institutes of Health Research (CIHR). LC is a clinical research coordinator and SKN is a clinical research dietitian at Glycemic Index Laboratories, Toronto, Ontario, Canada. RJdS is funded by a CIHR Postdoctoral Fellowship Award and has received research support from the CIHR, the Calorie Control Council, the Canadian Foundation for Dietetic Research and The Coca-Cola Company (investigator initiated, unrestricted grant). RJdS has served as an external resource person to WHO's Nutrition Guidelines Advisory Group and received travel support from the WHO to attend group meetings. RJdS is the lead author of systematic reviews and meta-analyses commissioned by the WHO on the relation of SFAs and trans-fatty acids with health outcomes. LSAA has received an honorarium from the Nutrition Foundation of Italy (NFI) to co-organise a glycaemic index summit. ARM is currently consultant for Jansen/Johnson and Johnson. JLS has received research support from the CIHR, American Society of Nutrition (ASN), Canadian Diabetes Association (CDA), Banting & Best Diabetes Centre (BBDC), Calorie Control Council, The Coca-Cola Company (investigator initiated, unrestricted), Dr Pepper Snapple Group (investigator initiated, unrestricted), Pulse Canada and the International Tree Nut Council Nutrition Research and Education Foundation. He has received travel funding, speaker fees and/or honoraria from American Heart Association (AHA), American College of Physicians (ACP), ASN, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), CDA, CNS, University of South Carolina, University of Alabama at Birmingham, Oldways Preservation Trust, NFI, Calorie Control Council, Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes (EASD), International Life Sciences Institute (ILSI) North America, ILSI Brazil, Abbott Laboratories, Pulse Canada, Canadian Sugar Institute, Dr Pepper Snapple Group, The Coca-Cola Company, Corn Refiners Association, World Sugar Research Organization, Dairy Farmers of Canada and Società Italiana di Nutrizione Umana (SINU). He has consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP and Tate & Lyle. He is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the CDA and EASD, as well as being on an ASN writing panel for a scientific statement on sugars. He is a member of the International Carbohydrate Quality Consortium (ICQC) and Board Member of the Diabetes and Nutrition Study Group of the EASD. He serves an unpaid scientific advisor for the International Life Science Institute (ILSI) North America, Food, Nutrition, and Safety Program (FNSP) and the Committee on Carbohydrates. His wife is an employee of Unilever Canada. CWCK has received research grants, travel funding, consultant fees, honoraria and 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, 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 Ltd, NFI, Oldways Preservation Trust, Orafti, Paramount Farms, Peanut Institute, Pepsi-Co, 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 Ltd., 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 Ltd., Bayer Consumer Care, Springfield, New Jersey, Pepsi/Quaker, International Nut & Dried Fruit (INC), Soy Foods Association of North America, the Coca-Cola Company (investigator initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company, Orafti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, the Canola and Flax Councils of Canada, the CCC, the

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