Chronic Ingestion of Flavan-3-ols and Isoflavones Improves Insulin Sensitivity and Lipoprotein Status and Attenuates Estimated 10-Year CVD Risk in Medicated Postmenopausal Women With Type 2 Diabetes

A 1-year, double-blind, randomized, controlled trial

OBJECTIVE—To assess the effect of dietary flavonoids on cardiovascular disease (CVD) risk in postmenopausal women with type 2 diabetes on established statin and hypoglycemic therapy.

RESEARCH DESIGN AND METHODS—Despite being medicated, patients with type 2 diabetes have elevated CVD risk, particularly postmenopausal women. Although dietary flavonoids have been shown to reduce CVD risk factors in healthy participants, no long-term trials have examined the additional benefits of flavonoids to CVD risk in medicated postmenopausal women with type 2 diabetes. We conducted a parallel-design, placebo-controlled trial with type 2 diabetic patients randomized to consume 27 g/day (split dose) flavonoid-enriched chocolate (containing 850 mg flavan-3-ols [90 mg epicatechin] and 100 mg isoflavones [aglycone equivalents])/day or matched placebo for 1 year.

RESULTS—Ninety-three patients completed the trial, and adherence was high (flavonoid 91.3%, placebo 91.6%). Compared with the placebo group, the combined flavonoid intervention resulted in a significant reduction in estimated peripheral insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR] −0.3 ± 0.2; P = 0.004) and improvement in insulin sensitivity (quantitative insulin sensitivity index [QUICKI] 0.003 ± 0.00; P = 0.04) as a result of a significant decrease in insulin levels (−0.8 ± 0.5 mU/L; P = 0.02). Significant reductions in total cholesterol/HDL-cholesterol (HDL-C) ratio (−0.2 ± 0.1; P = 0.01) and LDL-cholesterol (LDL-C) (−0.1 ± 0.1 mmol/L; P = 0.04) were also observed. Estimated 10-year total coronary heart disease risk (derived from UK Prospective Diabetes Study algorithm) was attenuated after flavonoid intervention (flavonoid +0.1 ± 0.3 vs. placebo 1.1 ± 0.3; P = 0.02). No effect on blood pressure, HbA1c, or glucose was observed.

CONCLUSIONS—One-year intervention with flavan-3-ols and isoflavones improved biomarkers of CVD risk, highlighting the additional benefit of flavonoids to standard drug therapy in managing CVD risk in postmenopausal type 2 diabetic patients.
increased habitual intake of soy isoflavones has also been associated with a reduced risk of CVD and type 2 diabetes (11), and recent meta-analyses suggest beneficial effects of increased isoflavone intake on CVD risk biomarkers and glycemic control (12–14).

In patients with type 2 diabetes, no long-term trials have been conducted to examine the effects of either isoflavones or flavan-3-ols on CVD risk biomarkers, although the available data from short-term studies (maximum duration 12 weeks in both flavonoid subclasses) are suggestive of favorable effects (15–17). To our knowledge, no studies have examined the long-term effects of a combined intervention of these bioactive flavonoids on CVD risk in medicated patients with type 2 diabetes, and given our knowledge of their specific mechanisms of action, there is the potential of synergistic effects. Therefore, we conducted a randomized, double-blind, placebo-controlled, parallel trial to examine the vascular protective effects of a 1-year combined intervention of flavan-3-ols and isoflavones in postmenopausal women with type 2 diabetes.

**RESEARCH DESIGN AND METHODS**

**Subjects**

One hundred and eighteen postmenopausal women (no menstruation for ≥12 months), aged 51–74 years and receiving standard U.K. care for type 2 diabetes (including statin therapy, established for ≥12 months and glycemic target of HbA1c of 7.0%) were recruited through general practitioners, specialist diabetes clinics, and local media advertisements (Fig. 1A). Exclusion criteria included use of hormone replacement therapy (within 6 months), known allergy to the study foods, history of vascular disease or cancer, and poor diabetes control or raised BP at screening (as outlined in Fig. 1B). All study investigations were conducted according to the principles expressed in the Declaration of Helsinki and the study was approved by the Norfolk Research Ethics Committee. All subjects provided written informed consent.

**Study protocol**

Subjects were randomized to placebo (n = 59) or flavonoid-enriched (n = 59) chocolate daily for 1 year. Treatment allocation was stratified according to age, BMI, years since menopause, insulin use, and patient characteristics are shown in Table 1.

The daily intake of 27 g flavonoid-enriched chocolate (conceptualized by the research team and formulated and produced by Barry Callebaut [Lebbeke-Wieze, Belgium] specifically for the trial) provided 90 mg epicatechin (850 mg total flavan-3-ols) and 100 mg isoflavones (aglycone equivalents), the optimal dose for biological efficacy on the basis of published findings from previous short-term trials (18,19). Flavonoid extracts...
Table 1—Baseline characteristics of the 93 postmenopausal patients with type 2 diabetes who completed the 1-year flavonoid intervention

<table>
<thead>
<tr>
<th></th>
<th>Flavonoid (n = 47)</th>
<th>Placebo (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.13 ± 0.73</td>
<td>62.98 ± 0.83</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.69 ± 1.09</td>
<td>31.85 ± 0.87</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>7.04 ± 1.05</td>
<td>5.76 ± 0.70</td>
</tr>
<tr>
<td>Years since menopause (years)</td>
<td>13.53 ± 1.27</td>
<td>13.47 ± 1.20</td>
</tr>
<tr>
<td>Medicated with insulin (n [% group])</td>
<td>9 [19%]</td>
<td>9 [20%]</td>
</tr>
<tr>
<td>Medicated for hypertension (n [% group])</td>
<td>28 [60%]</td>
<td>25 [54%]</td>
</tr>
<tr>
<td>Past smoker (n [% group])</td>
<td>14 [30%]</td>
<td>19 [41%]</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>7.82 ± 0.77</td>
<td>8.79 ± 0.83</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>7.58 ± 0.29</td>
<td>7.67 ± 0.29</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.34 ± 0.05</td>
<td>0.33 ± 0.05</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.13 ± 0.14</td>
<td>7.25 ± 0.15</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.26 ± 0.09</td>
<td>4.29 ± 0.11</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>2.21 ± 0.07</td>
<td>2.20 ± 0.10</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.44 ± 0.05</td>
<td>1.34 ± 0.05</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.44 ± 0.09</td>
<td>1.69 ± 0.12</td>
</tr>
</tbody>
</table>

Mean ± SEM or percentage.

were purchased (flavan-3-ols and Actiaco cocoa [Barry Callebaut]; isoflavones and SoyLife40 [Frutarom, Veenendaal, the Netherlands]), and intervention and placebo chocolates were produced by Barry Callebaut, which were matched for macronutrient content, appearance, and taste. Batch-to-batch variability and effect of storage on flavonoid content were independently determined using high-performance liquid chromatography (HPLC) (20).

Chocolate (13.5 g) was consumed twice daily (lunchtime and evening) to maintain circulating levels of metabolites, given our knowledge of the half-life of the compounds (21). Subjects were advised to exchange the study chocolate with foods of similar nutritional content (total daily intake provided 152 kcal, 10 g fat, and 13 g carbohydrate). Adherence to intervention was determined by counting returned wrappers and objectively assessed through quantification of 24-h urinary total epicatechin (sum of epicatechin, 3′-methyl epicatechin, 4′-methyl epicatechin, epicatechin-3-sulfate, and epicatechin-methyl-sulfate) and isoflavone (daidzein, genistein, and equol) excretion levels at 6 and 12 months determined by HPLC with mass spectrometric (MS) detection after enzyme hydrolysis using established methods. Intra-assay coefficients of variation (CVs) for total epicatechin, daidzein, genistein, and equol levels were 7.7, 6.3, 8.0, and 8.1%, respectively, and interassay CVs were 9.1, 11.0, 14.1, and 8.6%, respectively.

One week preceding and during the 1-year trial, habitual diet and exercise routines were maintained, with the exception of restricting the intake of specific flavonoid-rich foods (a list of which was provided). Four-day diet diaries were used to assess habitual dietary intake at baseline, 6 months, and 12 months (Supplementary Table 1), and adherence to study protocol was monitored by research staff between study assessments. Additionally, for 24 h before study assessments, subjects were asked to refrain from caffeine, alcohol, and strenuous exercise. Each volunteer consumed a low-flavonoid meal the evening before each assessment followed by an overnight fast (>10 h).

At baseline and 12 months, vascular measures were made at the research facility, including 2-h ambulatory BP monitoring (Spacelabs Healthcare, Issaquah, WA), with recordings every 10 min. Biological samples (24-h urine and fasting blood) were also collected (Fig. 1C), with levels of fasting glucose and lipoproteins (total cholesterol, HDL-cholesterol [HDL-C], and triglycerides) measured photometrically using a clinical chemistry autoanalyzer (ARCHITECT c Systems autoanalyzer; Abbott Laboratories, Abbott Park, IL). Fasting HbA1c was assessed by HPLC (A. Menarini Diagnostics, Florence, Italy). LDL-cholesterol (LDL-C) was determined using the Friedewald equation (22). Furthermore, plasma/urine aliquots were stored at −80°C for subsequent analyses. Anthropometric measures (body weight and height) were taken in duplicate, according to standardized protocols. From banked plasma, insulin concentrations were assessed using routine methods (insulin ELISA; Mercodia, Uppsala, Sweden). The intra-assay coefficients of variation were 2.90% (HbA1c), 2.82% (glucose), 1.24% (total cholesterol), 3.01% (HDL-C), 1.43% (triglycerides), and 3.84% (insulin). Insulin resistance and insulin sensitivity were calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) equation, HOMA-IR = glucose × insulin/22.5 (23), and the quantitative insulin sensitivity index (QUICKI) (24) equation, QUICKI = 1/ (log [fasting insulin] + log [fasting glucose]), respectively. HOMA-IR, QUICKI, glucose, and insulin data are reported for n = 45 (in both groups), triglycerides levels for n = 45 flavonoid and n = 44 placebo subjects, and LDL-C levels for n = 45 flavonoid and n = 42 placebo subjects.

Ten-year estimated risks for coronary heart disease (CHD), fatal CHD, stroke, and fatal stroke were calculated using the UK Prospective Diabetes Study (UKPDS) risk engine (version 2.0, www.dtu.ox.ac.uk/ukpds_trial/index.php; Diabetes Trials Unit, University of Oxford, Oxford, U.K.). The UKPDS risk engine includes age, diabetes duration, sex, presence of atrial fibrillation, ethnicity, smoking status, HbA1c (%), systolic BP (mmHg), total cholesterol (mmol/L), and HDL-C (mmol/L). The last observation carried forward was used to interpolate incomplete data (n = 3 observations for HbA1c, cholesterol, and HDL-C).

Statistical analysis

Results are expressed as mean ± SEM. At baseline (0 mol/L) and 12 months (12 mol/L), differences in patient characteristics were assessed using Student independent-sample t test (continuous data) and Pearson χ² test (categorical data). Data are presented for those completing the 1-year intervention per protocol, and the primary test of effect was univariate ANCOVA analysis (intervention group as fixed factor [flavonoid/placebo] versus change in variable [pre (0 mol/L)/post (12 mol/L)], with baseline value of variable as covariate). Further sensitivity analysis was conducted to exclude for low compliers (returning ≤70% wrappers), those with annual change in BMI of greater than or equal to ±5 kg/m², and one volunteer with atrial fibrillation (n = 5 flavonoid; n = 4 placebo). Statistical analyses were performed using SPSS, release 18.0.0 (IBM).
Type 2 diabetes and chronic flavanol intake

Table 2—Effect of 1-year combined intervention with flavan-3-ols and isoflavones on biomarkers of CVD risk in medicated postmenopausal patients with type 2 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Flavonoid</th>
<th>Placebo</th>
<th>Net intervention effect</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 months</td>
<td>12 months</td>
<td>0–12 months</td>
<td>0 months</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.67 ± 0.29</td>
<td>2.34 ± 0.20</td>
<td>-0.33 ± 0.19**</td>
<td>3.16 ± 0.37</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.343 ± 0.005</td>
<td>0.346 ± 0.005</td>
<td>0.003 ± 0.003*</td>
<td>0.336 ± 0.005</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>7.58 ± 0.29</td>
<td>7.48 ± 0.33</td>
<td>-0.10 ± 0.31</td>
<td>7.67 ± 0.29</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>7.82 ± 0.77</td>
<td>7.06 ± 0.60</td>
<td>-0.75 ± 0.41*</td>
<td>8.79 ± 0.83</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>1.44 ± 0.09</td>
<td>1.46 ± 0.09</td>
<td>0.02 ± 0.05</td>
<td>1.69 ± 0.12</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>2.21 ± 0.07</td>
<td>2.10 ± 0.07</td>
<td>-0.11 ± 0.05*</td>
<td>2.20 ± 0.10</td>
</tr>
<tr>
<td>HDL-C/LDL-C</td>
<td>0.66 ± 0.03</td>
<td>0.72 ± 0.03</td>
<td>0.06 ± 0.02**</td>
<td>0.68 ± 0.05</td>
</tr>
<tr>
<td>CHD risk (UKPDS) (%)</td>
<td>1.95 ± 0.56</td>
<td>1.94 ± 0.57</td>
<td>0.09 ± 0.37*</td>
<td>10.21 ± 0.65</td>
</tr>
<tr>
<td>Fatal CHD risk (UKPDS) (%)</td>
<td>6.14 ± 0.49</td>
<td>6.53 ± 0.51</td>
<td>0.39 ± 0.25</td>
<td>6.79 ± 0.56</td>
</tr>
<tr>
<td>Stroke risk (UKPDS) (%)</td>
<td>7.16 ± 1.11</td>
<td>8.07 ± 1.26</td>
<td>0.91 ± 0.17</td>
<td>6.52 ± 0.61</td>
</tr>
<tr>
<td>Fatal stroke risk (UKPDS) (%)</td>
<td>1.00 ± 0.15</td>
<td>1.15 ± 0.17</td>
<td>0.15 ± 0.03</td>
<td>1.00 ± 0.10</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>133.68 ± 1.63</td>
<td>135.62 ± 1.63</td>
<td>1.94 ± 1.28</td>
<td>137.38 ± 1.85</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.13 ± 0.14</td>
<td>7.22 ± 0.15</td>
<td>0.09 ± 0.13</td>
<td>7.25 ± 0.15</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>4.26 ± 0.09</td>
<td>4.22 ± 0.10</td>
<td>-0.04 ± 0.05</td>
<td>4.29 ± 0.11</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>1.40 ± 0.05</td>
<td>1.45 ± 0.05</td>
<td>0.05 ± 0.02</td>
<td>1.34 ± 0.05</td>
</tr>
<tr>
<td>Total cholesterol: HDL-C</td>
<td>3.19 ± 0.11</td>
<td>3.02 ± 0.10</td>
<td>-0.16 ± 0.05*</td>
<td>3.37 ± 0.14</td>
</tr>
</tbody>
</table>

Data are mean ± SEM. *P < 0.05. **P < 0.01.
Figure 2—The effect of the 1-year flavonoid intervention on insulin resistance in compliant patients. A: Plasma insulin. B: HOMA-IR (mean ± SEM). *P < 0.05, **P = 0.01; n = 42 flavonoid, n = 42 placebo.

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control (HbA1c and glucose levels) (Table 2). At 12 months, mean BMI was similar in both groups.

In sensitivity analyses, a similar magnitude of effect of the flavonoid intervention on HOMA-IR and insulin (Fig. 2) and estimated 10-year risk of CHD (flavonoid 0.0 ± 0.4%, placebo 1.2 ± 0.4%; P = 0.02) was observed. Moreover, stronger statistical associations were observed for the effects on estimated 10-year risk of fatal CHD (flavonoid 0.3 ± 0.3%, placebo 1.1 ± 0.3%; P = 0.04) and lipoprotein status: total C:HDL-C ratio (flavonoid −0.2 ± 0.1, placebo 0.0 ± 0.1; P = 0.004) and LDL-C (flavonoid −0.1 ± 0.1 mmol/L, placebo 0.1 ± 0.1 mmol/L; P = 0.03).

**CONCLUSIONS**—In this 1-year, randomized, placebo-controlled intervention trial, a combined intake of flavan-3-ols and isoflavones significantly improved lipoprotein status and markers of insulin sensitivity and attenuated the estimated 10-year risk of CHD in postmenopausal women receiving standard therapy for type 2 diabetes. To our knowledge, this is the only long-term flavonoid trial that has been conducted in medicated postmenopausal patients with type 2 diabetes, and these data highlight the additional benefit of dietary flavonoids to standard drug therapy in managing CVD risk in these patients.

All patients were receiving statin therapy (≥40 mg simvastatin or ≥10 mg atorvastatin) as part of standard medical care, but flavonoid intervention resulted in further improvements in lipoprotein status, specifically significant reductions in LDL-C and total-C:HDL-C ratio. The observed reduction of 0.16 mmol/L LDL-C is consistent with data from the meta-analysis of short term (maximum 12 weeks) cocoa (−0.15 mmol/L) (26) and soy isoflavone (−0.13 mmol/L) (14) intervention trials in healthy participants and with the magnitude of change observed in the few short-term trials on soy isoflavones (16,17) or chocolate (15) in type 2 diabetic patients. Our findings do not suggest any additive effect of our combined intervention on lipoprotein status in this medicated group.

The observed effect is of potential clinical significance. A 1.0 mmol/L reduction in LDL-C has been associated with a 21% decrease in vascular events in patients with type 2 diabetes (27), suggesting that long-term flavonoid intervention may be associated with a 3.4% reduction in vascular events. These effects are also supported by in vitro work, suggesting that flavan-3-ols increase apolipoprotein A1 and decrease apolipoprotein B production as a result of upregulation of sterol regulatory element binding proteins and an increase in LDL receptor activity (28). Likewise, isoflavones have been shown to decrease apolipoprotein B secretion in HepG2 cells through multiple mechanisms and may augment the efficacy of statins (29).

We also observed a significant reduction in insulin resistance (HOMA-IR) and improvements in insulin sensitivity (QUICKI) that were driven by a significant decrease in insulin concentrations. These findings are clinically important, as insulin resistance is not only a key determinant of the metabolic syndrome but is also associated with increased arterial stiffening (30) and risk of cardiovascular events even in individuals with no diabetes (31). Our recent meta-analysis of short-term cocoa/chocolate trials (≤4 months duration) also showed that intervention improved insulin resistance (HOMA-IR −0.67 [95% CI −0.98, −0.36]) due to significant reductions in serum insulin, although only 3 of the 42 studies were in patients with type 2 diabetes (A. Cassidy, personal communication). However another recent meta-analysis observed no effect of soy isoflavones on measures of glycemic control (32); although only 3 of the 24 trials were in type 2 diabetic patients, there was wide variability in source and dose of soy isoflavones fed, and few studies reported changes in HOMA-IR. In another review, only soy isoflavones and genistein exerted beneficial effects on HOMA-IR (14). There are supporting underlying mechanisms for these effects; in vitro, flavan-3-ols, isoflavones, and their metabolites enhanced insulin-stimulated glucose uptake in adipocytes through increased expression of GLUT4, and improved insulin secretory function of pancreatic β-cells (10,33).

Our combined intervention attenuated the UKPDS-estimated, 10-year CHD risk as a result of beneficial effects on lipoprotein status. The UKPDS algorithm incorporates additional risk factors for diabetes (i.e., HbA1c and duration of diabetes) beyond traditional risk factors, and, although validation studies have identified a tendency to overestimate CHD risk (34), it is still considered a useful tool (35) to compliment other CHD risk assessments. Over half of our study population was on antihypertensive medication, and this may have influenced our lack of effect on BP. In the few previous short-term studies with type 2 diabetic patients, flavan-3-ols alone did not improve BP (15,36), although in one study,
flavonoids reduced BP in patients with type 2 diabetes who were not on medication for hypertension (37). This is in contrast to flavonoid trials in participants without type 2 diabetes, where systolic BP and diastolic BP were reduced by short-term flavan-3-ol (by 4.5 and 2.5 mmHg, respectively) (38) and isoflavone intake (by 2.5 and 1.5 mmHg, respectively) (39).

Our study has a number of limitations. The dropout rate during the intervention was high (21%), with the most frequent reason for participant withdrawal (in both groups) attributable to palatability (Fig. 1A); however, these numbers are comparable to other nutrition trials in type 2 diabetic patients (40), and as observed in other studies, a small number of patients had changes in BP medication during the 1-year trial period (n = 10). Our findings also relate specifically to a combined flavonoid intervention given to postmenopausal women receiving standard diabetes therapy (including lipid-lowering medication), and further studies are now required to determine the relative influence of each flavonoid subclass (flavan-3-ols and isoflavones) on biomarkers of CVD risk in this population and to examine whether similar effects are observed in male patients or in other patient groups. Finally, although the flavonoid intake in our trial could potentially be attained through high intake of dietary flavonoid, an emerging range of flavonoid-rich functional foods may offer additional opportunities to consume flavonoids at optimal levels. Despite these limitations, our trial is the longest intervention to date to assess the effects of flavonoids on CVD risk factors in a population of medicated, postmenopausal patients with type 2 diabetes and benefits from objective assessment of compliance.

This pragmatic 1-year trial provides evidence to suggest that the intake of flavonoids results in sustained improvements in lipid profile and insulin sensitivity and an attenuation of estimated CHD risk, highlighting the additional benefit of flavonoids to standard drug therapy in managing CVD risk in patients with type 2 diabetes. Our study is the only combined flavonoid trial and the longest flavan-3-ol intervention to date, and our findings have potential clinical relevance. Long-term studies are now required to determine whether these effects are restricted to populations of medicated postmenopausal women with established type 2 diabetes and to determine whether chronic intake of flavan-3-ols or isoflavones is as effective when consumed independently.

Acknowledgments—This study was funded by Diabetes UK (06/0003397, principal investigator A.C.), with raw materials purchased from Frutarom Netherlands (isoflavones) and Barry Callebaut Belgium (Acticacoa cocoa) and trial chocolates manufactured by Barry Callebaut. P.A.K. and A.C. have received research funding from Unilever Research to conduct an anthocyanin trial and in vitro experimental work (BBSRC-Case PhD studentship). P.A.K. has been an independent member of the Coressence Science Board since 2006 and is in receipt of research funding from Danisco A/S. A.C. has received unrestricted funding from the chocolate industry to conduct a systematic review on chocolate and oxidative stress. No other potential conflicts of interest relevant to this article were reported.

P.J.C. provided input for the study conception and design, coordinated the trial, conducted laboratory and statistical analyses, interpreted data, and drafted the manuscript. M.S., J.P., and K.D. provided input for the study conception and design and read and approved the final draft of the manuscript. P.A.K. provided input for the study conception and design, analyzed levels of flavonoids in foods and biological samples, and read and approved the final draft of the manuscript. A.C. conceived and designed the study, interpreted data, drafted the manuscript, and is the guarantor of this article.

The authors thank Barry Callebaut Belgium and Frutarom Netherlands for their assistance in developing the trial foods and the Local Diabetes Research Network for invaluable nursing support.

References


