Adiponectin in a Native Canadian Population Experiencing Rapid Epidemiological Transition

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OBJECTIVE — Adiponectin is emerging as an important protein in the etiology of obesity and related metabolic disorders. The objectives of this study were to determine cross-sectional and prospective associations of adiponectin concentration with adiposity, type 2 diabetes, and cardiovascular disease (CVD) risk factors in a population-based study of Native Canadians, a group experiencing dramatic increases in diabetes and CVD.

RESEARCH DESIGN AND METHODS — During the 1993–1995 baseline survey, samples for glucose, insulin, adiponectin, and lipids were collected after an overnight fast. Waist circumference and percent body fat were measured, and a 75-g oral glucose tolerance test was administered: $n = 505$ with normal glucose tolerance (NGT), 74 with impaired glucose tolerance (IGT), and 149 with diabetes. In 1998, 95 high-risk subjects, defined as those who, at baseline, had either IGT or NGT with an elevated 2-h glucose concentration (≥7.0 mmol/l), participated in a follow-up examination using the protocol used at baseline.

RESULTS — After adjustment for covariates including percent body fat and homeostasis model assessment of insulin resistance (HOMA-IR), adiponectin concentrations were significantly lower among men versus women (10.8 vs. 15.0 μg/ml, $P < 0.0001$) and among diabetic versus NGT subjects (11.1 vs. 13.1 μg/ml, $P < 0.05$). Adiponectin was inversely correlated with percent body fat, waist circumference, HOMA-IR, and triglyceride and positively correlated with HDL ($r = |0.30| - |0.44|$, all $P < 0.0001$). In multivariate linear regression analysis in nondiabetic subjects, HDL and percent body fat were significantly related to adiponectin variation among both men and women ($R^2 = 28$–29%). Factor analysis returned three underlying factors among these variables, with adiponectin loading on the second factor along with insulin, waist circumference, triglyceride, and HDL. In the follow-up study, higher adiponectin at baseline was significantly associated with increases in HDL ($r = 0.24$, $P = 0.03$) and decreases in HOMA-IR ($r = -0.29$, $P = 0.009$) after adjustment for covariates, including age, adiposity, and diabetes status at baseline and follow-up.

CONCLUSIONS — These population-based findings support the hypothesis that low circulating levels of adiponectin are an important determinant of risk of CVD.

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Abbreviations: CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment of insulin resistance; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Adiponectin, a collagen-like plasma protein produced and secreted exclusively by adipose tissue, has been shown to have compelling antiatherogenic, anti-inflammatory, and insulin-sensitizing properties (1–4). Cross-sectional studies of human subjects have reported decreased concentrations of adiponectin in patients with type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease (CVD) compared with healthy individuals (5–7), and weight reduction has resulted in increases in adiponectin (5,8). In addition, inverse correlations of adiponectin with BMI, percent body fat, waist-to-hip ratio, glucose, insulin, and triglyceride and positive correlations with HDL and direct measures of insulin sensitivity have been consistently demonstrated (9,10). Two recent nested case-control studies reported that type 2 diabetes was less likely to develop in individuals with high concentrations of adiponectin at baseline than those with low concentrations (11,12). In addition, Stefan et al. (13) reported that low baseline levels of adiponectin were associated with decreases in directly measured insulin sensitivity after adjustment for age, sex, and percent body fat.

There have, however, been relatively few studies in large, population-based samples of humans and, other than a number of excellent studies among the Pima Indians (9,11,13), few investigations among other indigenous people, which is significant in light of recent and dramatic increases in obesity-associated chronic diseases in these populations (14). The objectives of this study were to determine cross-sectional and prospective associations of adiponectin concentration with adiposity, type 2 diabetes, and CVD risk factors in a population-based study of Native Canadians, a group undergoing rapid epidemiological transition, including recent large increases in both type 2 diabetes and heart disease (15–19).

RESEARCH DESIGN AND METHODS

Baseline prevalence survey, 1993–1995

The methodology of the Sandy Lake Health and Diabetes Project prevalence study has been presented in detail in previous publications (16–18). Briefly, between 1993 and 1995, 728 of 1,018 (72%) eligible residents of Sandy Lake aged 10–79 years participated in a population-based cross-sectional survey to determine the prevalence of type 2 diabetes and its associated risk factors. Signed informed consent was obtained from all participants, and the study was approved by the Sandy Lake First Nation Band Council and University of Toronto Ethics Review Committee.

Participants provided fasting blood samples for glucose, insulin, lipids, and adiponectin after an 8- to 12-h overnight fast. A 75-g oral glucose tolerance test (OGTT) was administered, and a second sample for glucose was collected after 120 min. Individuals were excluded from the OGTT if they had physician-diagnosed diabetes and were *1*) currently receiving treatment with insulin or oral hypoglycemic agents or *2*) had a fasting blood glucose concentration >11.1 mmol/l. Women who were pregnant at the time of initial contact underwent OGTT 3 months postpartum. Diabetes and impaired glucose tolerance (IGT) were diagnosed according to 1985 World Health Organization criteria (20).

Glucose concentration was determined using the glucose oxidase method. Insulin was measured using a radioimmunoassay technique (Pharmacia, Piscataway, NJ), which has a lower detection limit of 22 pmol/l and an interassay coefficient of variation of 7.2–8.8%. This assay displays a very high degree of cross-reactivity with proinsulin (100%), and therefore, the reported values refer to concentrations of total immunoreactive insulin (16). Fasting plasma adiponectin concentration was measured by radioimmunoassay (Linco Research, St. Louis, MO) with a coefficient of variation of 9.3%. Adiponectin was measured in plasma specimens that had been stored at −70°C for ~9 years. Cholesterol, triglyceride, and HDL cholesterol concentrations were determined using methods described in the Lipid Research Clinics manual of operations (21). LDL cholesterol concentration was calculated using the Friedewald formula (22). We estimated insulin resistance using indirect measures, including fasting insulin concentration (23) and the homeostasis model assessment of insulin resistance (HOMA-IR) of Matthews et al. (24), which is calculated from fasting glucose and insulin concentrations. These measures have been validated against gold standard techniques for determination of insulin resistance (23,24). We also calculated quantitative insulin sensitivity check index, a more recently proposed index (25). This index was very closely correlated with fasting insulin and HOMA-IR ($r \cong 0.99$) and yielded similar results in the analysis, and therefore, these data are not presented.

Anthropometric measurements were performed with the participant wearing either undergarments and a hospital gown or light athletic clothing but without shoes. Each measurement was performed twice, and the average was used in the analysis. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Weight was measured to the nearest 0.1 kg using a hospital balance beam scale. BMI was defined as weight divided by height squared (kg/m^2). The waist was measured to the nearest 0.5 cm at the point of narrowing between the umbilicus and xiphoid process; the hips were measured to the nearest 0.5 cm at the maximum extension of the buttocks. Percent body fat was estimated by bioelectrical impedance analysis using the Tanita TBF-201 Body Fat Analyzer (Tanita, Tokyo, Japan). High reproducibility of percent body fat estimates using this machine (intraclass correlation coefficient = 0.99) in a sample from this population has been documented (26), and the instrument has been validated by others against dual-energy X-ray absorptiometry in both diabetic and nondiabetic subjects (27,28).

Follow-up survey, 1998

During the summer of 1998, Sandy Lake residents who were found, at the time of the baseline survey, to have either IGT (n = 74) or normal glucose tolerance (NGT) with a 2-h postchallenge glucose concentration ≥7.0 mmol/l (n = 51) were invited to participate in a follow-up visit to determine current glucose tolerance status. Of the 125 individuals in the follow-up cohort, 3 patients (3 with IGT, 0 with NGT) had died, 11 patients (9 with IGT, 2 with NGT) were no longer living in the community, 2 patients (1 with IGT, 1 with NGT) were too sick to participate, and 14 patients (6 with IGT, 8 with NGT) refused to attend. Therefore, 95 (76%) members of this high-risk cohort participated in the follow-up examination. Nonparticipants did not differ significantly from participants in age, sex, or anthropometric or metabolic variables (data not shown). Concentrations of metabolic and cardiovascular variables and anthropometric measurements were assessed using field and laboratory methods and equipment identical to those used during the baseline survey. Signed informed consent was obtained from all subjects, and the follow-up protocol was approved by the Sandy Lake First Nation Band Council and the University of Toronto Ethics Review Committee

Statistical analyses

All analyses were performed using SAS software, version 6.12 (SAS Institute, Cary, NC). The distributions of continuous variables were assessed for normality, and the natural log transformations of skewed variables were used in subsequent analyses.

Cross-sectional study

Sex and glucose tolerance status differences in adiponectin concentration were assessed using ANCOVA with adjustment for demographic variables, percent body fat, HOMA-IR, lipids, and diabetes (sex comparison only). In analyses restricted to nondiabetic subjects (men, n = 239; women, n = 324), univariate associations of adiponectin with measures of adiposity, insulin, glucose, and lipids were determined using Spearman correlation analysis. Multiple linear regression analysis was used to assess variables that were independently associated with variation in log adiponectin concentration. Waist circumference was used in lieu of waist-to-hip ratio as a measure of abdominal adiposity, given that the former is superior as an estimate of intra-abdominal fat mass (29).

We used principal factor analysis (using the FACTOR procedure of SAS) to investigate the relationship of adiponectin with latent variables underlying the metabolic syndrome (30). The number of factors retained was based on scree plot analysis (factors above the break in the

Table 1—*Characteristics of participants in the baseline examination of the Sandy Lake Health and Diabetes Project, 1993–1995*

Variable	Men	Women	*P* value*
n	305	423	
Age (years)	30.4 ± 15.9	29.4 ± 15.8	0.40
BMI (kg/m^2)	25.6 ± 5.1	27.4 ± 6.1	<0.0001
Waist circumference (cm)	92.5 ± 14.5	90.6 ± 13.8	0.08
Body fat (%)	25.7 ± 8.6	41.6 ± 11.2	<0.0001
Fasting insulin (pmol/l)	93 (58–132)	110 (78–169)	<0.0001
HOMA-IR (units)	3.3 (2.1–5.2)	4.0 (2.5–7.0)	0.0002
Fasting glucose (mmol/l)	6.4 ± 2.9	6.5 ± 3.2	0.88
2-h glucose (mmol/l)	6.5 ± 4.3	7.1 ± 4.0	0.0375
Cholesterol (mmol/l)	4.6 ± 1.1	4.4 ± 0.8	0.008
LDL cholesterol (mmol/l)	2.7 ± 0.9	2.5 ± 0.7	0.0002
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.3 ± 0.3	0.02
Triglyceride (mmol/l)	1.2 (0.9–1.9)	1.3 (0.9–1.7)	0.75
Adiponectin (μg/ml)	12.6 (8.7–18.1)	14.1 (10.4–19.4)	0.002
IGT (%)	5.3	14.2	<0.001
Diabetes (%)	16.0	18.1	0.46

Data are means ± SD or median (interquartile range) unless otherwise indicated. *Student's *t* tests performed on log transformations of fasting insulin, HOMA-IR, triglyceride, and adiponectin.

curve were retained), proportion of common variance explained (>5%), and factor interpretability criteria, which have been described and recommended elsewhere (30,31). The often cited Kaiser criterion (retain factors with eigenvalues >1) is more appropriate for principal components analysis and may be relaxed for common factor analysis, depending on the number of variables (31). Varimax (orthogonal) rotation was used to obtain a set of independent uncorrelated factors. The resulting factor pattern was interpreted using factor loadings of ≥0.3. In the tables and text, we report the proportion of total variance (common variance plus specific variance plus error variance) explained by the factors.

Prospective study

Changes in metabolic and cardiovascular variables were calculated as the follow-up level (1998) minus the baseline level (1993–1995). The associations were assessed between baseline adiponectin concentration and *1*) follow-up levels and *2*) changes over time in measures of adiposity, glucose, insulin, HOMA-IR, and lipids. Due to skewness in the distribution of both dependent and independent variables, Spearman correlation coefficients were used to assess these relationships, with adjustment for age, sex, change in waist circumference, baseline and follow-up diabetes status, and baseline levels of the dependent variables. Duration of follow-up (median = 4.2 years) did not have any effect on these associations (data not shown).

RESULTS — Characteristics of men and women participating in the baseline examination are presented in Table 1. Women had higher levels of BMI, percent body fat, and HOMA-IR, higher concentrations of HDL cholesterol and adiponectin, and a higher prevalence of IGT. After adjustment for covariates including percent body fat and HOMA-IR, adiponectin concentrations were significantly lower among men versus women (10.8 vs. 15.0 μg/ml, $P < 0.0001$) and among subjects with type 2 diabetes versus subjects with NGT (11.1 vs. 13.1 μg/ml, $P < 0.05$). Among subjects with IGT, adiponectin levels were intermediate between NGT and type 2 diabetes, although the difference between IGT and NGT was not significant after covariate adjustment (11.7 vs. 13.1 μg/ml, $P = 0.10$).

In analyses restricted to nondiabetic subjects, adiponectin was inversely correlated with age ($r = -0.23$, $P < 0.0001$) as well as measures of adiposity including BMI, waist circumference, and percent body fat ($r = -0.38$, -0.41, and -0.27, respectively; all $P < 0.0001$). Furthermore, adiponectin showed inverse correlations with insulin, HOMA-IR, and triglyceride ($r = -0.29$, -0.29, and -0.36, respectively; all $P < 0.0001$) and a positive correlation with HDL ($r = 0.39$, $P < 0.0001$). The magnitude and direction of these associations were similar in separate analyses of men and women (data not shown). In multivariate linear regression analysis in these nondiabetic subjects, HDL (positive) and percent body fat (inverse) were significantly related to adiponectin variation among both men and women (R^2 = 28–29%; Table 2). In addition, there were significant inverse associations with age among men and 2-h glucose concentration among women.

Factor analysis of adiponectin and core variables of the metabolic syndrome returned three factors, which ex-

Table 2—*Multiple linear regression analysis of independent variables associated with adiponectin concentrations in nondiabetic subjects, by sex, Sandy Lake Health and Diabetes Project, 1993–1995**

	Dependent variable = adiponectin					
	Men			Women		
Variable	β	*t*	*P*	β	*t*	*P*
Log age	−0.200	−2.53	0.012	−0.040	−0.61	0.54
Percent body fat	−0.015	−2.81	0.006	−0.012	−3.97	<0.0001
Log HOMA-IR	0.018	0.23	0.81	−0.059	−0.70	0.33
Log triglyceride	−0.112	−1.17	0.24	−0.117	−1.73	0.09
HDL	0.574	4.46	<0.0001	0.355	3.69	0.0003
LDL	0.082	1.65	0.10	0.023	0.52	0.60
Fasting glucose	−0.010	−0.14	0.89	0.053	0.96	0.34
2-h glucose	−0.012	−0.58	0.56	−0.040	−2.58	0.0104
R^2	0.29			0.28		

*Results were very similar using forward stepwise regression.

Table 3—*Results of factor analysis of anthropometric and metabolic variables in nondiabetic subjects, Sandy Lake Health and Diabetes Project, 1993–1995

	Factor		
Variable	Adiposity-insulin	Lipids-insulin	Glucose-insulin
Log fasting insulin	**0.42**	**−0.34**	**0.51**
Waist circumference	**0.66**	**−0.39**	0.27
Percent body fat	**0.73**	−0.16	0.25
Log triglyceride	0.29	**−0.53**	0.30
HDL cholesterol	−0.08	**0.57**	−0.13
Fasting glucose	0.12	−0.16	**0.56**
2-h glucose	0.24	−0.15	**0.46**
Log adiponectin	−0.21	**0.50**	−0.14
Percent total variance	36.1	5.0	3.7
Percent cumulative total variance	36.1	41.1	44.8

*Loadings >0.30 in bold type.

plained 44.8% of the total variance in the dataset (Table 3). Factor 1 ("adiposity-insulin") had positive loadings of insulin, waist circumference, and percent body fat. Factor 2 ("lipids-insulin") had inverse loadings of insulin, waist circumference, and triglyceride and positive loadings of HDL cholesterol and adiponectin. Factor 3 ("glucose-insulin") had positive loadings of fasting and 2-h glucose and insulin. When adiponectin was removed from the factor analysis, a three-factor solution was returned, containing a generally similar factor pattern, although the lipids-insulin factor explained less of the variance than the glucose-insulin factor (data not shown). Factor patterns were similar in separate analyses of men and women (data not shown).

In the prospective study of high-risk subjects, higher adiponectin at baseline was significantly associated with increases in HDL ($r = 0.24$, $P = 0.03$) and decreases in HOMA-IR ($r = -0.29$, $P = 0.009$) after adjustment for covariates including age, adiposity, and diabetes status at baseline and follow-up (Table 4). Baseline adiponectin was not associated with risk of progression to diabetes (adjusted odds ratio = 1.01, $P = 0.98$ per SD change).

CONCLUSIONS — In this population-based study of a Native Canadian population undergoing rapid epidemiological transition, we found that adiponectin concentrations were significantly lower in men versus women and in subjects with type 2 diabetes versus those with NGT. In addition, body fat and HDL cholesterol were significantly associated with variation in adiponectin concentration in multiple linear regression analysis. The most important contributions of the current study were *1*) the demonstration, using factor analysis, of the loading of adiponectin with an underlying lipids-insulin factor and *2*) the documentation, in a prospective analysis of high-risk subjects, of associations of elevated baseline adiponectin with increases in HDL and reductions in insulin resistance over the follow-up period.

Adiponectin concentrations were higher in women than in men, even after adjustment for covariates including percent body fat, lipids, and glucose tolerance status. This observation has been reported previously in studies of human subjects (5,10,32–34) as well as in rodents (32,35).

We found that adiponectin concentrations were reduced in subjects with diabetes and that adiponectin was inversely correlated with measures of insulin resistance, including insulin concentrations and HOMA-IR, in cross-sectional analy-

Table 4—*Anthropometric and metabolic characteristics of high-risk subjects from the follow-up phase of the Sandy Lake Health and Diabetes Project (men = 29, women = 66) and associations between baseline levels of adiponectin with follow-up levels and changes over time in these variables*

			Correlation between baseline adiponectin and level of metabolic variable at follow-up†		Correlation between baseline adiponectin and change in metabolic variable at follow-up‡	
Variable	Baseline values	Change over 4-year follow-up period	Partial *r*	*P* value	Partial *r*	*P* value
NGT/IGT/diabetes (*n*)	41/54/0	54/17/24				
Age at baseline (years)	35.1 ± 17.0	—				
Adiponectin (μg/ml)	11.7 (8.8–16.2)	—				
Body fat (%)	41.5 ± 10.6	6.0 (0.1–10.1)	−0.01	0.92	0.04	0.73
Waist (cm)	96.4 ± 11.4	3.4 (−0.5 to 6.5)	0.15	0.16	0.14	0.19
HOMA-IR (units)	4.8 (3.4–6.7)	−0.3 (−1.9 to 0.6)	−0.41	<0.0001	−0.29	0.009
Triglyceride (mmol/l)	1.5 (1.1–1.9)	0.1 (−0.3 to 0.4)	−0.03	0.79	−0.07	0.52
HDL cholesterol (mmol/l)	1.2 ± 0.3	0.0 (−0.1 to 0.2)	0.21	0.0558	0.24	0.0341

Data are means ± SD or median (interquartile range). Spearman correlation analysis, sample sizes vary slightly due to occasional missing values. High risk defined as subjects with baseline IGT or NGT with a 2-h postchallenge glucose concentration of ≥7.0 mmol/l. †Analyses adjusted for age, sex, change in waist circumference, baseline and follow-up diabetes status, and baseline level of the dependent follow-up variable; ‡analyses adjusted for age, sex, change in waist circumference, baseline and follow-up diabetes status, and baseline level of the dependent change variable.

ses, findings that are consistent with those from a growing body of studies in various populations (1–4). There have been fewer investigations, however, using larger, population-based samples, and only a limited number of studies from populations undergoing westernization. Data from these settings are of interest in light of the recent emergence and rapidly increasing prevalence of obesity and associated metabolic complications (14).

Among subjects at high risk for diabetes in the present study, higher baseline adiponectin concentrations were associated with improvements over the follow-up period in HDL and reductions in surrogate measures of insulin resistance, although there were no associations with changes in measures of adiposity or triglyceride concentration. Our prospective insulin and adiposity findings are consistent with those from prospective studies of the Pima Indians (13,36).

Our finding of no prospective association between baseline adiponectin concentration and subsequent development of type 2 diabetes among high-risk individuals is in contrast with the results of two recent nested case-control studies, which reported that type 2 diabetes was less likely to develop in individuals with high concentrations of adiponectin at baseline (11,12). However, there are some very important differences between these studies and the present investigation that are likely to have influenced the associations. In the study by Lindsay et al. (11), all subjects at baseline had both normal fasting glucose and NGT confirmed by OGTT. The baseline glucose tolerance status of subjects in the study by Spranger et al. (12) is unclear. Subjects in the present study, on the other hand, had either IGT or an otherwise elevated post-challenge glucose concentration at baseline and were thus at a more advanced stage in the natural history of glucose intolerance. It is clear that adiponectin concentrations in subjects at this phase of glucose tolerance deterioration were already decreased compared with those with NGT. This observation of a decrease in adiponectin early in the course of glucose intolerance is consistent with the findings of a longitudinal investigation of adiponectin and glucose tolerance deterioration in rhesus monkeys (37). In this study, it was demonstrated that adiponectin levels begin to decrease at an early phase in diabetes pathogenesis, in parallel with increases in adiposity and reductions in insulin sensitivity, and before the appearance of frank hyperglycemia.

Positive cross-sectional associations of adiponectin with HDL cholesterol have been consistently reported in the literature (1–4,34,38) and represent one of several lines of evidence supporting an antiatherogenic role for adiponectin. In the present study, we found that this association was independent of other factors, including HOMA-IR and percent body fat, in a population-based sample of Native Canadians, a group that has experienced dramatic increases in coronary heart disease hospitalizations over the past 2 decades (76–186 per 10,000 between 1981 and 1997) despite significant reductions in other sectors of the population (19). Further, we documented a novel prospective association of baseline adiponectin with increases in HDL over time in subjects from this population who were at high risk for type 2 diabetes. The physiological mechanism underlying the link between adiponectin and lipids is unknown. Although this relationship may be explained by the insulin-sensitizing effect of adiponectin, a recent study demonstrated that the inverse association between adiponectin and HDL was independent of directly measured insulin sensitivity, which suggests that adiponectin may have an independent effect on hepatic lipoprotein metabolism (33,34).

Factor analysis is a multivariate correlation technique that reduces a large number of intercorrelated variables to a smaller set of latent or underlying independent factors (30,31), and therefore, it has the potential to increase our understanding of the complex physiological and statistical interactions underlying the metabolic syndrome. The use of statistical techniques (including factor analysis and structural equation modeling) that aid in the reduction of complexity and unveiling of underlying "common threads" has taken on greater importance with the recent identification of several novel proteins associated with adipose tissue (leptin, adiponectin, and resistin). Over the past several years, a number of publications have appeared reporting factor analyses of the metabolic syndrome in various populations (39–43). As reviewed by Meigs (30), a number of common findings have emerged from these studies, including *1*) the identification of between two and four factors; *2*) the loading of insulin on more than one factor, including those that have been interpreted as "glycemia," "obesity," and "dyslipidemia;" and *3*) a separate factor for blood pressure. In the present study, factor analysis showed three underlying factors (adiposity-insulin, lipids-insulin, and glucose-insulin), with fasting insulin concentration loading on all three factors, observations that are consistent with the literature on this topic (30). When added to the factor analysis, adiponectin loaded positively with the second lipids-insulin factor, which also included inverse loadings of insulin, waist circumference, and triglcyeride, and a positive loading of HDL. This novel observation lends further support to the proposed multiple metabolic roles of adiponectin as an insulin-sensitizing and antiatherogenic protein (1–4).

In conclusion, these population-based findings support the hypothesis that low circulating levels of adiponectin are an important determinant of risk for both insulin resistance and CVD and extend the notion to a population undergoing rapid epidemiological transition. The observations in this context are of interest given recent and dramatic increases in both diabetes and CVD in this group (15–19). Results of recent studies demonstrating increases in adiponectin with thiazolidinedione treatment (44,45) indicate that these agents would be attractive to evaluate in clinical trials for the primary prevention of type 2 diabetes and heart disease.

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